

Investigational HIV Drugs and Emergent Strategies



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Gulick reported no relevant financial relationships with ineligible companies. (Updated September 16, 2026)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe new innovations and strategies in antiretroviral therapy with existing drugs
- List new investigational antiretrovirals in the pipeline

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Cabotegravir (CAB)



- Current formulation: CAB-LA 200 mg/ml q2 months
- New formulations: **CAB-ULA (ultra long-acting) q4 months**
 - **Phase 1 study ("2 to 4")**: CAB-LA q2→CAB-ULA q4 months [NCT06786520](#)
 - **Phase 2b study (EXTEND4M)**: CAB-ULA q4 months [NCT06741397](#)
 - **Phase 3 study (CUATRO)**: virologically suppressed people [NCT07650916](#)
CAB-LA + RPV-LA q2 months vs. CAB-ULA + RPV-ULA q4 months
 - **Pre-clinical**: Pro-Drug CAB Stearate (**VH-310**) q6-12 months [Kearney CROI 2024 #656](#)
- **CAB + RPV** in participants with viremia
 - **Meta analysis** (N=244): virologic success 87% [Barda HIV Medicine 2025;26:993-1003](#)
 - **A5359 LATITUDE** (N=249): randomized study of CAB+RPV vs. continued oral ART
 - Results: regimen failure 24% (CAB/RPV) vs. 38% (oral ART) [Rana NEJM 2026;394:858-871](#)
 - **CROWN Study** [NCT06694805](#)
 - Eligible patients (N=332): VL 1000-100,000 cps/ml on current oral ART
 - Study design: 3:1 randomization to LA-CAB+RPV vs continue oral ART



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CAB + LEN with Viremia

- **Case Series: Call for a Trial** (N=34 viremic participants):
 - 32/34 (94%) VS at median 8 weeks [Gandhi OFID 2024;11:ofae125](#)
- **ACTG 5431 (PALACE)**: People with Active Viremia Treated with LEN and CAB for Effectiveness)
 - Single-arm proof-of-concept study (N=38)
- **ACTG 5433 (LANCET)**: LEN and CAB in Viremic Adolescents and Adults on TDF/3TC/DTG in Low-Middle Income Countries
 - Phase 3b randomized open-label study of oral vs. LA ART (N=420)



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Lenacapavir (LEN)

- **PrEP**: q6 month injectable
- New formulations with yearly dosing [Jogiraju Lancet 2025;405:1147](#)
 - **Phase 3** single-arm trial (**PURPOSE-365**): 3000 mg new LEN IM (2 X 3 cc) for PrEP (recruiting) [NCT07047716](#)
- Oral bridge therapy (LEN 300 mg daily for up to 6 months) currently approved when injections are delayed
- PK support LEN 300 mg weekly oral dosing for PrEP
 - Submitted to FDA June 2026; PDUFA date 2/2/27
- **Treatment**
 - Phase 2 treatment-naïve (**CALIBRATE**) LEN SC or IM with TAF/FTC or BIC
 - High rates of virologic suppression [Hagins AIDS 2026;40:302-311](#)
 - Novel combinations for treatment at all stages

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ARTISTRY-2: BIC/LEN Switch

- Phase 3, double-blind, randomized study
- Pt population: On TAF/FTC/BIC with VL <50 (N=577)
- Study rx: Randomized 2:1 to BIC/LEN (75/50 mg) or continue TAF/FTC/BIC
- Results: VL at week 48
 - >50 copies/ml: 1.3% BIC/LEN vs. 1.0% TAF/FTC/BIC (Δ +0.3%, 95% CI -1.9%, +2.4%)
 - <50 copies/ml: 93.5% BIC/LEN vs. 91% TAF/FTC/BIC
- Drug-related adverse events: 10% BIC/LEN vs. 12% TAF/FTC/BIC
- Conclusion: BIC/LEN non-inferior to TAF/FTC/BIC

Meissner Lancet HIV 2026;13:e538-e547

Cahn IAS 2026 #TUPEB103



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ARTISTRY-1: BIC/LEN Substitution

- Phase 3 randomized open-label non-inferiority (4%) study
- Pt population: VL<50 on "complex" ART regimen X 6 mos; no BIC resistance, no prior LEN exposure (N=557)
 - Complex regimen: >2 pills, >2X/day, $\geq$ 2 anchor drugs, parenteral drug, etc.
 - At baseline, avg age 60, on ART 28 years, 53% had >2 comorbidities, 60% on concomitant meds, 1/3 $\geq$ 3 pill ART, 39% bid regimens, 77% on PI/b
- Study rx: Randomized 2:1 BIC/LEN (75/50 mg) or continue complex ART
- Results (wk 48):
 - VL <50: 96% BIC/LEN vs. 93% complex ART
 - VL >50: 3 (1%) BIC/LEN vs. 2 (1%) complex ART (Δ -0.3%; 95% CI -2.3%, +1.8%)
 - No drug resistance
 - Discontinued ART due to AE: 2% (BIC/LEN) vs. 1% (complex ART)
- Conclusion: BIC/LEN non-inferior, similar safety, better rx satisfaction

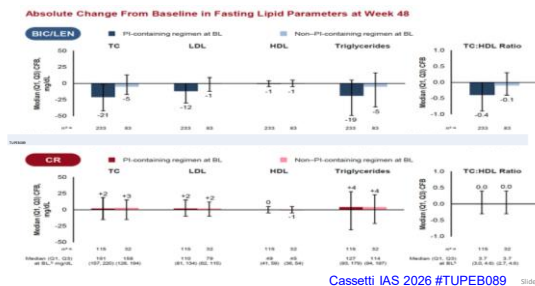
Orkin Lancet HIV 2026;407:1249-1258; Orkin IAS 2026 #TUPEB099



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ARTISTRY 1: Metabolic



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ISLEND-1: ISLATRAVIR (ISL)/BIC Weekly Switch

- **Phase 3**, double-blind, randomized, non-inferiority study
- Pt population: On BIC/FTC/TAF with VL<50 for ≥6 mo; no history of VF; no HBV infection (N = 607)
- Study rx: Randomized **ISL/LEN** (2/300 mg) weekly or continue **TAF/FTC/BIC**
- Results: VL at week 48
 - >50 copies/ml: 0% **ISL/LEN** vs. 0.3% **TAF/FTC/BIC** (Δ -0.3%, 95% CI -1.4%, +0.8%)
 - <50 copies/ml: 93% **ISL/LEN** vs. 92% **TAF/FTC/BIC**
- No emergent resistance; similar CD4 cell counts
- Conclusion: **ISL/LEN** weekly non-inferior to TAF/FTC/BIC daily
[Rockstroh IAS 2026 #OAB1406LB](#) + [Rockstroh NEJM 7/29/26](#) (online)

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ISLEND-2: ISLATRAVIR (ISL)/BIC Weekly Switch

- **Phase 3**, open-label, randomized, non-inferiority study
- Pt population: On standard daily ART with VL<50 for ≥6 mo; no history of VF; no HBV infection (N = 626)
- Study rx: Randomized **ISL/LEN** (2/300 mg) weekly or continue **oral ART**
- Results: VL at week 48
 - >50 copies/ml: 0.3% **ISL/LEN** vs. 1.3% **oral ART** (Δ -1%, 95% CI -3%, +1.1%)
 - <50 copies/ml: 95% **ISL/LEN** vs. 96% **oral ART**
- No emergent resistance; CD4 -45 **ISL/LEN** vs. -8 **oral ART**
- Conclusions: **ISL/LEN** weekly non-inferior to **oral ART** daily
[Colson IAS 2026 #OAX1106LB](#) + [Colson Lancet 2026;408:821-832](#)

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Investigational Agents – NRTTIs

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Alimatravir (AMI, MK-8527): NRTTI

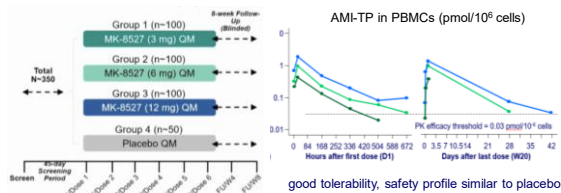
- **Phase 1** in PWoH: Long half-life ($t_{1/2}$ 200-300 hrs) supports weekly-monthly oral dosing [Gillespie Clin Transl Sci 2025;18:e70331](#)
- Two **Phase 1** oral single-dose studies [Carstens CROI 2024 #115](#)
 - Study population: PWH, ages 18-60 with no prior ART (N=31)
 - Study treatment: Single doses of AMI: 0.5, 1, 3, or 10 mg
 - Results: VL (log c/ml at day 7): -1.39 (0.5 mg), -1.21 (1 mg), -1.66 (3 mg), -1.39 (10 mg)
 - Conclusion: Single doses as low as 0.5 mg achieved >1 log copies/ml decreases at day 7
- Weekly oral PrEP with AMI protects rhesus macaques from rectal SHIV challenge [Diamond J Infect Dis 2026;233:e923-e931](#).

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Phase 2 MK-8527-007 Study: AMI Monthly Oral PrEP

- Study population: 18-65 yo without HIV, low risk
- Study rx: randomized 2:2:2:1



Mayer IAS 2025 #OAS0106LB

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Alimatravir (MK-8527)

- **AMI Monthly PrEP Dose Selection:** [Kapoor CROI 2026 #126](#)
 - Metabolism: Glucuronidated, renally eliminated
 - Fast-acting: achieved target doses 1 hour after dosing
 - Optimal dose: 11 mg
- AMI selects M184I/V *in vitro* [Diamond IAS 2026 #LB27](#)
- AMI could be mass-produced for \$15/year! [Cross IAS 2026 #OAE0504](#)
- Manufacturer commits to voluntary licensing agreement in >129 low- and middle-income countries following AMI approval [Press Release 7/24/26](#)
- **Phase 3 PrEP studies**
 - Blinded, placebo-controlled trials of oral AMI 11mg qmonth vs. TDF/FTC qd
 - **EXPRESSIVE-10** (N=4580 girls/women in SSA) [NCT07071623](#)
 - **EXPRESSIVE-11** (N=4390 at risk in 16 countries) [NCT07044297](#)

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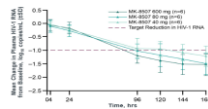
Investigational Agents – NNRTIs

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Ulonivirine (ULO, MK-8507): Investigational NNRTI

- Potent in vitro (IC50 ~50nM); DOR analog with similar resistance [Diamond CROI 2021 #129](#)
- active in vitro against common NNRTI-resistant variants
- $T_{1/2}$ ~ 70 hours -- supports once-weekly oral dosing [Ankrom AAC 2021;65:e0093521](#)
- ↓ CNS side effects
- **Phase 1 study** (N=18)
 - PWH rx-naïve
 - Single doses tested: 40, 80, 600 mg



[Schurmann JAIDS 2022;89:191-198](#)

- **Phase 2a switch study:** ULO (100, 200, 400 mg) + ISL 20 mg qweek vs. BIC/TAF/FTC (N=140)
 - ↓ in total lymphocyte and CD4 observed in all ISL 20 mg + ULO arms by 8-12 weeks

[Molina IAS 2025 #OAB0102](#)

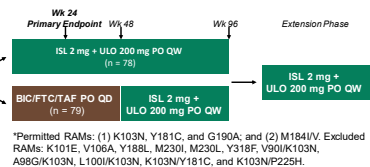
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Oral Weekly ISL + ULO: Phase 2B Switch Study

- Multicenter, randomized, open-label phase IIb study of ISL + ulonivirine (ULO)

Adults with VL <50 copies/mL X ≥6 mo on BIC/FTC/TAF, no prior VF, no ULO resistance*, CD4+ cell count ≥200; no HBV or HCV coinfection (N = 157)

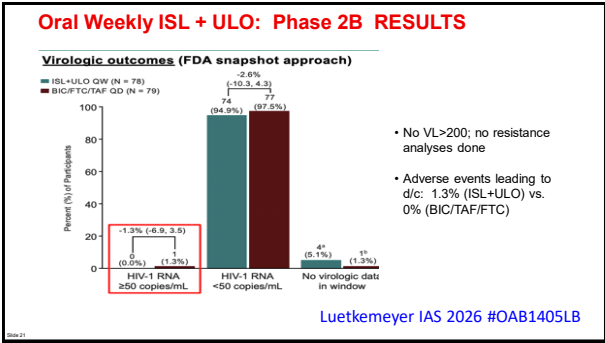


- **Primary endpoints:** HIV-1 RNA ≥50 copies/mL at Wk 24, safety/tolerability

[Luetkemeyer IAS 2026 #OAB1405LB](#)

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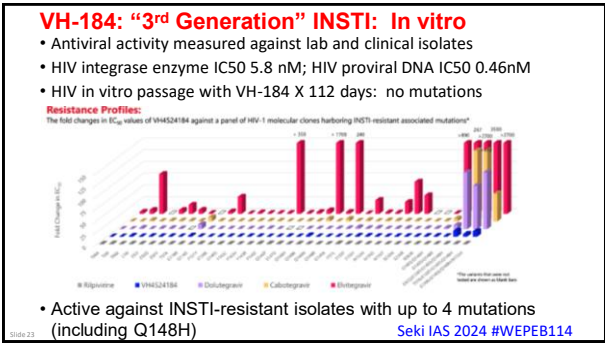
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Investigational Agents – INSTIs

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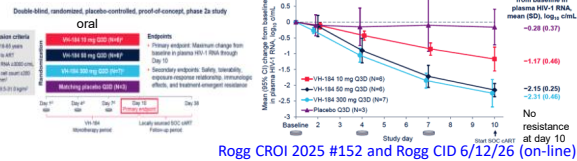


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VH-184: “3rd Generation” INSTI: Clinical

- **Phase 1:** People without HIV; t ½ 24 hours; dose-proportional ↑ concentrations up to 300mg; minimal impact on midazolam (CYP3A4 substrate); generally safe/well-tolerated; +moderate food effect [Rogg CID 2025;81:510-520](#)

- **Phase 2a:**

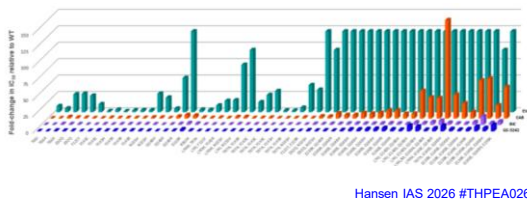


- **Further studies:**
 - **Phase 1:** oral + q6 month injectables [Back CROI 2026 #176](#)
 - **Phase 2b in rx-naïve (INNOVATE):** Oral VH-184/TAF/ETC vs. DTG/3TC

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GS-3242: INSTI: In vitro

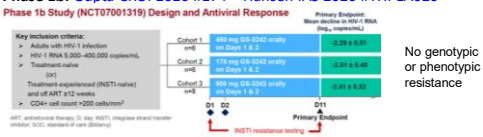
- Potent investigational INSTI; EC₅₀=0.8 nM
- Antiviral activity against 55 INSTI-resistant HIV isolates
 - Similar to BIC



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GS-3242: INSTI: Clinical

- **Phase 1b:** Gupta CROI 2026 #174 + Hansen IAS 2026 #THPEA026



- **Phase 1a and 1b:** q4 month injections [Gupta CROI 2026 #174](#)

- Phase 2 studies: recruiting

- **Pulsar 1: Australia, Canada, U.S. (including PR)** [NCT07645287](#)
 - Study population: On TAF/FTC/BIC with VL <50 X >6 months
 - Study rx: GS-3242 + LEN injections vs. continued oral TAF/FTC/BIC
- **Pulsar 2: Canada, U.S. (including PR)** [NCT07708727](#)
 - Study population: treatment-naïve (except oral PrEP)
 - Study rx: GS-3242 + LEN injections vs. oral TAF/FTC/BIC

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Investigational Agents – Capsid Inhibitors

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VH-499: Capsid Inhibitor

- **Preclinical:** binds to the mature capsid hexamer, binding contact similar to LEN, Potent in vitro: HIV EC50 23 pM, selects resistance mutations
[Wang AAC 2025;69:e0030925](#)
- **Phase 1a:** People without HIV: VH-499 exceeded target levels, half-life >2 days, and generally well tolerated
[Thakkar Infect Dis Ther 2025;14:1011](#)
- **Phase 1b:**

Study Design

An ongoing double-blind, randomized, placebo-controlled, adaptive, phase 1 study (NCT08724840)

Part A: Single ascending doses of SC or IM VH-499 or placebo (subcutaneous)



Conclusion: Modeling supports q6m IM dosing

[Thakkar CROI 2026 #175](#)

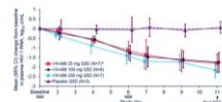
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VH-499: Capsid Inhibitor

- **Phase 2a:** in PWH

Double-blind, randomized, placebo-controlled, adaptive, proof-of-concept, phase 2a study



[Griesel CID 2026 \(online 7/29/26\)](#)

- Additional studies in progress
- **Phase 2b CINERGY** trial in treatment-naïve adults:
VH-499 + CAB IM q6 mos vs. oral DTG/3TC

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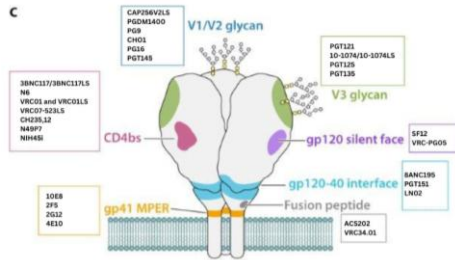
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Investigational Agents – bNAbs

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HIV Broadly Neutralizing Antibodies (bNAbs)



Mahomed Clin Micro Rvw 2024;37:e0015222

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HIV Broadly Neutralizing Antibodies (bNAbs)

- >20 bNAbs evaluated for safety and PK in >6000 humans
- Clinical trials generally demonstrate safety and antiretroviral activity
- “Vaccinal effect”: enhancing host immunity
- Strategies to improve potency, breadth, serum half-life and delivery
 - More potent, broader and multi-specific antibodies
 - Longer half-lives → dosing every 2-6 months
 - Subcutaneous dosing [Awan Curr Opin HIV AIDS 2022;17:247-257](#)
- Combination strategies: **Phase 1 and 2** studies
 - 2, 3, and 4 BnAb combinations
 - **bNAbs + long-acting ARV** (CAB or LEN)

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Lenacapavir + 2 BNAb (TAB and ZAB)

- **teropavimab (TAB, 3BNC117-LS, GS-5423):** long-acting CD4-binding site bNAb
- **zinlirvimab (ZAB, 10-1074-LS, GS-2872):** long-acting V3 glycan site-binding bNAb

• Pilot phase 1b:

- 20 PWVH sensitive to TAB and ZAB with VS
- Study Rx: LEN (oral/SC) + bNAb infusions (once!)
- Results: 18 (90%) had VL <50 cps at 26 weeks

[Eron Lancet HIV 2024;11:e146-e155](#)

• Pilot phase 1b:

- 11 PWVH sensitive to TAB or ZAB (not both) with VS
- Study Rx: LEN (oral/SC) + bNAb infusions
- Results: 8/10 VS; 2 had virologic failure at 26 weeks

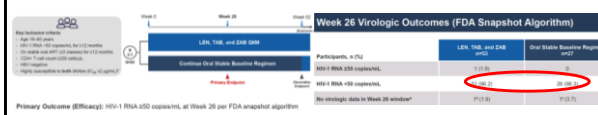
[Eron JID 2025;231:1440-1444](#)

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LEN + 2 bNAb (TAB and ZAB)

• Phase 2:



Conclusions:
In PWVH highly-susceptible to both bNAb, switching to LEN, TAB, and ZAB every 6 months was consistent with oral SOC ART.

[Ogbuagu Lancet Microbe 2026;7:101283](#)

- Update at Week 52 (n=53): 89% <50 copies/ml
- Update at Week 104 (n=41): 98% <50 copies/ml

[Ogbuagu EACS 2025 #PS09.2](#)
[McMahon IAS 2026 #OAB1403](#)

Phase 3 planned: **DAYBREAK 1** [NCT07682961](#) and **2** [NCT07683000](#)

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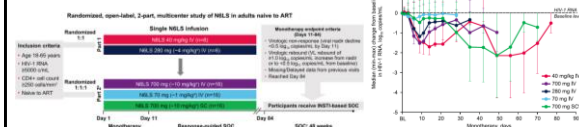
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Lotivibart + CAB: BANNER -- Phase 2a Study

- Lotivibart (LVB, N6LS, VH-109): LA CD4-binding site bNAb
- **Phase 1** study in people without HIV showed LVB well-tolerated IV and SC

[Wu Lancet HIV 2025;12:e485-e495](#)

• Phase 2



Conclusion:
LVB was generally safe and efficacious; supports further development of IV or SC dosing

[Leone JID 2025;232:e1022-1032](#)

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LVB + CAB: EMBRACE Phase 2b Study

- Phase 2b: EMBRACE Part 1

Study Design

Randomized, open-label, multicenter, phase 2b study conducted at 43 sites in the United States and 1

Key inclusion/exclusion criteria

- Age 18-59 years
- At least 10 weeks of suppressive ART
- At least 12 months before screening
- No prior ART within 12 weeks of screening
- CD4 cell count >350 cells/mm³
- On stable ART for at least 12 weeks
- No active HIV co-infection
- Pharmacologic sensitivity to HIV-1
- At least 12 weeks of suppressive ART

(N=125)

Primary endpoint

Plasma HIV-1 RNA viral load at Week 48

Conclusion:

High VS rates; IV better tolerated than SC

EMBRACE Part 2: LVB IV q4m + CAB q2m -- fully enrolled
LVB subcutaneous discontinued, changed to IV

Efficacy at Month 12 (FDA Snapshot, full analysis set)

Group	n	VS (%)	VS (95% CI)
LVB IV + CAB (n=40)	40	85	78-92
LVB SC + CAB (n=40)	40	75	68-82
CAB SOC ART (n=45)	45	70	63-77

Participants in EMBRACE

Group	n	VS (%)	VS (95% CI)
LVB IV + CAB (n=40)	40	85	78-92
LVB SC + CAB (n=40)	40	75	68-82
CAB SOC ART (n=45)	45	70	63-77

Role CROI 2026 #178

Gutner IAS 2026 #WEPEB097 Slide 38

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Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH
- For slides:
 - Alexandra Calmy, Brenda Crabtree, Judy Currier, Charlie Flexner, Raj Gandhi, Raphy Landovitz, James McMahon, Chloe Orkin, Paul Sax, Melanie Thompson; HIV iBASE, NATAP, TAG
- The patient volunteers!

Logos: CCTU, ACTG, HPTN

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Q and A Session

IAS-USA
International AIDS Society - USA

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