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State of the ART Symposium

Antiretroviral Therapy (ART): What's Next

Acknowledgements: Jose Arribas; Melanie Thompson; Trip Gulick; Cindy Donovan, Babafemi Taiwo, Rafael Campo, Martin Rhee; Wanqing Xu; Malini Gandhi; Malachi Keo

ART: What's Next

But we're going to try!

Why we need new ART

Why we need new ART

New Drugs

New Drugs

How we will use new drugs

How we will use new drugs

Why we need new ART

- >30 drugs for treating people with HIV: high rates of viral suppression, low rates of toxicity

- Current regimens have limitations:
  - Weight gain, drug interactions
  - Daily oral dosing: challenge for some of the most vulnerable people
  - Concerns about drug resistant HIV
  - High costs in many countries around the world

Why we need new ART: Examples

People Doing Well on ART	25 yo F. Virologically suppressed on ART. Wants to take fewer medicines: worried about side effects **Need: Simplified regimens with fewer drugs**
People Struggling with Daily Oral ART	45 yo M. Depression. Intermittent adherence with daily oral therapy. **Need: Long-acting regimens (oral or injectable)**
People with Multi-drug Resistant HIV	55 yo M with HIV since 1990s. Has been on multiple regimens. Now has virus resistant to all classes. **Need: New drugs with activity against resistant virus**

Desiderata: “Things Wanted or Needed”

Need	People doing Well on ART	People Struggling with Daily Oral ART	People with Multi-drug Resistant HIV
Fewer drugs	✓✓	✓	--
Less toxicity	✓✓	✓	✓
Reduced Dosing Frequency	✓	✓✓✓	--
High Barrier to Resistance	✓	✓	--
Active against drug resistant HIV	--	--	✓✓✓
Less Visibility/Reduced Stigma	--	✓✓✓	✓
Safety During Pregnancy	✓	✓	✓

New Drugs and Formulations in Development

Entry inhibitors:

Ibalizumab -- approved

Fostemsavir – approved

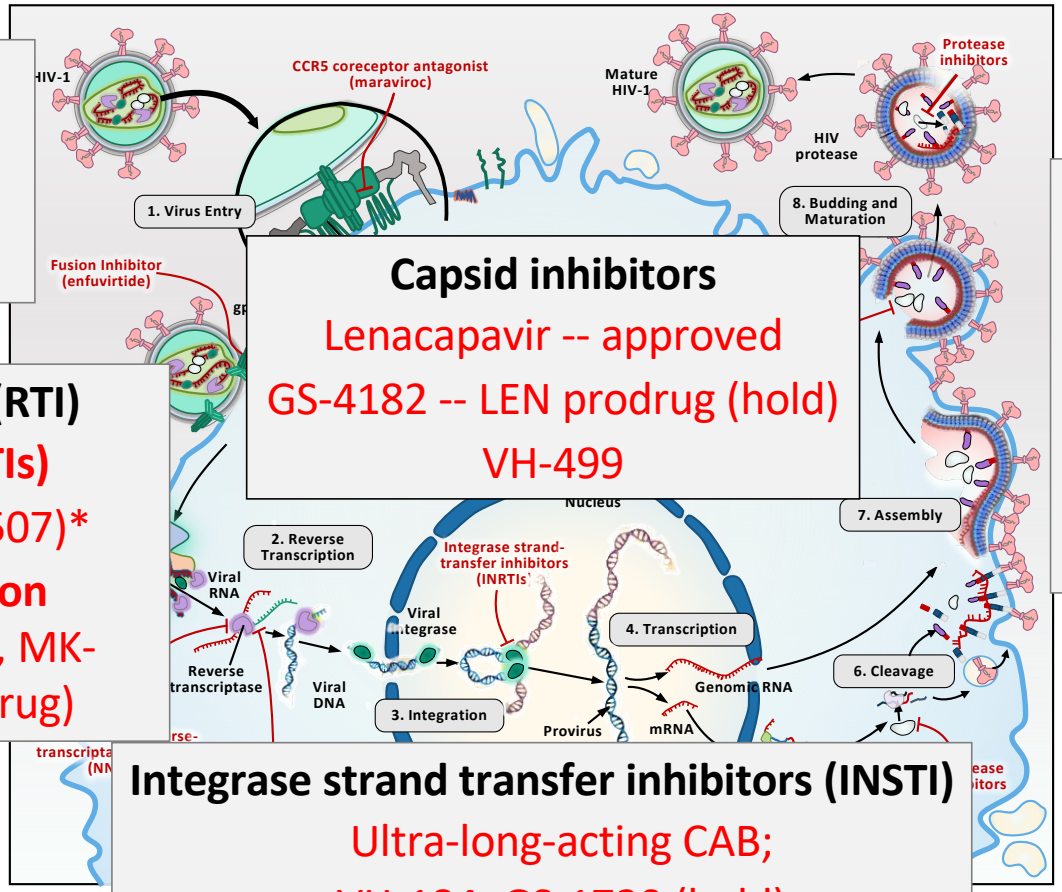
Broadly neutralizing Abs*

Reverse Transcriptase Inh. (RTI)

Nonnucleoside RTI (NNRTIs)

Ulonivirine (ULO; MK-8507)*

Nucleoside RT translocation inhibitors: Islatravir (ISL)*, MK-8527*, GS-1614 (ISL pro-drug)



Capsid inhibitors

Lenacapavir -- approved

GS-4182 -- LEN prodrug (hold)

VH-499

Integrase strand transfer inhibitors (INSTI)

Ultra-long-acting CAB;

VH-184; GS-1720 (hold)

Maturation inhibitor*

GSK3640254 – discontinued

VH3739937

HRF-10071 - phase 2 results*

Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

* Presentation at:

IAS 2025

Need #1: Simplified Daily Regimen with Fewer Drugs

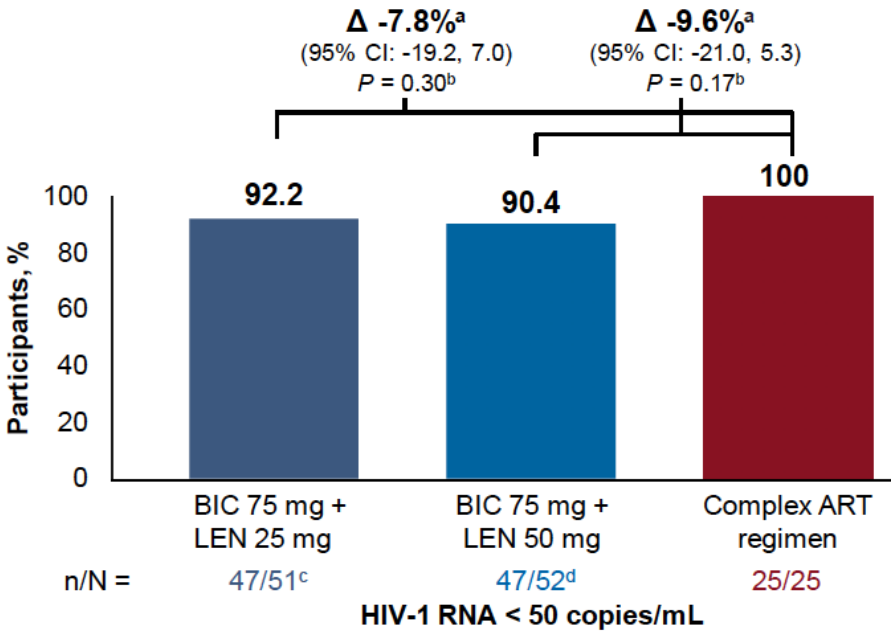
Doravirine (DOR)/Islatravir (ISL)

- ISL: nucleoside reverse transcription translocation inhibitor (NRTTI)
  - Dose (0.25 mg daily) not anticipated to cause lymphopenia
- Doravirine (DOR): NNRTI
- Phase 3 trials: PWH with HIV RNA <50: DOR/ISL vs. continuing BIC/FTC/TAF (n=513; double blind); DOR/ISL vs. continuing oral ART (n=551; open label)
- Switching to DOR/ISL non-inferior to continuing previous regimen
- CD4 and lymphocyte counts stable in ISL/DOR group
- Submitted to US FDA for switch indication: July 10, 2026; PDUFA: April 28, 2026
- ISL/DOR vs. BIC/FTC/TAF for initial therapy trial fully enrolled; results expected, 2026

Colson A et al, CROI 2025, Abs 204A. Orkin C et al, CROI 2025 Abst 204B. https://clinicaltrials.gov/study/NCT05705349; https://www.merck.com/news/u-s-fda-accepts-new-drug-application-for-mercks-doravirine-islatravir-an-investigational-once-daily-oral-two-drug-regimen-for-treatment-of-adults-with-virologically-suppressed-hiv-1-infe/

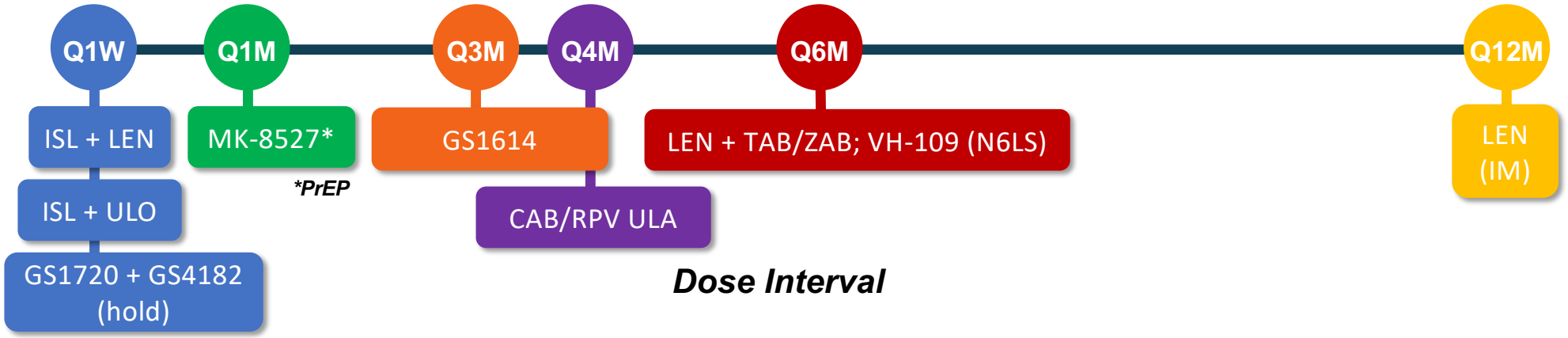
Simplified Daily Regimen with Fewer Drugs:
BIC + LEN in People on Complex ART Regimens

- Randomized study (ARTISTRY-1): switching complex ART regimens to oral Bictegravir + Lenacapavir (capsid inhibitor) in virologically suppressed PWH (n=128)
- BIC+LEN: Sustained HIV suppression (>90%)
- BIC 75 mg/LEN 50 mg single pill combination: phase 3 study ongoing (enrollment complete)



Mounzer K, et al. AIDS 2024. Abstract OAB2602.

Additional Needs: Long-Acting; Activity against Drug Resistant HIV



- **Weekly oral dosing**
  - **ISL + LEN**
  - **ISL + ULO**
  - **GS1720 + GS4182 (on hold)**

Dose Interval

- **Longer acting (LA) options**
  - **Monthly: MK-8527 for PrEP**
  - **Every 3 months: GS1614**
  - **Every 4 months: CAB/RPV ULA**
  - **Every 6 months: LEN + TAB/ZAB; VH-109 (N6LS)**
  - **Every 12 months: LEN**
  - VH-499, VH-184
  - Implants

Acknowledgment: Malachi Keo

Weekly Oral Dosing

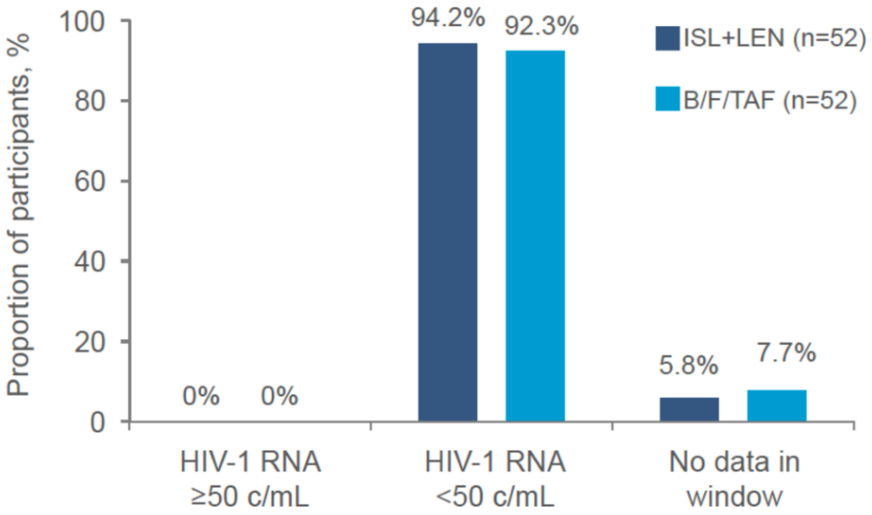
Switching to Oral Weekly Islatravir (ISL) + Lenacapavir (LEN) in Virologically Suppressed PWH

- PK of ISL and LEN support once weekly dosing
- Phase 2: switching virologically suppressed PWH to BIC/FTC/TAF daily or oral ISL 2 mg + oral LEN 300 mg weekly
- >90%: continued HIV suppression
- No differences in lymphocyte, CD4 counts

Phase 3: ISLEND-1 and -2
ISL/LEN (2 mg/300 mg): one tablet per week (enrollment complete; results likely in 2026)

https://clinicaltrials.gov/study/NCT06630286

Week 48 HIV RNA results



Colson A, et al. ID Week 2024. Abstract 577.

Weekly Oral Dosing

MK-8507 (Ulonivirine, ULO) + Islatravir

- ULO: Oral non-nucleoside reverse transcriptase inhibitor (NNRTI)
- T1/2 ~ 70 hours; once weekly dosing. Resistance profile similar to doravirine
- Phase 2b study: switching to ISL 20 mg + ULO weekly maintained HIV suppression
  - Decreases in lymphocyte and CD4 counts

IAS 2025

ART strategies

Oral abstract session

A double-blind, active-controlled, phase 2b study to evaluate the efficacy and safety of ulonivirine in combination with islatravir in virologically suppressed adults living with HIV-1

Jean-Michel MOLINA
University of Paris Cité, France

Phase 2B: ISL 2 mg + ULO 200 mg weekly: switch study ongoing (NCT06891066)

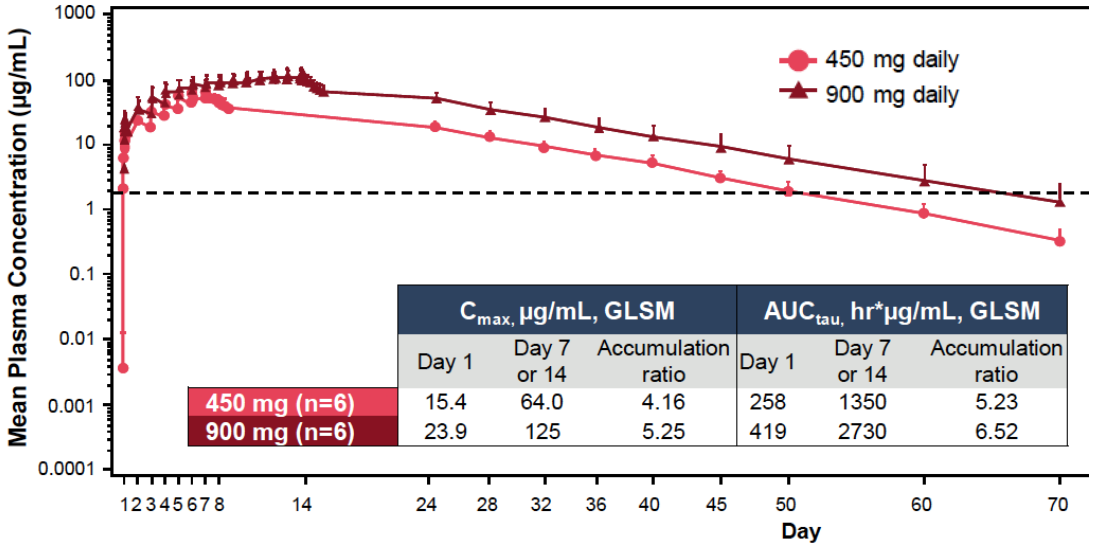
Diamond T, et. al. CROI 2021; Ankrom W, et. al. HIV Glasgow 2020; Ankrom W, et. al. AAC 2021. doi:10.1128/ACC.00935-21; Ankrom W, et. al. IAS 2021; Molina JM et. al., IAS 2025 Kigali OAB0102

Weekly Oral Dosing

GS-1720 (Integrase Inhibitor) plus GS-4182 (LEN pro-drug)

- Phase 2 studies: oral weekly GS-1720 plus GS-4182 (WONDERS-1 and -2)

June 10, 2025: U.S. FDA placed clinical hold on trials of GS-1720 and/or GS-4182. Decreases in CD4 and lymphocyte counts in a subset of participants receiving combination.



	C_{max}, µg/mL, GLSM			AUC_{tau}, hr*µg/mL, GLSM		
	Day 1	Day 7 or 14	Accumulation ratio	Day 1	Day 7 or 14	Accumulation ratio
450 mg (n=6)	15.4	64.0	4.16	258	1350	5.23
900 mg (n=6)	23.9	125	5.25	419	2730	6.52

Fichtenbaum CJ et al, CROI 2024, abstract 116;
Shaik N et al, AIDS 2024 (Munich), abstract WEPEB117;
Zhang H, ID Week 2024, abstract 154.

Long-Acting Investigational Agents

- **MK-8527 (Nucleoside reverse transcriptase translocation inhibitor, NRTTI)**
  - Being studied for monthly oral pre-exposure prophylaxis (PrEP)
  - Phase 2 data (n=350): similar safety profile as placebo
  - Phase 3 clinical trials (EXPrESSIVE) starting soon
- **Cabotegravir (CAB) Ultra-long acting (ULA) (Integrase inhibitor). Phase 2**
  - Every 4-month intramuscular (IM) dosing
  - Being evaluated for PrEP (EXTEND 4 M; results expected in 3rd quarter 2026)
  - CAB ULA + RPV every 4 months for treatment trial planned
- **Islatravir Prodrug, GS 1614 (in combination with lenacapavir)**
  - GS 1614: Every 3 months dosing

IAS 2025

Mayer K et al, IAS 2025 (Kigali), OAS0106LB
https://www.merck.com/news/merck-to-initiate-phase-3-trials-for-investigational-once-monthly-hiv-prevention-pill/
Han, et al. CROI 2024, Oral presentation 120
NCT06741397; NCT05418868; NCT06786520

Long-Acting Investigational Agents

- **VH-499: Capsid inhibitor**
  - Treatment naïve PWH (oral dosing): mean maximum 2.2 log reduction in HIV RNA
  - 1 out of 20 participants developed emergent capsid inhibitor mutation (Q67Q/H)
  - Long-acting injectable formulations: phase 1 studies
  - Also being developed for treatment

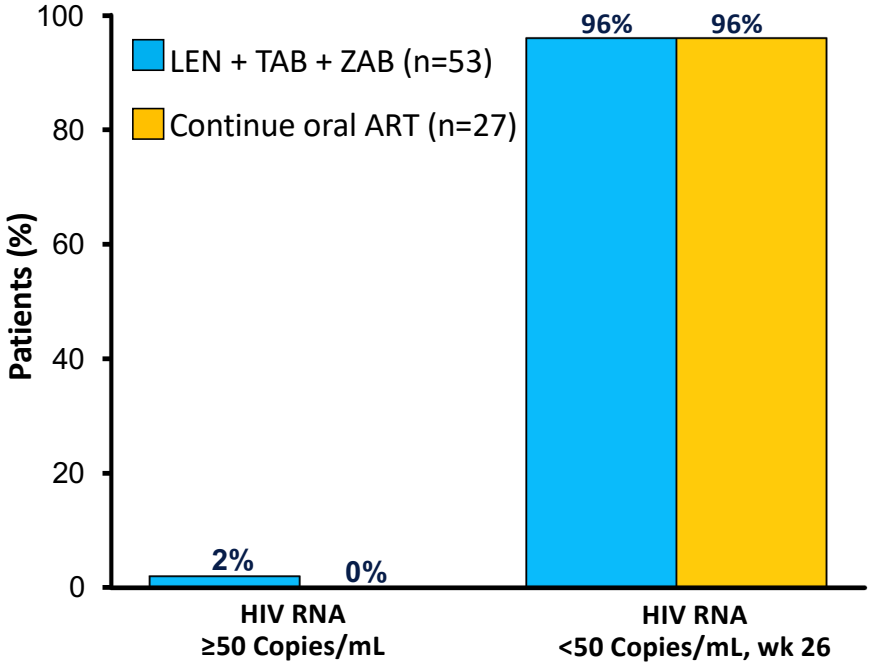
- **VH-184: Third generation integrase inhibitor**
  - Active in vitro against HIV resistant to dolutegravir
  - Treatment naïve PWH (oral dosing): HIV RNA declines >2 log
  - Long-acting injectable formulations being evaluated in adults without HIV (phase 1)
  - Also being developed for treatment

Griesel R et al, CROI 2025, Abstract 153. Rogg L et al, CROI 2025, Abstract 152. NCT06310551

Every 6-month Dosing

- **Broadly neutralizing antibodies (bNAb):**
  - **Lenacapavir (capsid inhibitor) + 2 bNAbs, Teropavimab (TAB), Zinlirvimab (ZAB):** Phase 2
    - 1 participant: virologic failure, LEN resistance, loss of ZAB susceptibility; Low LEN levels
    - Phase 3 trial planning in progress
  - **N6LS** every 6 months plus CAB LA every 2 months (EMBRACE part 2; enrolling)

PWH with virologic suppression who switched to LEN, TAB and ZAB or continued daily oral therapy



Ogbuagu O et al, CROI 2025, Abstract 151.

Every 12-month Dosing

Lenacapavir in People without HIV

- Formulations with 5 or 10% ethanol.
- Intramuscular (IM) injection
- Dose, volume higher than every 6-month approved dose (5000 mg vs. 927 mg) → achieved high trough levels
- Phase 3 single arm trial with 3000 mg LEN IM (PURPOSE-365). n=300. (not yet recruiting)

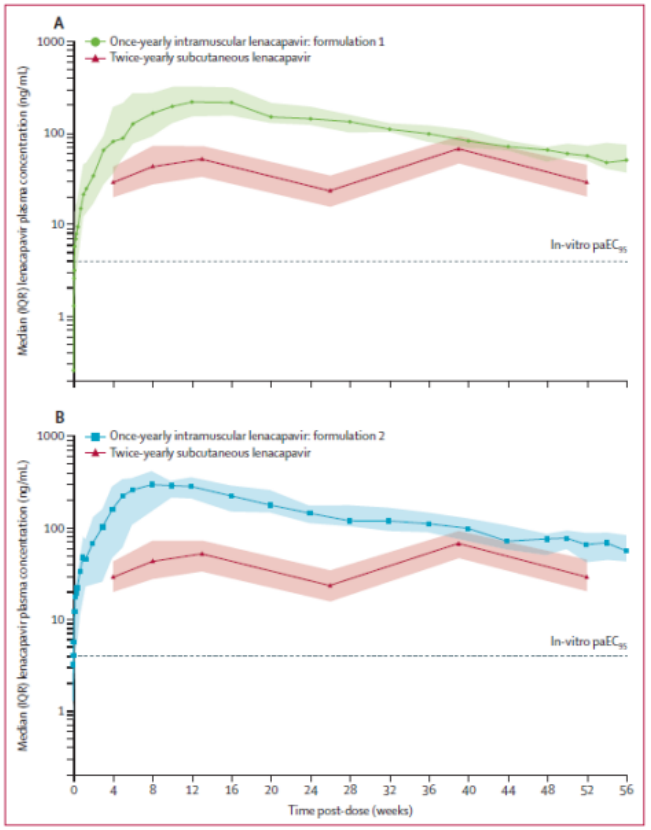


Figure 1: **Median (IQR) plasma concentration-time profiles of once-yearly intramuscular lenacapavir versus twice-yearly subcutaneous lenacapavir for formulation 1 (A) and formulation 2 (B)**

Jogiraju V et al, Lancet 2025;
https://clinicaltrials.gov/study/NCT07047716?aggFilters=phase:4%203,studyType:int

How we will use new drugs (if and when approved)

People doing Well on ART	25 yo F wants to take fewer medicines → New daily and weekly regimens with fewer drugs, offer greater flexibility
People Struggling with Daily Oral ART	45 yo M intermittent viral suppression → long-acting formulations may improve adherence; need supportive systems to facilitate delivery and ensure follow-up
People with Multi-drug Resistant HIV	55 yo M with virus resistant to all available classes → novel drugs in new classes promise hope

Cost and Access

- Novel agents may not be cost-effective if price is high
- **New drugs need to be priced to ensure access to people in countries around the world**
  - By 2030, up to 4.6 million people may need 2nd line therapy in Africa, and some will need novel drugs for drug resistant HIV

Millham et al, JAIDS, 2020; Jonsen, J Law, Medicine and Ethics, 1986; McKie and Richardson, Social Science and Medicine, 2003; Orr and Wolf, Theory Dec, 2015; Estill J, Lancet HIV, 2016

ART: What's Next

But we're going to try!

Why we need new ART: need to overcome limitations of current therapies with fewer drugs, less frequent dosing, activity against resistant HIV

New drugs in development: target novel mechanisms; pipeline of long-acting agents; however, need to develop innovative access and delivery systems

How we will use new drugs: depends on person and their needs. For all people with HIV, must redouble efforts to provide more options, reduce costs, and ensure equitable access around the world