

Beyond the Horizon:
HIV Treatments in the Making



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

Dr Currier reported serving as a consultant for Merck & Co,
Inc. (Updated October 25, 2025)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe why we still need new drugs for the treatment of HIV
- List investigational drugs currently in development and the gaps these drugs might fill

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1981: First AIDS cases are reported in the United States.

Drug Class Abbreviations:

A1, Attachment Inhibitor; CAI, CCR5 Antagonist; CR, Capsid Inhibitor; FDC, Fixed-Dose Combination; FI, Fusion Inhibitor;
HIV-1, HIV-1 Integrase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI, Nucleoside Reverse Transcriptase
Inhibitor; PI, Protease Inhibitor; PPI, Proton Pump Inhibitor; PRN, As Needed; R, Regimen; TDF, Tenofovir Disoproxil Fumarate;
TDF/FZ, Tenofovir Disoproxil Fumarate/Zalcitabine; ZDV, Zalcitabine

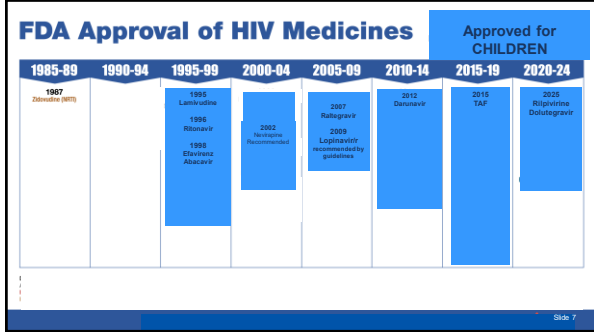
Note: Approvals are for HIV treatment, unless otherwise indicated.
*Drugs in gray are no longer available and/or are no longer recommended for use
in the United States by the HHS/HIV/AIDS medical practice guidelines. These
drugs may still be used in fixed-dose combination formulations.



[https://en.wikipedia.org/wiki/File:Peter_Paul_Rubens_-_Abundance_\(Abundantia\)_-_Google_Art_Project.jpg](https://en.wikipedia.org/wiki/File:Peter_Paul_Rubens_-_Abundance_(Abundantia)_-_Google_Art_Project.jpg)

Approved for
PREGNANCY

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Why we need new ART

- Current regimens have limitations:
 - Weight gain after starting ART
 - Drug Interactions
 - Daily oral dosing: challenge for some of the most vulnerable people
 - Drug resistant HIV
 - High costs in many countries around the world

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Gaps to Fill: "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	✓	✓	✓
Cost/Accessibility	✓✓✓	✓✓✓	✓✓✓

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New Drugs and Formulations in Development

Entry inhibitors:
Ibalizumab -- approved
Fostemsavir -- approved
Broadly neutralizing Abs*

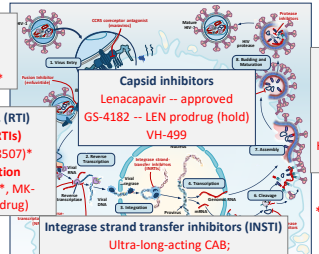
Reverse Transcriptase Inh. (RTI)
Nonnucleoside RTI (NNRTIs)
Ulofinvirine (ULO; MK-8507)*
Nucleoside RT translocation inhibitors: Islatravir (ISL)*, MK-8527*, GS-1614 (ISL pro-drug)

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*

* Presentation at:

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

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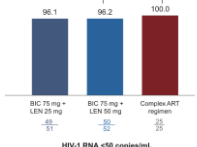
Simplified Daily Regimen with Fewer Drugs: BIC + LEN in People on Complex ART Regimens

- Randomized study (ARTISTRY-1): switching complex ART regimens to oral Bictegravir + Lenacapavir (capsid inhibitor) in virologically suppressed PWH, no resistance to BIC or prior LEN (n=128)
- 19% female, 30% Black, median age 60, 27 yrs on ART
- 27% of participants were currently on 5 or more pills per day
- BIC+LEN: Sustained HIV suppression (>95%)
- BIC 75 mg/LEN 50 mg single pill combination: phase 3 study ongoing (enrollment complete)

Virologic outcome week 24

Δ -3.9% (95% CI, -13.5 to 10.7) P>.38

Δ -3.8% (95% CI, -13.5 to 10.7) P>.38



HIV-1 RNA <50 copies/mL

Mounzer K, et al.CID, 80(4), 15 April 2025; 881-896. <https://doi.org/10.1093/cid/ciae522>

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Need #1: Simplified Daily Regimen with Fewer Drugs Doravirine (DOR)/Islatravir (ISL)

- 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, 2025; 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, Abstr 204A, Orlin C et al. CROI 2025 Abstr 204B. <https://clinicaltrials.gov/ct2/show/study/NCT02933448>

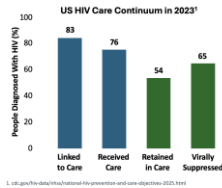
<https://www.merck.com/news/merck-submits-new-drug-application-for-merck-doravirine-islatravir-as-investigational-capsid-inhibitor-daily-pill-two-drug-regimen-for-treatment-of-adults-with-virologically-suppressed-hiv-1-intrv/>

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The IAS–USA Annual Update on HIV Management in Chicago, Illinois, November 18, 2025

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Will long-acting ART help us close the gap?



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RESEARCH Open Access

Patient preferences for long-acting HIV treatment: a preference heterogeneity assessment

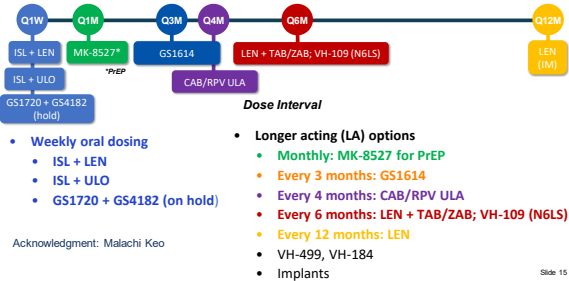
Emmanuel M. Sabaingwa^{1,2}, Brent Heister^{1,2}, Douglas Barthol^{1,2}, Aaron T. Bratt¹, Jacinda Tsui¹, Vincent C. Mancini^{1,2}, Joseph S. Ross^{1,2}, and Catherine M. Sabaingwa^{1,2}

- 699 PWH surveyed about preferences for LA-ART and current oral therapy
- Three groups emerged
 - 29% LA implant, 35% LA oral or injection, 36% LA oral or current Rx
- Groups differed by demographics and prior current state of suppression
- One size will not fit all.

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What is coming: Long-Acting; Activity against Drug Resistant HIV



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Weekly Oral Therapy: ISL + LEN

- **Phase 2** randomized, open-label, controlled study, 48-week results
- Study population: PWH on TAF/FTC/BIC with VL <50 at least 24 weeks without prior VF, CD4 $\geq 350/\text{mm}^3$, absolute lymphocyte count $\geq 900/\text{mm}^3$, no active/occult HBV (N=104)
- Study treatment:
 - ISL 2 mg + LEN 300 mg weekly oral dosing
 - TAF/FTC/BIC daily dosing
- Results (48 wks);
 - VL <50: 94.2 % (ISL + LEN wkly) vs. 92.3% (T/F/BIC)
 - CD4: -12 (ISL + LEN wkly) vs. -29 (T/F/BIC) (p=0.3)
 - ALC: -0.07 (ISL + LEN wkly) vs. -0.03 (T/F/BIC) (p=0.6)
- Conclusion: First oral **weekly** regimen efficacious/well-tolerated

Colson AE, et al. Open Forum Infect Dis. 2025 Jan 29;12(Suppl 1):ofae631.015. doi: 10.1093/ofid/ofae631.015. PMID: PMC11777299. ID week Late Breaker 2024 Slide 16

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

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Weekly Oral Dosing MK-8507 (Ulonivirine, ULO) + Islatravir

- ULO: Oral non-nucleoside reverse transcriptase inhibitor (NNRTI)
- T_{1/2} ~ 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 with the higher dose of islatravir – returned to baseline after 24 weeks



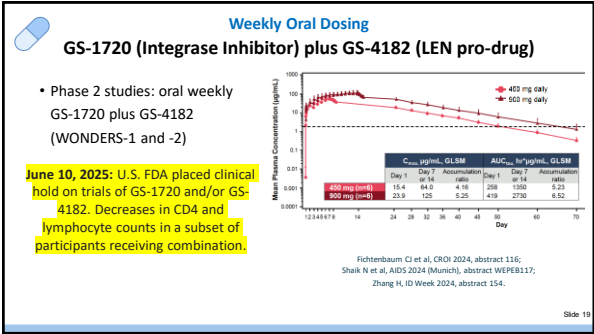
ART strategies
Oral abstract session

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 Poitiers, France

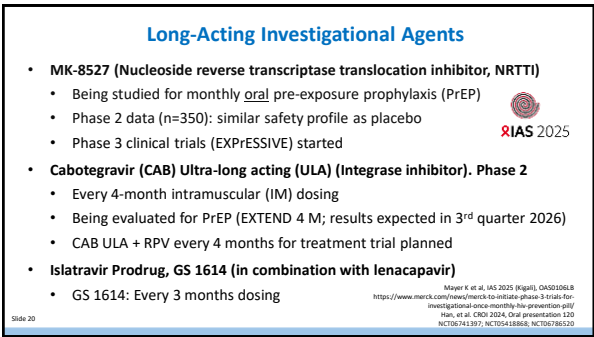
Phase 2B: ISL 2 mg + ULO 200 mg weekly: switch study ongoing (NCT06891066)

Diamond T, et al. CROI 2021; Antikrom W, et al. HIV Glasgow 2020; Antikrom W, et al. AAC 2021. doi:10.1128/AAC.00935-21; Antikrom W, et al. IAS 2021; Molina JM et al. IAS 2025 Kigali 0480202 Slide 18

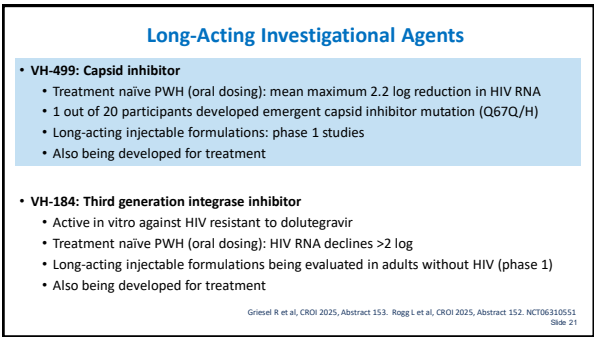
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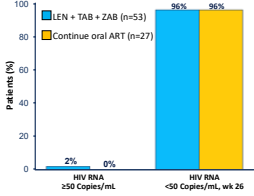
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Every 6-month Dosing

- Broadly neutralizing antibodies (bNAb):
 - Lenacapavir (capsid inhibitor) + 2 bNAb, Teropavimab (TAB), Zilnirvimab (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



Group	n	HIV RNA <50 Copies/mL, wk 26 (%)
LEN + TAB + ZAB	53	96%
Continue oral ART	27	0%

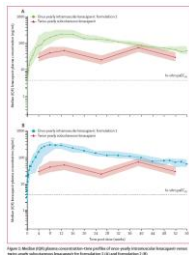
Ogbuagu O et al, CROI 2025, Abstract 151. Slide 22

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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)



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

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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 on complex regimens	67 yo M history of MDR HIV became suppressed on boosted PI, NNRT, TAF, reluctant to simplify regimen but has drug interactions
People with Multi-drug Resistant HIV	55 yo M with virus resistant to all available classes → novel drugs in new classes promise hope

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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
 - Over 50% of PWH are female and majority are of child bearing age- safety in pregnancy is essential



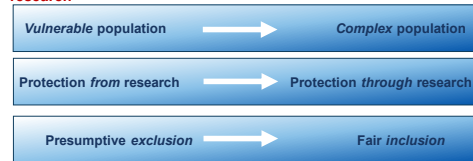
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Mihm et al. AIDS, 2020; Jonsen, J. Law, Medicine and Ethics, 1986; McKie and Richardson, Social Science and Medicine, 2003; Orr and Wolf, Theory Dec, 2016; East J. Lancet HIV, 2016

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Pregnancy: How do we improve upon the status quo?

The PHASES Working Group, call to action, 2020

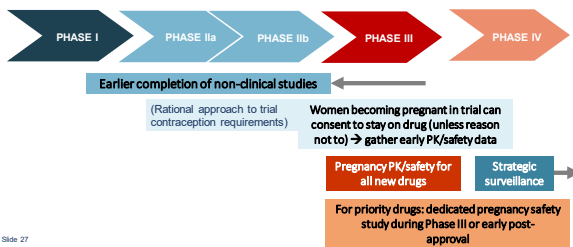
Conceptual shifts that will facilitate inclusion of pregnant women in research



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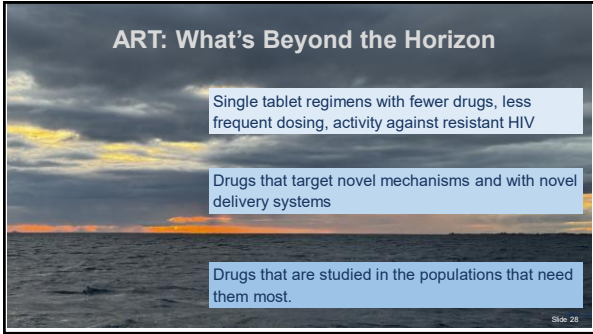
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A new framework for accelerating ethical inclusion of pregnant women in research

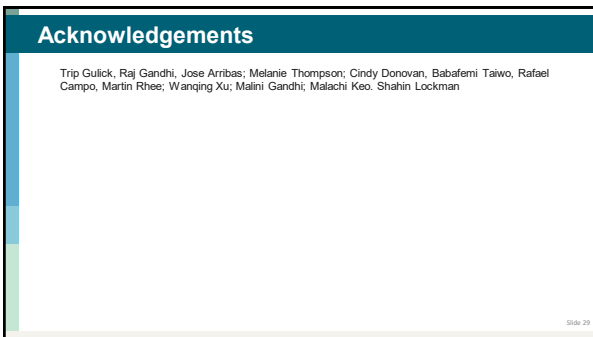


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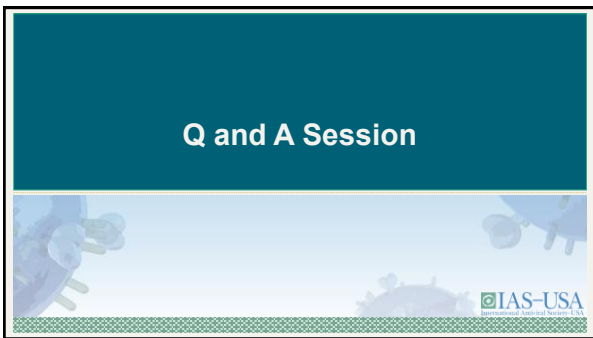
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