New Antiretrovirals and New Strategies

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

Dr Eron has served as an ad hoc consultant to Janssen, ViiV Healthcare, Merck & Co, Inc, and Gilead Sciences, Inc. His institution receives contracts for clinical research on which Dr Eron is the local principal investigator from Janssen Therapeutics, ViiV Healthcare, and Gilead Sciences, Inc. (Updated 03/22/21)

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Learning Objectives

Upon completion of this webinar, learners will be able to:

- Describe why new antiretrovirals are still needed for the treatment and prevention of HIV-1
- List at least 2 new long-acting antiretroviral treatment strategies that are in development

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Goals of Antiretroviral Therapy

- Maintain or restore the health of people living with HIV-1 (PWH) through suppression of HIV-1 replication
- Minimize or eliminate short and long-term adverse effects of the therapy
- Have therapies that are accessible to all PWH
- Prevent transmission of HIV-1 to others via any route of exposure

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Why Do We Need New Agents?

What we have now

- Oral therapy - Multiple single tablet daily regimens
  - Many without food restrictions, several with almost no DDI
  - Few frequent AE (weight gain?), rare serious AE (? DM, massive weight gain)
  - INSTI based and PI-based therapy almost resistance proof
  - Relatively simple therapy for PWH with resistant virus if suppressed on therapy w/o INSTI resistance
- Long-acting injectable therapy with CAB/RPV
  - Non-inferior to gold-standard oral therapy in PWH suppressed without previous virologic failure
  - Twice monthly IM Injection and no need for oral lead-in (SOLAR and others)
  - Clear interest for many PWH
  - Social behavioral, QoL and internal and external stigma benefits for many who choose LA
  - Potential to extend our reach to hardly engaged populations (USCF experience)

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Why Do We Need New Agents?

Liabilities of current therapy and what we need

- Oral therapy
  - An alternative to daily oral therapy (weekly or monthly?)
  - A convenient, safe, resistance-resistant oral therapy without an INSTI or booster?
  - Simpler and less complex therapy for PWH with MDR INSTI resistant HIV; whether rebounding or suppressed
- Long-acting therapy
  - No resistance risk with on-time administration
  - More convenient delivery allowing home or non-office administration
  - Broad inclusion – previous virologic failure, current viremia, adolescents, children, pregnant people
  - **Longer acting**
  - **Affordable and scalable**

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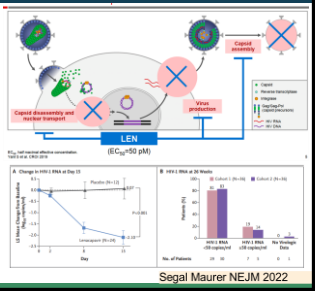
New Agents Recently Approved

- Lenacapavir
  - First in class capsid inhibitor
  - Oral loading followed by two SQ injections every 6 months
  - Approved for heavily treatment-experienced PWH whose HIV cannot be successfully treated with other available treatments due to resistance, intolerance, or safety considerations.
  - No current long-acting partner agents
  - Resistance emergence has been observed – especially if oral agents have limited activity or adherence challenges



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Segal Maurer NEJM 2022

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New Agents in New Classes

ISLATRAVIR

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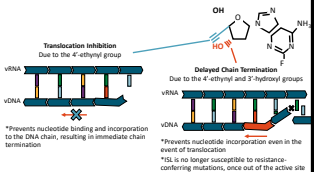
Islatravir (MK-8591, ISL): Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)

- First-in-class NRTTI
  - High potency; half-life up to 128 hours, once per year dosing feasible

- Nano-molar potency in vitro
- Selects for M184V in vitro and in animal models
- Maintain antiviral activity in macaques with M184V containing SIV
- Single dose in PWH > 1 $\log_{10}$ Response (0.5 to 30 mg)



Multiple mechanisms may contribute to high potency, use in drug-resistant virus, and high genetic barrier to resistance

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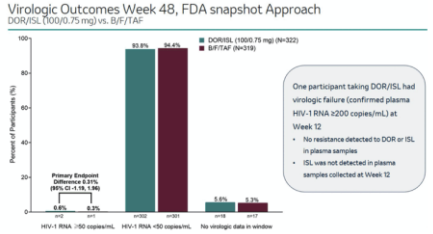
ISLATRAVIR – Switch B/F/TAF vs DOR/ISL 100/0.75 mg

Randomized blinded placebo-controlled trial in PWH suppressed on B/F/TAF



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ISLATRAVIR

- Clinical development paused 2º to reduced lymphocyte and CD4 counts in HIV treatment and prevention studies
  - Apoptosis likely due to the level of triphosphate in lymphocytes
  - Extensive evaluation to understand mechanism and thresholds; unrelated to mitochondrial toxicity

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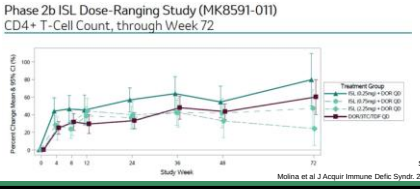
ISLATRAVIR

- Once monthly oral therapy for prevention – program discontinued
- Long-acting implant for prevention and treatment being re-assessed
- Once daily therapy with ISL/doravirine 0.25/100 mg going in treatment naïve and suppressed switch going forward
- Once weekly LEN/ISL 300/2 mg in suppressed switch going forward
- Program for highly treatment experienced PWH with resistant virus on hold



Squires et al CROI 2023

Molina et al J Acquir Immune Defic Syndr. 2022 Sep 1;91(1):68-72

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New Small Molecule Agents in Early Development

- Integrase Inhibitors
  - VH-184 – 3rd generation INSTI (Phase 1 https://clinicaltrials.gov/ct2/show/NCT05631704)
- Capsid Inhibitors
  - VH-280 – (Phase 1 FIHT https://clinicaltrials.gov/ct2/show/NCT05163522)
- Maturation Inhibitors
  - GSK3640254 – discontinued development
  - GSK3739937 – (Phase 1 FIHT https://clinicaltrials.gov/ct2/show/NCT04493684)

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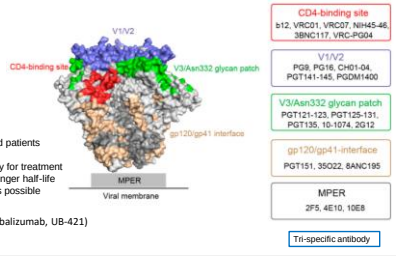
Broadly Neutralizing Monoclonal Antibodies against HIV



Phase 2 studies in HIV infected patients
Clear antiretroviral activity
Combinations will be necessary for treatment
Almost all being modified for longer half-life
Every 4- to 6-monthly infusions possible

Cellular targets (e.g. ibalizumab, UB-421)

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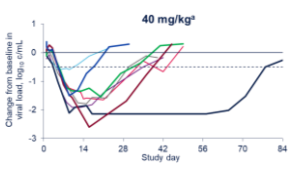
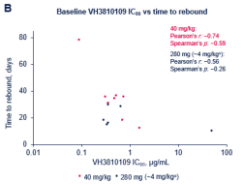
VH3810109 (N6LS); bNAb with broad and potent neutralization activity in vitro targeting the CD4 binding site of the HIV-1 envelope protein

Single infusion in PWH off therapy



Leone et al Glasgow 2022

Relationship btw susceptibility and time to rebound



Leone et al CROI 2023

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Next Steps

LONG-ACTING THERAPY

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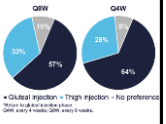
Long-Acting Therapy – Partners needed Cabotegravir

- IM injections in the thigh
  - ATLAS 2M optional thigh injection study in 121 participants
  - Both 1 monthly and 2 monthly
  - Similar PK profiles when transitioning for IM gluteal injections
- Cabotegravir plus VRC-07 523 LS
  - Suppressed switch study
  - CAB LA q 4 week, VRC-07 q 8 week
  - 75 enrolled – 48 week follow-up ends 2nd QTR 2023
  - https://clinicaltrials.gov/ct2/show/NCT03739996
- CAB plus N6-LS planned
  - N6 – slightly broader prolife and likely longer ½ life



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Long-Acting Therapy – Partners Needed

- Lenacapravir - Phase II study – Treatment Naïve patients
  - Initiate with oral then SQ lenacapravir plus F/TAF (oral) for 28 weeks
  - Week 28 second SQ LCV and either TAF or Bictegravir (2 drug therapy)
- Lenacapravir – Phase Ib – Treatment experienced suppressed
  - Oral then SQ lenacapravir plus
  - Two long-acting monoclonal antibodies
  - GS-5423 (3BNC117-LS) and GS-2872 (10-1074-LS)
  - Every 6 months – 50 patients
  - https://clinicaltrials.gov/ct2/show/NCT04811040

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CALIBRATE STUDY: LEN PLUS ORAL ART BACKBONE IN NAÏVE

THE LANCET
HIV

Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial

Wednesday
Poster Session-H2 ANTIRETROVIRAL THERAPY: PROSPECTIVE CLINICAL TRIALS
2:30 PM - 4:00 PM

522 LONG-ACTING LENACAPAVIR IN A COMBINATION REGIMEN FOR TREATMENT-NAIVE PWH: WEEK 80
Debbie Hagins, Ellen Koenig, Rachel Safran, Lizette Santiago, Michael Wohlfeiler, Chiu-Bin Hsiao, Shan-Fu Liu, Laurie A. Vanderveen, Hadas Dvory-Sobol, Martin S. Rhee, Jared M. Baeten, Samir Gupta

Slide: a Generous Gift From Monica Gandhi

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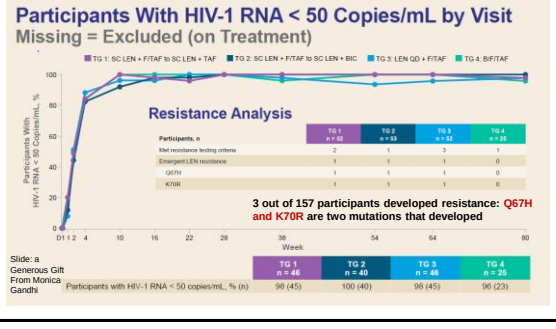

Slide: a Generous Gift From Monica Gandhi

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Lenacapavir with bNAbs Teropavimab (GS-5423) and Zinlirvimab (GS-2872) Dosed Every 6 Months in People with HIV

[1]Joseph Eron, [2]Susan J. Little, [3]Gordon Crofoot, [4]Paul Cook, [5]Peter J. Ruane, [6]Dushyantha Jayaweera, [7]Edwin DeJesus, [8]Sarah E. Waldman, [9]Megha L. Mehrotra, [9]Laurie VanderVeen, [9]Hailin Huang, [9]Sean Collins, [9]Jared Baeten, [10]Marina Caskey

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Presenting Author Disclosure: Joseph Eron is a consultant with Gilead Sciences, Inc., ViiV Healthcare, and Merck. He is also an investigator for Gilead Sciences, Inc., and ViiV Healthcare.

CROI 2023, 19–22 February, Seattle, Washington: Oral #193

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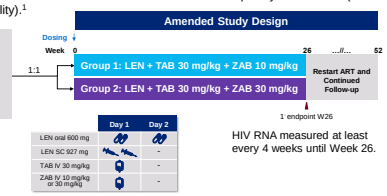
Study Design

- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]

Key Inclusion Criteria
- Adults living with HIV-1
- Virologically suppressed ≥ 18 months
- Viral susceptibility to both TAB and ZAB
- CD4 nadir ≥ 350
- CD4 at entry ≥ 500



	Day 1	Day 2
LEN oral 600 mg		
LEN SC 927 mg		-
TAB IV 30 mg/kg		-
ZAB IV 10 mg/kg or 30 mg/kg		-

HIV RNA measured at least every 4 weeks until Week 26.

[1] FDA lifts clinical hold on investigational lenacapavir for the treatment and prevention of HIV. Press release. May 16, 2022.

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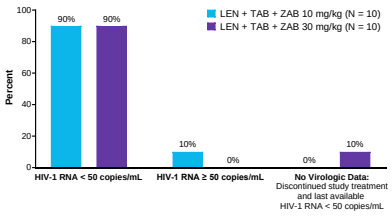
Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

[1] Participant withdrew due to personal decision.

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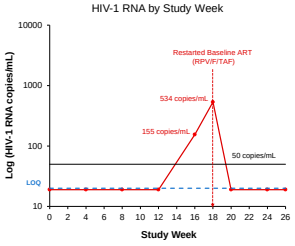
HIV-1 RNA by Study Week in Participant with Viral Rebound



- Rebound participant had baseline phenotypic susceptibility to teropavimab and zinlirvimab, and no pre-existing LEN resistance mutations were detected.
  - Resistance testing of rebound samples resulted in assay failure.
- Participant's CD4 count remained above 500 through Week 26.

The limit of quantification (LOQ) is 20 copies/mL. For the rebound participant, except for Weeks 16 and 18, HIV-1 RNA levels were < 20 copies/mL.

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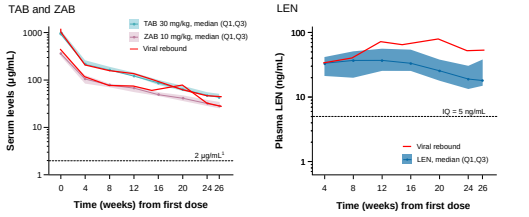
Pharmacokinetics in Participant with Viral Rebound



- TAB, ZAB, and LEN PK for virologic rebound participant was consistent with others in their dosing group.

[1] 2 µg/mL was the level required for sensitivity in the screening assay.

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Why Do We Need New Agents?

Summary

- The needs for new oral therapy are limited
  - Less frequent dosing (e.g. weekly or monthly) may be appealing to many PWH
  - Once daily oral therapies will have very high bar to replace current options
  - Motivation for new drug development may wane
- Long-acting therapy is the new frontier
  - Longer intervals may be the first hurdle to be overcome
  - Partners to lenacapavir are hard to come by – and barrier to resistance is unproven
  - May be more cumbersome or require susceptibility testing to start
  - bNAb, while promising, many questions remain about susceptibility feasibility, cost, manufacture
  - Novel delivery mechanism for small molecules may provide one answer

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Question-and-Answer Session

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