# New and Investigational ART Drugs and Strategies

**Judith S. Currier, MD, MSc**

Division of Infectious Diseases
David Geffen School of Medicine
University of California Los Angeles

2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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

Dr Currier has no relevant financial relationships with ineligible companies to disclose. (Updated 9/20/21)

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## Learning Objectives

At the end of this presentations, learners will be able to:

- List 2 investigational drugs currently in phase III trials
- Describe how these investigational agents might be used in treatment in the future

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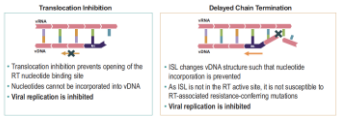
## New Drugs on the Horizon

Islatravir
Lenacapravir
GSK 3640254 (aka GSK "254)
Investigational Aspects of Recently approved Agents
Long acting Cabotegravir and Rilpivirine

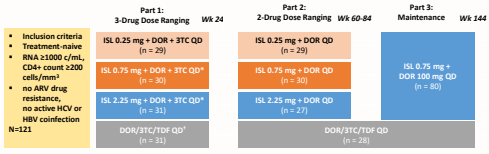
## Islatravir

- **Other Names:** EFdA, ISL, MK-8591
- **Drug Class:** Nucleoside Reverse Transcriptase Translocation Inhibitors




- Currently under evaluation for both prevention and treatment, including both a pill formulation and an implant.
- For treatment: Phase 3 trials combined as a single tablet with Doravirine.

## **Islatravir**: P011 Study Design: from 3 to 2 drugs, 3 doses




RNA < 50 copies/ml at wk 20

**Key findings:** 1 Serious drug related AE in the ISL +DOR part 3 arm, No discontinuations for safety events after week 48
Most common AE in ISL + DOR groups: **headache** (6.5%) ; most common AE in DOR/3TC/TDF group: **diarrhea** (19%)
Similar Incidence of both at Weeks 48 and 96

Cunningham. IAS 2021. Abstr OAB0304.

## **Islatravir**: Safety Data Laboratory (P011 Study)

| Laboratory abnormality in ≥ 2 participants in any group, n/N (%) | ISL 0.25 mg + DOR QD | ISL 0.75 mg + DOR QD | ISL 2.25 mg + DOR QD | DOR/ 3TC/ TDF QD |
|---|---|---|---|---|
| **Fasting triglycerides ( mg/dL)** **Grade 3: > 500-1000** | 2/29 ( 6.9) | 0/30 (0) | 1/29 (3.4) | 0/26 (0) |
| **Alanine aminotransferase (IU/ L)** • **Grade 3: 5.0 to < 10.0 x ULN** | 0/29 (0) | 1/30 (3.3) | 2/31 (6.5) | 1/31 (3.2) |
| **Creatinine kinase ( IU/L)** • **Grade 3: 10.0 to < 20.0 x ULN** • **Grade 4: ≥20.0 x ULN** | 4/29 (13.8) 1/29 (3.4) | 0/30 (0) 2/30 (6.7) | 0/31 (0) 3/31 (9.7) | 1/31 (3.2) 1/31 (3.2) |

No apparent dose related changes in grade 3 and 4 AE's

Cunningham. IAS 2021. Abstr OAB0304.

## Islatravir: Efficacy at 96 weeks

| | ISL (0.25 mg) + DOR QD | ISL (0.75 mg) + DOR QD | ISL (2.25 mg) + DOR QD | ISL Combined | DOR/ 3TC/ TDF QD |
|---|---|---|---|---|---|
| | N=29 | N=30 | N=31 | N=90 | N=31 |
| **Outcome (FDA Snapshot Approach)** | | | | | |
| HIV-1 RNA < 50 copies/ mL, n (%) | 25 (86.2) | 27(90.0) | 21(67.7) | 73(81.1) | 25(80.6) |
| HIV-1 RNA ≥ 50 copies/ mL, n (%) | 2 (6.9) | 2 (6.7) | 5 (16.1) | 9 (10.0) | 2 (6.5) |
| No virologic data at Week 96 window , n (%) | 2 (6.9) | 1 (3.3) | 5 (16.1) | 8 (8.9) | 4 (12.9) |
| **Reasons for no virologic data in window** | | | | | |
| Discontinued due to death or Ae[a] , n (%) | 0 | 0 | 2 (6.5) | 2 (2.2) | 1 (3.2) |
| Discontinued for other reasons, n (%) | 1 (3.4) | 1 (3.3) | 3 (9.7) | 5 (5.6) | 3 (9.7) |
| On treatment but missing data, n (%) | 1 (3.4) | 0 | 0 | 1 (1.1) | 0 |

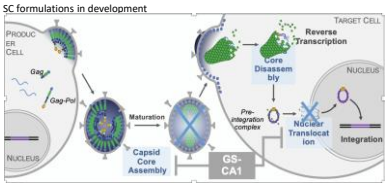
Molina JM et al. HIV Glasgow 2020, abstract O415.
Orkin C et al. HIV Glasgow 2020, abstract PD07.

## **Islatravir**: Ongoing trials

- Phase III studies of treatment-naive people (NCT04233879),
- Heavily treatment-experienced people (NCT04233216)
- People with viral suppression who are switching from other regimens (NCT04223778 and NCT04223791).
- A phase II study of children and adolescents is also planned (NCT04295772).

## Lenacapravir: Background

- Lenacapavir: HIV capsid inhibitor that prevents nuclear assembly, virus assembly and release, and capsid assembly. $EC_{50}$ 50 picomolar
  - Retains full activity against NRTI-, NNTRI-, PI-, and INSTI-resistant HIV-1 in vitro[3-5]
  - Oral and SC formulations in development




1. Link. Nature. 2020;584:614. 2. Bester. Science. 2020;370:360. 3. Yant. CROI 2019. Abstr 480. 4. Margot. CROI 2020. Abstr 529. 5. VanderVeen. CROI 2021. Abstr 128. 6. Segal-Maurer. CROI 2021. Abstr 127. 7. Molina. IAS 2021. Abstr OALX01LB02.

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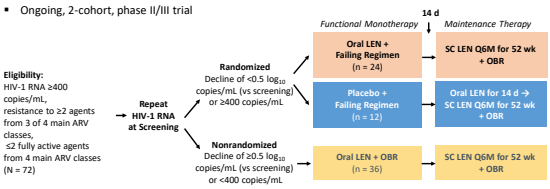
## CAPELLA: Study Design with Lenacapravir

- Ongoing, 2-cohort, phase II/III trial




- Primary endpoint achieved in prior analysis: ≥0.5 $log_{10}$ copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort (90% of LEN vs 17% placebo)
  - 1.93 log 10 reduction in viremia in LEN group in first 14 days
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

Molina. IAS 2021. Abstr OALX01LB02.

Adapted from Slide: clinicaloptions.com

## CAPELLA: Baseline Characteristics

| Characteristic | Randomized | | Nonrandomized | Total (N = 72) |
|---|---|---|---|---|
| | LEN (n = 24) | Placebo (n = 12) | LEN (n = 36) | |
| Median age, yr (range) | 55 (24-71) | 54 (27-59) | 49 (23-78) | 52 (23-78) |
| Female at birth, % | 29 | 25 | 22 | 25 |
| Black, % | 42 | 55 | 31 | 38 |
| Hispanic/Latinx, % | 25 | 36 | 14 | 21 |
| Median HIV-1 RNA, $\log_{10}$ copies/ml (range)<br>▪ >75,000 copies/mL, % | 4.2 (2.3-5.4)<br>17 | 4.9 (4.3-5.3)<br>50 | 4.5 (1.3-5.7)<br>28 | 4.5 (1.3-5.7)<br>28 |
| Median CD4+ cell count, cells/mm$^3$ (range)<br>▪ ≤200 cells/mm$^3$, % | 172 (16-827)<br>67 | 85 (6-237)<br>92 | 195 (3-1296)<br>53 | 150 (3-1296)<br>64 |
| Median time since HIV diagnoses, yr (range) | 27 (13-39) | 26 (14-35) | 23 (9-44) | 24 (9-44) |
| Median prior ARVs, No. (range) | 9 (2-24) | 9 (3-22) | 13 (3-25) | 11 (2-25) |
| Median ARVs in failing regimen, No. (range) | 3 (1-7) | 3 (2-6) | 4 (2-7) | 3 (1-7) |
| Resistance to ≥2 drugs in class, %<br>▪ NRTI<br>▪ NNRT<br>▪ PI<br>▪ INSTI | <br>96<br>92<br>83<br>83 | <br>100<br>100<br>67<br>58 | <br>100<br>100<br>83<br>64 | <br>99<br>97<br>81<br>69 |

Molina. IAS 2021. Abstr OALX01LB02.

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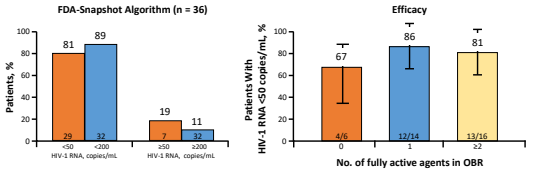
## CAPELLA Secondary Endpoints: LEN Efficacy at Week 26 in Randomized Cohort




- Mean change in CD4+ cell count: +81 cells/mm$^3$
- Incidence of very low CD4+ cell count (<50 cells/mm$^3$) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

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## CAPELLA: Emergence of LEN Resistance

| Outcome, n (%) | Randomized Cohort (n = 36) |
|---|---|
| Patients meeting criteria for resistance testing* | 11 (31) |
| No emergent LEN resistance | 7 (19) |
| Emergent LEN resistance<br>▪ M66I<br>▪ Q67H<br>▪ K70N/R/S<br>▪ N74D | 4 (11)<br>4<br>1<br>1<br>1 |

* Capsid genotypic and phenotypic resistance testing performed in any patients with HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA decrease from Day 1 at Week 4 appt, at any appt after attaining HIV-1 RNA <50 copies/mL and rebound to ≥50 copies/mL, and at any appt with >1 $\log_{10}$ increase from nadir. If suboptimal virologic response or rebound were confirmed: HIV-1, reverse transcriptase, protease, and integrase genotypic and phenotypic testing were done.

- All 4 patients with emergent LEN resistance remained on LEN
  - 3 patients achieved HIV-1 RNA resuppression at a later visit, 2 without and 1 with OBR change
  - 1 patient with no fully active agents never achieved suppression (max decline in HIV-1 RNA: 1.7 $\log_{10}$ copies/mL)
- No patients developed additional resistance to OBR agents

Molina. IAS 2021. Abstr OALX01LB02.

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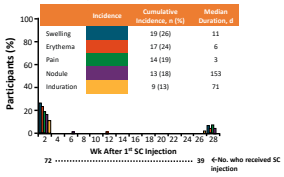
## CAPELLA: Wk 26 Safety, Injection Site Reactions in Randomized and Nonrandomized Cohorts

| Outcome with incidence ≥5%, n (%) | Total (N = 72) |
|---|---|
| Adverse event | |
| ▪ Diarrhea | 6 (8) |
| ▪ Nausea | 6 (8) |
| ▪ Cough | 5 (7) |
| ▪ Headache | 5 (7) |
| ▪ Pyrexia | 5 (7) |
| ▪ Urinary tract infection | 5 (7) |
| ▪ Abdominal distension | 4 (6) |
| ▪ Arthralgia | 4 (6) |
| ▪ Back pain | 4 (6) |
| ▪ Constipation | 4 (6) |
| ▪ Oral candidiasis | 4 (6) |
| ▪ Rash | 4 (6) |
| Any grade 3/4 lab abnormality | 19 (26) |
| ▪ Low creatinine clearance/high creatinine | 8 (11) |
| ▪ Glycosuria | 4 (6) |
| ▪ Nonfasting/fasting hyperglycemia | 4 (6) |

Injection site reactions (ISRs)




- 56% (40 of 72) had ≥1 ISR related to LEN; 28 grade 1, 2 grade 3, no grade 4
- All 36 patients in randomized cohort received second LEN injection

Molina. IAS 2021. Abstr OALX011B02.

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## CAPELLA: Lenacapravir in MDR HIV

- Lenacapavir, in combination with OBR, demonstrated favorable efficacy and safety at Week 26 in heavily treatment-experienced patients with MDR HIV-1 infection
  - High rate of virologic suppression (81%)
  - Increase in CD4+ cell count (+81 cells/mm$^3$)
    - No patients had CD4+ cell count <50 cells/mm$^3$ at Week 26 vs 22% at baseline
  - Treatment well tolerated with no AEs leading to discontinuation
  - All randomized patients received second SC lenacapavir injection
- Data support ongoing evaluation of lenacapavir for HIV-1 treatment and prevention in heavily treatment-experienced patients with MDR HIV-1 infection
- More information on resistance needed

Molina. IAS 2a021. Abstr OALX01LB02.

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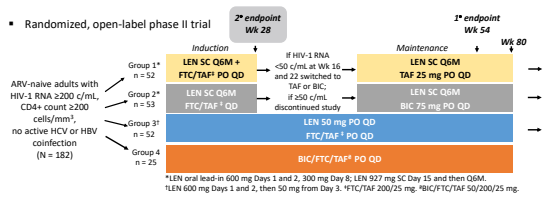
## CALIBRATE: Lenacapavir in Treatment-Naive

- Randomized, open-label phase II trial




*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ¹FTC/TAF 200/25 mg. ²BIC/FTC/TAF 50/200/25 mg.

- Participants at baseline: median age 29 yr; 93% male; 52% Black race; 45% Latinx ethnicity
- Primary outcome: proportion with HIV-1 RNA <50 c/mL at Wk 54; **secondary outcomes: proportion with HIV-1 RNA <50 c/mL at Wk 28**, 38, and 80; change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Wk 28, 38, 54, and 80

Gupta. IAS 2021. Abstr OALB0302.

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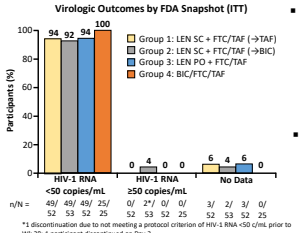
## CALIBRATE: Wk 28 Virologic Outcomes




*1 discontinuation due to not meeting a protocol criterion of HIV-1 RNA <50 c/mL prior to Wk 28; 1 participant discontinued on Day 2.

Gupta. IAS 2021. Abstr OALB0302.

- One participant in LEN SC + FTC/TAF → BIC arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (LEN fold change = 20)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

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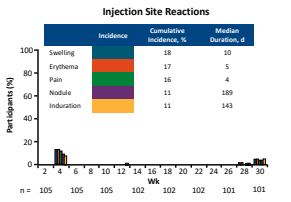
## CALIBRATE: Adverse Events and Injection Site Reactions

- LEN was well tolerated with favorable safety profile
  - No SAEs or grade 4 AEs related to study drug
  - Most common AEs: headache and nausea (11% each)
  - GI AEs in SC vs oral LEN:
    - Nausea: 12% vs 8%
    - Diarrhea: 6% vs 8%
- ISRs in 39% of participants; 83% were grade 1 and generally resolved in days
- 2 discontinuations due to ISRs (grade 1 injection site induration)




Gupta. IAS 2021. Abstr OALB0302.

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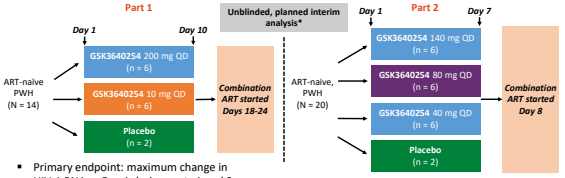
## Next Generation Maturation Inhibitor: GSK3640254

- GSK'254
  - Prevents the proteolytic cleavage of specific portions of the Gag protein which prevents processing of the Gag-Pol polyprotein in late stage of HIV replication.
  - Pre-existing mutations at the cleavage site led to termination of development of an earlier maturation inhibibitor (bevirimat).

-Phase 2 A results of a two part study of GSK '254 presented at CROI 2021.

## Phase IIa Study of GSK3640254: Study Design

- Multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled trial




- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*Detection of resistance mutations at interim analysis resulted in protocol amendment, reducing duration of monotherapy from 10 days to 7 days in Part 2.

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## Phase IIa Study of GSK3640254: Baseline Characteristics

| Characteristic | GSK3640254 | | | | | Placebo (n = 4) | Total (N = 34) |
|---|---|---|---|---|---|---|---|
| | 10 mg* (n = 6) | 40 mg† (n = 6) | 80 mg† (n = 6) | 140 mg† (n = 6) | 200 mg* (n = 6) | | |
| Mean age, yrs (SD) | 32.7 (8.3) | 27.7 (6.9) | 32.8 (6.2) | 33.2 (8.2) | 29.3 (3.9) | 36.5 (9.3) | 31.8 (7.2) |
| Male, n (%) | 6 (100) | 5 (83) | 6 (100) | 5 (83) | 6 (100) | 4 (100) | 32 (94) |
| Mean BMI (SD) | 25.3 (3.7) | 23.9 (4.3) | 24.8 (3.7) | 23.4 (1.6) | 22.6 (2.2) | 23.0 (1.3) | 23.9 (3.0) |
| Race, n (%) | | | | | | | |
| ▪ White | 2 (33) | 5 (83) | 4 (67) | 5 (83) | 5 (83) | 3 (75) | 24 (71) |
| ▪ Black | 0 | 1 (17) | 2 (33) | 1 (17) | 0 | 0 | 4 (12) |
| ▪ Other | 4 (67) | 0 | 0 | 0 | 1 (17) | 1 (25) | 6 (18) |
| Mean HIV-1 RNA, $\log_{10}$ copies/mL (SD) | 4.19 (0.311) | 4.67 (0.233) | 4.43 (0.510) | 4.53 (0.577) | 4.82 (0.476) | 4.25 (0.417)* 4.25 (0.417)† | 4.47 (0.489)* 4.57 (0.592)† |

*Part 1. †Part 2.

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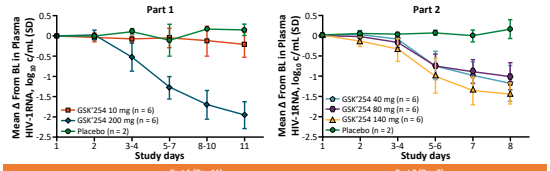
## Phase IIa Study of GSK3640254: Antiviral Activity




| Mean Change in HIV-1 RNA vs BL, $\log_{10}$ copies/mL (SD) | Part 1 (Day 11) | | | Part 2 (Day 8) | | | |
|---|---|---|---|---|---|---|---|
| | GSK3640254 10 mg (n = 6) | GSK3640254 200 mg (n = 6) | Placebo (n = 2) | GSK3640254 40 mg (n = 6) | GSK3640254 80 mg (n = 6) | GSK3640254 140 mg (n = 6) | Placebo (n = 2) |
| Primary endpoint | -0.22 (0.309) | -1.96 (0.337) | 0.14 (0.134) | -1.18 (0.436) | -1.02 (0.330) | -1.45 (0.235) | 0.15 (0.226) |
| Maximum change | -0.36 (0.252) | -2.01 (0.329) | -0.21 (0.262) | -1.18 (0.436) | -1.02 (0.330) | -1.49 (0.267) | -0.03 (0.127) |

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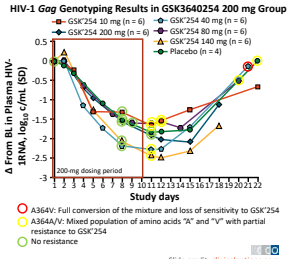
## Phase IIa Study of GSK3640254: Resistance

- Resistance mutation A364A/V detected in 4 of 6 patients receiving GSK3640254 200 mg QD at Day 11 in part 1
  - Full conversion and phenotypic resistance in 1 of 4
- No resistance in 10 mg QD group
- Protocol amendment reduced duration of monotherapy from 10 days to 7 days in Part 2
- No resistance detected at any dose in part 2 (140 mg, 80 mg, or 40 mg)

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## GSK'254 Summary

- In ART-naive persons with HIV, novel HIV-1 maturation inhibitor, GSK3640254, demonstrated dose-response activity
  - HIV-1 RNA decreased 1.5 $log_{10}$ copies/mL with 140-mg QD dose and 2.0 $log_{10}$ copies/mL with 200-mg QD dose
- GSK3640254 was well-tolerated
  - No grade 3/4 AEs and no AEs leading to d/c
- Investigators conclude these findings support evaluation of GSK3640254 (100 mg QD, 150 mg QD, and 200 mg QD) in combination with 2 NRTIs in phase IIb study

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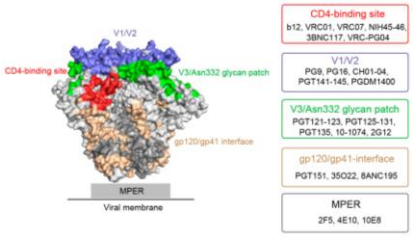
## Broadly Neutralizing Antibodies against HIV




CD4-binding site
b12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

V1/V2
PG9, PG16, CH01-04, PGT141-145, PGDM1400

V3/Asn332 glycan patch
PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

gp120/gp41-interface
PGT151, 35O22, 8ANC195

MPER
2F5, 4E10, 10E8

## Future Combinations and Approaches in the works

- Long acting cabotegravir and a broadly neutralizing antibodies
  - A5357: A single arm trial of long-acting cabotegravir and VRC07LS (a broadly neutralizing antibody; bNAb) as maintenance ART
  - A5364: A single arm trial of two bNAbs (3BNC117-LS & 10-1074-LS) to prevent relapse of viremia of discontinuation of oral ART
  - A5377, a first-in-human Phase 1 clinical trial of a tri-specific monoclonal antibody (SAR441236) to establish safety, pharmacokinetics, and preliminary antiviral activity
- Ongoing Phase 1 study combined with GS-5423 (AKA 3BNC117-LS) in people with virologic suppression

## Investigational Approaches with recently approved agents: Long Acting Cabotegravir and Rilpivirine

- Long acting cabotegravir and rilpivirine approved for use in patients with viral suppression and no prior resistance in an every 4 week dosing schedule in US and Canada. January 21, 2021. (approved for q8 in EU)
- Approved in both an oral formulation cabotegravir 30 mg and rilpivirine and in the sustained release injection to be initiated after an oral lead in.
- ATLAS 2M compared 4 week with 8 week dosing in people who were suppressed on 4 week dosing or suppressed on ART outside the trial
  - Week 96 follow-up (CROI 2021) HIV RNA during q 8 week (91% < 50 copies) non-inferior to q 4 week dosing (90% < 50 copies/ml)
  - Very few grade 3 ISR- rates decreased over time

**ACTG 5359**
**A Phase III Randomized-Control Trial to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals**

**Co- Chairs:** Aadia Rana, Jose Castillo-Mancilla **Co- Vice Chairs**: Raphael J. Landovitz, Karen Tashima

**Utilizes cash incentives to help obtain viral suppression followed by use of long acting Cabotegravir**

**Study Population:**

- ART-experienced, HIV-infected males and non-pregnant females ≥18 years of age with:
  - HIV-1 RNA >200 copies/mL
  - Evidence of non-adherence according to at least one of the following criteria:
    - Poor virologic response within 18 months prior to entry in individuals who have been prescribed ART for at least 6 consecutive months.
    - Loss to clinical follow-up within 18 months prior to study entry with ART non-adherence for ≥6 consecutive months.
  - No evidence of any clinically relevant RPV or INSTI resistance-associated mutations (historically or upon screening).
  - Ability of site clinician, in conjunction with participant, to construct a ≥3-drug ART regimen with ≥2 drugs predicted to be fully active, including a boosted PI/cobi and/or an INSTI.

## Summary

- New drugs with novel mechanisms of action and less frequent dosing are progressing in development.
  - Islatravir
  - Lenacapravir
  - GSK'254
- Use of approved combination of long acting cabotegravir/rilpivirine slowly being rolled out
  - Investigational approaches with q 8 week dosing, combination with other agents and use in populations that have struggled with adherence in progress.