New and Investigational ART Drugs and Strategies

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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)

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
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

- **Inclusion criteria**
  - Treatment-naive
  - RNA ≥1000 copies/mL, CD4+ count ≥200 cells/mm³
  - No ARV drug resistance, no active HCV or HBV coinfection

**N=121**

**Part 1:** 3-drug Dose Ranging
- ISL 0.25 mg + DOR + 3TC QD (n = 29)
- DOR/3TC/TDF QD† (n = 31)
- ISL 0.75 mg + DOR + 3TC QD* (n = 30)
- ISL 2.25 mg + DOR + 3TC QD* (n = 31)

**Part 2:** 2-drug Dose Ranging
- Wk 24
- Wk 60 - 84

**Part 3:** Maintenance
- ISL 0.75 mg + DOR 100 mg QD (n = 80)
- Wk 144

**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

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

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>ISL 0.25 mg</th>
<th>ISL 0.75 mg</th>
<th>ISL 2.25 mg</th>
<th>DOR/3TC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting triglycerides (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 5 &gt; 1000</td>
<td>2/29 (6.9)</td>
<td>0/30 (0)</td>
<td>1/29 (3.4)</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>Grade 4 &gt; 500 - 1000</td>
<td>1/29 (3.4)</td>
<td>0/30 (0)</td>
<td>2/29 (6.9)</td>
<td>0/26 (0)</td>
</tr>
</tbody>
</table>

| Alanine aminotransferase (IU/L) |
| Grade 4: 10 - 100x ULN | 4/29 (13.8) | 1/29 (3.4) | 0/30 (0) | 3/30 (10.0) |
| Grade 4: > 100x ULN | 0/29 (0) | 1/29 (3.4) | 0/30 (0) | 3/30 (10.0) |

| Creatinine kinase (IU/L) |
| Grade 4: 20 - 100x ULN | 0/29 (0) | 1/29 (3.4) | 2/30 (6.7) | 1/31 (3.2) |
| Grade 4: > 100x ULN | 0/29 (0) | 1/29 (3.4) | 3/30 (10.0) | 1/31 (3.2) |

No apparent dose-related changes in grade 3 and 4 AEs

**Islatravir: Efficacy at 96 weeks**

<table>
<thead>
<tr>
<th>Outcome (FDA Snapshot Approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt; 40 copies/mL</td>
</tr>
<tr>
<td>HIV RNA &lt; 10 copies/mL</td>
</tr>
<tr>
<td>No virologic data at week 96 window</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for no virologic data in window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or AE</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
</tr>
<tr>
<td>On treatment but missing data</td>
</tr>
</tbody>
</table>
**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).

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**Lenacapravir: Background**

- Lenacapravir: HIV capsid inhibitor that prevents nuclear assembly, virus assembly and release, and capsid assembly. EC₅₀ 50 picomolar.
  - Retains full activity against NRTI-, NNRTI-, PI-, and INSTI-resistant HIV-1 in vitro.
  - Oral and SC formulations in development.

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**CAPELLA: Study Design with Lenacapravir**

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

  - **Eligibility:**
    - HIV-1 RNA ≥400 copies/mL, resistance to ≥2 agents from ≥3 of 4 main ARV classes,
    - ≤2 fully active agents from 4 main ARV classes (P< 12).
    - Repeat HIV-1 RNA at screening.

  - **Randomized:></p>
    - Oral LEN + Failing Regimen (n=24)
    - Oral LEN + OBR (n=36)

  - **Nonrandomized:></p>
    - Oral LEN + CD4 (n=12)
    - Oral LEN + CD4 (SC) (n=12)

  - **Maintenance Therapy:></p>
    - SC LEN Q6M for 52 wk + CD4
    - SC LEN Q6M for 52 wk + CD4

- Primary endpoint achieved in prior analysis: 3.6 log₁₀ copies/mL decline in HIV-1 RNA at Day 24 in randomized cohort (80% of LEN vs 17% placebo).
- 3.58 log₁₀ reduction in viral load in initial group in 1st 24 days.
- Secondary endpoints: HIV-1 RNA ≥50 copies/mL, ≤400 copies/mL at Week 26 in randomized cohort.
CAPELLA: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized</th>
<th>Nonrandomized</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEN (n = 24)</td>
<td>Placebo (n = 12)</td>
<td>LEN (n = 36)</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>55 (24-71)</td>
<td>54 (27-59)</td>
<td>49 (23-78)</td>
</tr>
<tr>
<td>Female at birth, %</td>
<td>29</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Black, %</td>
<td>35</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Hispanic/Latinx, %</td>
<td>25</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Median HIV-1 RNA, log_{10} copies/ml (range)</td>
<td>4.2 (2.3-5.4)</td>
<td>6.8 (5.6-8.5)</td>
<td>5.9 (5.6-8.5)</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm^3 (range)</td>
<td>50 (23-78)</td>
<td>85 (10-237)</td>
<td>92</td>
</tr>
<tr>
<td>Median time since HIV diagnoses, yr (range)</td>
<td>27 (13-39)</td>
<td>26 (14-35)</td>
<td>23</td>
</tr>
<tr>
<td>Median prior ARVs, No. (range)</td>
<td>9 (2-24)</td>
<td>9 (3-22)</td>
<td>13</td>
</tr>
<tr>
<td>Median ARVs in failing regimen, No. (range)</td>
<td>3 (1-7)</td>
<td>3 (2-6)</td>
<td>4</td>
</tr>
<tr>
<td>Resistance to ≥2 drugs in class, %</td>
<td>96</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in CD4+ cell count: +81 cells/mm^3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of very low CD4+ cell count (&lt;50 cells/mm^3) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

CAPELLA: Emergence of LEN Resistance

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

- 56% (40 of 72) had ≥1 ISR related to LEN; grade 1, 2 grade 3, no grade 4

All 36 patients in randomized cohort received second LEN injection.

Outcome with incidence ≥5%, n (%)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Total (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Anuria</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Any grade 3/4 lab abnormality

- Low creatinine clearance/high creatinine 19 (26)
- Glycosuria 8 (11)
- Nonfasting/fasting hyperglycemia 4 (6)

Injection site reactions (ISRs)

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>Median Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>11</td>
</tr>
<tr>
<td>Erythema</td>
<td>6</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
</tr>
<tr>
<td>Nodule</td>
<td>15</td>
</tr>
<tr>
<td>Induration</td>
<td>7</td>
</tr>
</tbody>
</table>

Participants (%)

- 0
0
0
0

Wk After 1st SC Injection

If HIV-1 RNA <50 c/mL at Wk 16 and 22 switched to TAF or BIC; if ≥50 c/mL discontinued study

Maintenance endpoint Wk 54

CAPELLA: Lenacapavir 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/mm³)
  - No patients had CD4+ cell count <50 cells/mm³ 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

CALIBRATE: Lenacapavir in Treatment-Naive

- Randomized, open-label phase II trial

- ARV-naive adults with HIV-1 RNA >200 c/mL, CD4+ count ≥350, no active HCV or HBV coinfection (N = 182)

- Patients at baseline: median age 39 yr; 33% 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 log₁₀ HIV-1 RNA and CD4+ cell count at Wk 28, 38, and 80

- Group 1* n = 52
- Group 2* n = 53
- Group 3† n = 52
- Group 4 n = 25

- LEN SC Q6M + Induction
- LEN SC Q6M

If HIV-1 RNA <50 c/mL at Wk 16 and 22 switched to TAF or BIC; if ≥50 c/mL discontinued study

Maintenance endpoint Wk 54
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

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: 13% 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)

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 inhibitor (bevirimat).
- Phase 2A 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

**Slide adapted from: clinicaloptions.com**

**Phase IIa Study of GSK3640254**: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GSK3640254 10 mg*</th>
<th>GSK3640254 60 mg</th>
<th>GSK3640254 200 mg*</th>
<th>Placebo (n = 4)</th>
<th>Total (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>32.7 (8.3)</td>
<td>27.7 (6.9)</td>
<td>32.8 (6.2)</td>
<td>33.2 (8.2)</td>
<td>29.3 (3.9)</td>
</tr>
<tr>
<td>Male, n (%): White</td>
<td>2 (33)</td>
<td>5 (83)</td>
<td>6 (100)</td>
<td>5 (83)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>25.3 (3.7)</td>
<td>23.9 (4.3)</td>
<td>24.8 (3.7)</td>
<td>23.4 (1.6)</td>
<td>22.6 (2.2)</td>
</tr>
<tr>
<td>Mean HIV-1 RNA, log_{10} copies/mL (SD)</td>
<td>4.19 (0.311)</td>
<td>4.67 (0.233)</td>
<td>4.43 (0.510)</td>
<td>4.53 (0.577)</td>
<td>4.82 (0.476)</td>
</tr>
</tbody>
</table>

*Part 1. †Part 2.

**Phase IIa Study of GSK3640254**: Antiviral Activity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary endpoint</th>
<th>Maximum change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>0.22 (0.309)</td>
<td>-1.96 (0.337)</td>
</tr>
<tr>
<td>Part 2</td>
<td>0.14 (0.134)</td>
<td>-1.18 (0.436)</td>
</tr>
<tr>
<td>Part 1</td>
<td>0.36 (0.252)</td>
<td>-2.01 (0.329)</td>
</tr>
<tr>
<td>Part 2</td>
<td>0.21 (0.262)</td>
<td>-1.18 (0.436)</td>
</tr>
<tr>
<td>Part 1</td>
<td>0.15 (0.226)</td>
<td>-1.02 (0.330)</td>
</tr>
<tr>
<td>Part 2</td>
<td>0.03 (0.127)</td>
<td>-1.49 (0.267)</td>
</tr>
</tbody>
</table>

**Slide adapted from: clinicaloptions.com**
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)

Abs. Change in Virus Load from Baseline

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

Broadly Neutralizing Antibodies against HIV
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-S423 (AKA 3BNC117-LS) in people with virologic suppression

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

- 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: Audia Rana, Jose Castillo-Marcella, 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 4 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 FPV or INI 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/rtv and/or an INSTI.
Summary

• New drugs with novel mechanisms of action and less frequent dosing are progressing in development.
  • Istravir
  • Lenacaprevir
  • 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.

Question-and-Answer Session