New Drugs in Development
Are We Ready for Long-Acting ART?

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Disclosures

• Faculty and Planning Committee Disclosures: Please consult your program book or the conference app.
• Off-label Disclosure: None of the agents discussed in this talk have yet been approved by the FDA
## Learning Objectives

After attending this presentation, learners will be better able to:

- Discuss the efficacy and challenges of long acting therapy with CAB LA + RPV LA
- Describe the mechanisms of action and pharmacokinetic profiles for MK-8591, GS 6207 and PRO 140
- Describe the efficacy and safety of fostemsavir in treatment experienced patients

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>Sponsor</th>
<th>Ph I</th>
<th>Ph II</th>
<th>Ph III</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB LA + RPV LA</td>
<td>INSTI/NNRTI</td>
<td>Viiv</td>
<td></td>
<td></td>
<td>x</td>
<td>IM monthly</td>
</tr>
<tr>
<td>Fostemsavir</td>
<td>Attachment Inhibitor</td>
<td>Viiv</td>
<td></td>
<td></td>
<td>x</td>
<td>Treatment-experienced pts Twice daily</td>
</tr>
<tr>
<td>MK 8591 (EFdA)</td>
<td>NRT Translocation Inhibitor</td>
<td>Merck</td>
<td></td>
<td></td>
<td>x</td>
<td>Long acting potential; treatment &amp; prevention</td>
</tr>
<tr>
<td>PRO 140 (Ieronlimab)</td>
<td>Anti-CCR5 mAb</td>
<td>CytoDyn</td>
<td></td>
<td></td>
<td>IIb/III</td>
<td>SC once weekly</td>
</tr>
<tr>
<td>Albuvirtide</td>
<td>Fusion inhibitor</td>
<td>Frontier</td>
<td></td>
<td></td>
<td>x</td>
<td>Approved in China; no US data available yet</td>
</tr>
<tr>
<td>3BNC117</td>
<td>bNAb</td>
<td>Rockefeller; Frontier</td>
<td></td>
<td></td>
<td>x</td>
<td>Ph II w/ albuvirtide; no data available</td>
</tr>
<tr>
<td>GS-9131</td>
<td>NRTI</td>
<td>Gilead</td>
<td></td>
<td></td>
<td>X</td>
<td>Active against NRTI resistant viruses</td>
</tr>
<tr>
<td>GSK-2838232</td>
<td>Maturation Inhibitor</td>
<td>GSK</td>
<td></td>
<td></td>
<td>IIa</td>
<td>Requires boosting; resistance concerns</td>
</tr>
<tr>
<td>GS-6207</td>
<td>Capsid Inhibitor</td>
<td>Gilead</td>
<td></td>
<td></td>
<td>X</td>
<td>Long acting potential</td>
</tr>
<tr>
<td>PGT121</td>
<td>bNAb</td>
<td>IAVI*</td>
<td></td>
<td></td>
<td>X</td>
<td>*GS 9722 licensed to Gilead</td>
</tr>
<tr>
<td>TAF Implant</td>
<td>NRTI</td>
<td>Gilead, others</td>
<td></td>
<td></td>
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</tbody>
</table>
Long Acting
Cabotegravir and Rilpivirine

FLAIR and ATLAS

CAB LA + RPV LA: Summary

• Monthly CAB LA + RPV LA noninferior to
  – DTG/ABC/3TC as initial therapy
  – Combo ARV for maintenance of viral suppression
• Rare grade 3/4 or serious AEs
• Low rates of virologic failure, but some with treatment emergent mutations for both NNRTI and INSTI
• Injection site reactions common, grade 1-2
• Patient-reported satisfaction high in both studies
• Limited expanded access for those unable to take pills:
  GSKClinicalSupportHD@gsk.com; 877-379-3718
FLAIR: Randomized, Open-Label, Noninferiority Study in ART-Naïve Adults

**Screening Phase**
- N=809
- ART-naïve
- HIV-1 RNA ≥1000
- Any CD4 count
- HBsAg-negative
- NNRTI RAMs excluded

**Induction Phase**
- N=629
- DTG/ABC/3TC single-tablet regimen for 20 weeks

**Maintenance Phase**
- DTG/ABC/3TC
- Oral daily n=283
- CAB LA (400 mg) + RPV LA (600 mg) IM monthly n=278

**Extension Phase**
- Oral CAB + RPV n=283

ATLAS: Randomized, Open-Label, Noninferiority Study in Adults with Viral Suppression

**FLAIR & ATLAS Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FLAIR N=566</th>
<th>ATLAS N=616</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) – year</td>
<td>34 (18–68)</td>
<td>42 (18–82)</td>
</tr>
<tr>
<td>Age ≥50 years – n (%)</td>
<td>62 (11)</td>
<td>162 (26)</td>
</tr>
<tr>
<td>Female – n (%)</td>
<td>127 (22)</td>
<td>203 (33)</td>
</tr>
<tr>
<td>Race – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White – n (%)</td>
<td>417 (74)</td>
<td>421 (68)</td>
</tr>
<tr>
<td>Black or African American – n (%)</td>
<td>103 (18)</td>
<td>139 (23)</td>
</tr>
<tr>
<td>Other or missing – n (%)</td>
<td>46 (8)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>HIV-1 RNA, copies/mL – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>454 (80)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>112 (20)</td>
<td></td>
</tr>
<tr>
<td>Median baseline CD4+ cell count (IQR) cells/mm³</td>
<td>444 (320, 604)</td>
<td>653 (150–2543)</td>
</tr>
<tr>
<td>HIV-1–HCV co-infection – n (%)</td>
<td>28 (5)</td>
<td></td>
</tr>
<tr>
<td>Median duration of prior ART (range) – year</td>
<td></td>
<td>4 (1–21)</td>
</tr>
<tr>
<td>Baseline third ART agent class – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td>310 (50)</td>
</tr>
<tr>
<td>INSTI</td>
<td></td>
<td>201 (33)</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td>105 (17)</td>
</tr>
</tbody>
</table>

FLAIR & ATLAS Adverse Events

Any AE (≥10%), n (%)  
- Nasopharyngitis: FLAIR CAB+RPV (LA) 56 (20), FLAIR DTG/ABC/3TC 48 (17), ATLAS CAB+RPV (LA) 52 (17), ATLAS Combo ART 42 (14).
- Headache: FLAIR CAB+RPV (LA) 39 (14), FLAIR DTG/ABC/3TC 21 (7), ATLAS CAB+RPV (LA) 34 (11), ATLAS Combo ART 17 (6).
- Upper resp tract infection: FLAIR CAB+RPV (LA) 38 (13), FLAIR DTG/ABC/3TC 28 (10), ATLAS CAB+RPV (LA) 32 (10), ATLAS Combo ART 25 (8).
- Diarrhea: FLAIR CAB+RPV (LA) 32 (11), FLAIR DTG/ABC/3TC 25 (9), ATLAS CAB+RPV (LA) NR, ATLAS Combo ART NR.

Drug-related AEs (≥3%), n (%)  
- Any event (per participant): FLAIR CAB+RPV (LA) 79 (28), FLAIR DTG/ABC/3TC 28 (10), ATLAS CAB+RPV (LA) 88 (29), ATLAS Combo ART 8 (3).
- Fatigue: FLAIR CAB+RPV (LA) NR, FLAIR DTG/ABC/3TC NR, ATLAS CAB+RPV (LA) 11 (4), ATLAS Combo ART 0.
- Pyrexia: FLAIR CAB+RPV (LA) 13 (5), FLAIR DTG/ABC/3TC 0, ATLAS CAB+RPV (LA) 11 (4), ATLAS Combo ART 0.
- Nausea: FLAIR CAB+RPV (LA) NR, FLAIR DTG/ABC/3TC NR, ATLAS CAB+RPV (LA) 11 (4), ATLAS Combo ART 0.
- AEs leading to withdrawal: FLAIR CAB+RPV (LA) 9 (3), FLAIR DTG/ABC/3TC 4 (1), ATLAS CAB+RPV (LA) 10 (3), ATLAS Combo ART 5 (2).

FLAIR Virologic Snapshot ITT-E Outcomes at Week 48  
Noninferiority Achieved for Primary and Secondary Endpoints

Virologic nonresponse (≥50 c/mL)  
- FLAIR CAB+RPV (LA) 93.6 (n=283), DTG/ABC/3TC 93.3 (n=283).
- Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

Adjusted Treatment Difference (95% CI)*  
- Primary endpoint: FLAIR CAB LA + RPV LA (n=283) vs DTG/ABC/3TC (n=283).
- Key secondary endpoint: FLAIR CAB LA + RPV LA vs DTG/ABC/3TC (n=283).

3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).
**ATLAS Virologic Snapshot ITT-E Outcomes at Week 48**

Noninferiority Achieved for Primary and Secondary Endpoints

**Primary endpoint:**
LA noninferior to CAR (HIV-1 RNA \( \geq 50 \) c/mL) at Week 48

**Difference (%):**

<table>
<thead>
<tr>
<th>CAR</th>
<th>CAB LA + RPV LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6% NI margin</td>
<td>0.6</td>
</tr>
<tr>
<td>-1.2</td>
<td>-0.6</td>
</tr>
<tr>
<td>-3.0</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

**Key secondary endpoint:**
LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

**Difference (%):**

<table>
<thead>
<tr>
<th>CAR</th>
<th>CAB LA + RPV LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10% NI margin</td>
<td>-6.7</td>
</tr>
<tr>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Virologic Outcomes**

Adjusted Treatment Difference (95% CI)*

| CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine. |

*Adjusted for sex and baseline third agent class.

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 139.

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**Confirmed Virologic Failure**

<table>
<thead>
<tr>
<th>FLAIR</th>
<th>ATLAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virologic failure (VF) rate, CAB + RPV arm (week of suspected VF):</strong></td>
<td>1.4%</td>
</tr>
<tr>
<td>(Wk 20, 28, 48)</td>
<td>(Wk 8, 12, 20)</td>
</tr>
<tr>
<td><strong>HIV RNA at confirmed VF:</strong></td>
<td>287 - 488 c/mL</td>
</tr>
<tr>
<td><strong>Mutations at baseline:</strong></td>
<td>RT None</td>
</tr>
<tr>
<td><strong>Mutations at VF (Treatment Emergent):</strong></td>
<td>RT E138A/K/T K101E E138K</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV-1 subtype:</strong></td>
<td>All A1; Russia</td>
</tr>
</tbody>
</table>

* 1 pt with prior nevirapine use had NNRTI but no INSTI mutations at VF
What About the Practical Implications?

Considerations for In-Clinic Administration of LA CAB/RPV

• Loading = 2 injections of 3mL; maintenance = 2 injections of 2mL
  – Need private space for administration
• IM administration technique: Z-tracking into gluteus medius
  – Will require staff training
  – Not tested in persons with buttock implants
• Staffing for retention to ensure monthly (bimonthly?) injections
• Alternative delivery systems: Pharmacy? Home health? Mobile units?
• Visit reminders: running out of pills often triggers visits
Cost Considerations

• How will the drugs be priced?
• Who will purchase the drugs? Patient or provider?
  – Availability of drugs “in stock” for drop in visits for patients who do not
    keep scheduled appointments? Shelf life?
  – Copay cards do not cover drugs purchased and administered by clinics
• Will reimbursement cover drug cost?
  – Cautionary tale: benzathine penicillin G reimbursed at below drug cost
• Will administration be reimbursed?
• What will be the impact on ADAP and health system costs as a whole?

ÉCLAIR Study: Cabotegravir Concentration Post Injection:
Drug Persists in 17% of Subjects 52 Weeks After Last Injection

14 subjects had detectable CAB
52 weeks after last injection

Ford et al. HIVR4P
2016; Chicago, IL
Abstract
OA12.06LB.z
Management of Long Acting Treatments

- Will we see INSTI/NNRTI resistance for those who do not return for treatment?
- How will we manage treatment-emergent drug-related toxicities?
- How will we manage drug interactions, including for TB treatment?
- Will teratogenicity be a problem (neural tube defects)?

ARS 1: For what proportion of your patients might you prescribe CAB LA + RPV LA?

- 0% (Interesting but I’m just not there yet)
- < 10%
- 11-25%
- 26-50%
- 51-75%
- 100% (Greatest thing since sliced bread)
- It will totally depend on logistics and reimbursement
ARS 2: What is your primary concern about CAB LA + RPV LA?

• Patients won’t come back for visits
• Toxicity management
• Pregnancy and potential teratogenicity
• Out of pocket costs to patient (or clinic)
• Logistics of administration
• I have no major concerns. Bring it on!

MK-8591: NRTTI

A Nucleoside Reverse Transcriptase Translocation Inhibitor
MK 8591 for Treatment and Prevention

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Blocks translocation and terminates the DNA chain
  - Also has delayed chain termination effect after incorporation
  - Also known as EFdA (4’ethynyl-2 fluoro-2'deoxyadenosine)
- Very potent: dose as low as 0.25mg for treatment
- Very long half-life of tri-phosphate form: 78-128 hours
  - MK 8591-TP levels above pharmacokinetic target ≥ 30 days after last oral dose (0.25 – 5.0 mg)

Matthews R, CROI 2018; Markowitz M, CROI 2018; Grobler, J et al. CROI 2019; Abstract 0481

MK 8591: Higher Inhibitory Quotient (C_{trough} /IC_{90}) than FTC, 3TC, TAF, TDF

Grobler, J et al. CROI 2019; Abstract 0481
MK-8591 Has Highest IQ Against Wild Type and Resistant Viruses

MK 8591: Long Acting Implant Formulations

Extended Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

- Potentially therapeutic TP levels in rodents persist > 6 months

MK-8591: Summary

- Highly potent: IC50 of MK-8591-TP >4-fold lower than any marketed NRTI
- More active against NRTI-resistant viruses than TDF, TAF, 3TC
- High genetic barrier to resistance
- Very long TP intracellular half-life = potential for weekly oral dosing, long acting parenteral
- Being developed simultaneously for treatment and prevention based on positive macaque studies

Grobler, J et al. CROI 2019; Abstract 0481

Fostemsavir: Attachment Inhibitor
**Fostemsavir : Proposed Mechanism of Action**

**No drug**
- gp120
- gp41
- Conformational changes
- CD4 binding site
- CD4 binding

**Temsavir**
- gp120
- gp41
- Temsavir binding
- Conformational changes inhibited
- CD4 binding
- CD4 binding
- CCR5 co-receptor


Llamoso C et al. HIV Glasgow 2016; Glasgow, UK. Oral # 335A/B.

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**Fostemsavir in Treatment Experienced Patients – 192 Weeks**

<table>
<thead>
<tr>
<th>Key entry criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE participants with current or previous exposure to ≥1 week of ART therapy</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA ≤1,000 c/mL and CD4+ T-cell count ≥500 cells/μL</td>
</tr>
<tr>
<td>Susceptibility to RAL, TDF, and ATV/r verified via resistance testing</td>
</tr>
<tr>
<td>TMR IC50 &lt;0.1 μM (100 nM) by screening PhenoSense® Entry Assay (Monogram Biosciences, CA, USA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FTR dose</th>
<th>N</th>
<th>Treatment arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTR 400 mg BID + RAL + TDF</td>
<td>50</td>
<td>treated</td>
</tr>
<tr>
<td>FTR 800 mg BID + RAL + TDF</td>
<td>49</td>
<td>treated</td>
</tr>
<tr>
<td>FTR 600 mg QD + RAL + TDF</td>
<td>51</td>
<td>treated</td>
</tr>
<tr>
<td>FTR 1200 mg QD + RAL + TDF</td>
<td>50</td>
<td>treated</td>
</tr>
<tr>
<td>ATV/r 300/100 mg QD + RAL + TDF (REF)</td>
<td>51</td>
<td>treated</td>
</tr>
</tbody>
</table>

Thompson, M, et al. CROI 2019, Abstract 0483
Fostemsavir: Virologic Response to Week 192 - Observed

Fostemsavir: Summary

- HIV RNA and CD4 response comparable to ATV/r-RAL-TDF through 192 weeks
- Fewer safety events compared with ATV/r-RAL-TDF
  - Lower rates of Grade 2–4-drug related AEs, Grade 3–4 AEs, and AEs leading to discontinuation
- Requires twice-daily dosing
- Development slowed due to manufacturing issues
- Phase 3 Highly Treatment Experienced (BRIGHTE) study ongoing

Thompson, M, et al. CROI 2019, Abstract 0483
GS–6207: Capsid Inhibitor

- GS-6207 inhibits multiple processes essential for viral replication
- GS-6207 modulates the stability and/or transport of capsid complexes

GS-6207: Support for Dosing Interval of ≥ 12 Weeks

- At doses ≥100 mg, GS-6207 plasma concentrations at 12 weeks were above the paEC$_{95}$ of 3.87 ng/mL

*EC$_{95}$ determined in MT-4 T-Cell Line with WT HIV-1 (IIIb strain). C$_{v12}$, GS-6207 plasma concentration on Day 84; IQ, inhibitory quotient; paEC$_{95}$, protein adjusted EC$_{95}$

GS-6207: Summary

- HIV capsid inhibitor with picomolar antiviral activity
- Following a single subcutaneous dose in healthy volunteers:
  - No serious safety issues (safety still blinded)
  - Maintained systemic exposure for ≥ 24 weeks; most doses exceeded paEC$_{95}$ for ≥ 12 weeks
- Potential for quarterly or less frequent dosing
- Ongoing Phase I in persons living with HIV
PRO-140 (leronlimab): Anti-CCR5 mAb

PRO 140: A CCR5-Directed Monoclonal Antibody

- Humanized IgG4 monoclonal antibody blocks HIV-1 entry
- High genetic barrier to resistance
- Active against multidrug resistant viruses, including those resistant to maraviroc
- Weekly SC injections
- Single dose HIV RNA reduction to 1.83 log
- Tx-experienced: $\geq 0.5 \log_{10}$ HIV RNA decline (1 wk)
- Rolling FDA BLA: plan to file for approval 4Q2019

CD-03 PRO 140
Monotherapy
Maintenance of Viral Suppression

- Stable ART with < 50 c/mL for 6 months
- CD4 > 350/µL; nadir > 200/µL
- Improved response with higher doses; study still enrolling; n=500

Dhody K, et al, CROI 2019, Abstract 486

bNAbs (or bnAbs?)

Broadly neutralizing monoclonal antibodies for prevention, treatment, cure
Antibody infusions: 0, 3, 6 wks
9 pts maintained HIV RNA < 200c/mL up to median 21 weeks
Well tolerated

Questions About Long-Acting Agents

How long is long enough?
How long is too long? (resistance, toxicity, teratogenicity)
What is the optimal administration mode? SC, IM, IV, implant, stent, microneedle patch? Self-administered vs provider-administered?
For clinic-administered therapy, what will be the impact on patient flow, provider time?
What will the drugs cost, and will cost of administration be reimbursed? Impact on health care financing as a whole?
Will they solve or just reinvent issues with adherence?
But...the half life doesn’t matter if the drug doesn’t get into the patient!

US Care Continuum (2015)
And 39,782 New Diagnoses – 2017

CDC HIV Surveillance Report, 2018; 23(3)
Acknowledgements

• Many patients participated in clinical trials to generate the results presented today – Thank You!
• Thanks to study sponsors and presenters who shared their slides with me.