CROI 2020 Review: Long-Acting ART

Brian R. Wood, MD
Associate Professor of Medicine
University of Washington
Mountain West AIDS Education & Training Center

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No conflicts of interests or relationships to disclose.
Outline

• Today: update on long-acting ART
  - IM cabotegravir + rilpivirine: FLAIR, ATLAS, ATLAS-2M
  - SubQ GS-6207 (capsid inhibitor)

• Next week: update on dual ART and HIV cure
  - DTG/3TC initial ART: 96-week results
  - Ilatravir + doravirine metabolic outcomes
  - Sustained HIV remission in the London Patient
Long-Acting IM Cabotegravir + Rilpivirine
Long-Acting IM Cabotegravir-Rilpivirine (*Cabenuva*)
General Administration Strategy and Outstanding Questions

**Oral (Daily) Lead-In**
- Cabotegravir 30 mg QD
- + Rilpivirine 25 mg QD

**Loading (Injectable) x 1**
- Cabotegravir (600 mg)
- Rilpivirine (900 mg)

**Maintenance (Injectable)**
- Cabotegravir (400 mg)
- Rilpivirine (600 mg)

**Questions:**
- Optimal lead-in time?
- Maintenance frequency?
- Necessary oral bridge/tail?
Summary of Key Studies
Cabotegravir-Rilpivirine

• Phase 2 Trials in Treatment Naïve
  - LATTE: Oral CAB-RPV daily versus EFV plus 2 NRTI’s
  - LATTE-2: IM CAB-RPV q1 or 2 months vs. oral CAB + ABC-3TC

• Phase 3 Trials in Treatment Naïve
  - FLAIR: IM CAB-RPV every month versus oral DTG-ABC-3TC

• Phase 3 Trials in Treatment Experienced
  - ATLAS: Switch to monthly IM CAB-RPV or stay on 3-drug ART
  - ATLAS-2M: switch to IM CAB-RPV every one or two months
  - LATITUDE: IM CAB-RPV for persons with detectable HIV RNA
Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction

FLAIR Study
**Study Design: FLAIR**

- **Background**: Phase 3, randomized, open-label, trial assessing IM CAB-RPV after oral induction for treatment-naïve adults

- **Inclusion Criteria**
  - Age ≥18
  - Antiretroviral-naïve
  - HIV RNA ≥1,000 copies/mL
  - Any CD4 count
  - No chronic hepatitis B
  - No NNRTI resistance

**Lead-In Phase**

- Week 16
- Week 20

- Switch to oral CAB+RPV if randomized to IM arm

**Maintenance Phase**

- IM CAB + RPV Every 4 Weeks (n = 283)

- Continue DTG-ABC-3TC (n = 283)

Both arms: continued to Maintenance Phase if HIV RNA <50 copies/mL from week 16 to 20

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction FLAIR Study: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IM CAB + RPV (n = 283)</th>
<th>Oral ART (n = 283)</th>
<th>Overall (n = 566)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Female, n, %</td>
<td>63 (22)</td>
<td>64 (23)</td>
<td>127 (22)</td>
</tr>
<tr>
<td>White, n, %</td>
<td>216 (76)</td>
<td>201 (71)</td>
<td>417 (74)</td>
</tr>
<tr>
<td>Black, n, %</td>
<td>47 (17)</td>
<td>56 (20)</td>
<td>103 (18)</td>
</tr>
<tr>
<td>Median body-mass index</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>CD4 count &lt;200 cells/mm³, n, %</td>
<td>16 (6)</td>
<td>23 (8)</td>
<td>39 (7)</td>
</tr>
<tr>
<td>CD4 count ≥500 cells/mm³, n, %</td>
<td>108 (38)</td>
<td>108 (38)</td>
<td>216 (38)</td>
</tr>
<tr>
<td>HIV RNA &gt;200k copies/mL, n, %</td>
<td>26 (9)</td>
<td>23 (8)</td>
<td>39 (7)</td>
</tr>
<tr>
<td>HIV RNA 10k-50k copies/mL, n, %</td>
<td>95 (34)</td>
<td>113 (40)</td>
<td>208 (37)</td>
</tr>
</tbody>
</table>

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction FLAIR Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)

Long-Acting IM Cabotegravir and Rilpivirine after Oral Induction FLAIR Study: Results

Week 96: Virologic Response by FDA Snapshot Analysis (ITT)

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>96 weeks</th>
<th>IM CAB + RPV</th>
<th>Oral DTG-ABC-3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>86.6</td>
<td></td>
<td>89.4</td>
</tr>
</tbody>
</table>

HIV RNA ≥50 copies/mL at 96 weeks: 3.2% CAB-RPV, 2.5% DTG-ABC-3TC

### Participants in the IM CAB + RPV arm with viral rebound meeting protocol-defined criteria for genotype resistance testing

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype, Viral Load (Baseline)</th>
<th>Baseline INSTI RAMs</th>
<th>Baseline NNRTI RAMs</th>
<th>Viral Load at Confirmed Virologic Failure</th>
<th>INSTI RAMs at Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A1, 54,000 copies/mL</td>
<td>L74I</td>
<td>None</td>
<td>456 copies/mL</td>
<td>L74I, Q148R</td>
</tr>
<tr>
<td>M, Russia, A1, 23,000 copies/mL</td>
<td>L74I</td>
<td>None</td>
<td>299 copies/mL</td>
<td>L74I, G140R</td>
</tr>
<tr>
<td>F, Russia, A1, 20,000 copies/mL</td>
<td>L74I</td>
<td>None</td>
<td>440 copies/mL</td>
<td>L74I, Q148R</td>
</tr>
</tbody>
</table>

There were also 3 virologic failures in the DTG-ABC/3TC arm; no new RAM’s detected

Abbreviations: RAMs = resistance associated mutations

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### Drug-Related Adverse Events and Injection Site Reactions (ISRs)

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>IM CAB + RPV (N = 283)</th>
<th>Oral ART (N = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>236</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Any AE, excluding ISR</td>
<td>79 (28)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>14 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 or 4 AE, excluding ISR</td>
<td>4 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Any injection site pain</td>
<td>227 (80)</td>
<td>NA</td>
</tr>
<tr>
<td>Grade 3 or 4 injection site pain</td>
<td>11 (4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Conclusions: “Therapy with long-acting cabotegravir plus rilpivirine was noninferior to oral therapy with dolutegravir–abacavir–lamivudine with regard to maintaining HIV-1 suppression. Injection-site reactions were common.”
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS Study
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Design

**Study Design: ATLAS**

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB-RPV after oral induction for adults taking 3-drug oral ART
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an INSTI, NNRTI, boosted PI, or unboosted atazanavir, plus 2 NRTI’s
  - Stable regimen & HIV RNA <50 copies/mL for ≥ 6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance (K103N allowed)
  - No chronic hepatitis B

## ATLAS: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IM CAB + RPV (n = 308)</th>
<th>Oral ART (n = 308)</th>
<th>Overall (n=616)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median</td>
<td>40</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Female, n, %</td>
<td>99 (32)</td>
<td>104 (34)</td>
<td>203 (33)</td>
</tr>
<tr>
<td>White, n, %</td>
<td>214 (69)</td>
<td>207 (67)</td>
<td>421 (68)</td>
</tr>
<tr>
<td>Black, n, %</td>
<td>62 (20)</td>
<td>77 (25)</td>
<td>139 (23)</td>
</tr>
<tr>
<td>Median body-mass index</td>
<td>26</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>CD4 count &lt;350 cells/mm³, n, %</td>
<td>23 (7)</td>
<td>27 (9)</td>
<td>50 (8)</td>
</tr>
<tr>
<td>Time since first ART (months), median, range</td>
<td>52 (7-222)</td>
<td>52 (7-257)</td>
<td>52 (7-257)</td>
</tr>
<tr>
<td>Third class agent, n, %</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>NNRTI</td>
<td>155 (50)</td>
<td>155 (50)</td>
<td>310 (50)</td>
</tr>
<tr>
<td>INSTI</td>
<td>102 (33)</td>
<td>99 (32)</td>
<td>201 (33)</td>
</tr>
<tr>
<td>PI</td>
<td>51 (17)</td>
<td>54 (18)</td>
<td>105 (17)</td>
</tr>
</tbody>
</table>

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance ATLAS Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis

HIV RNA < 50 copies/mL (%)

- IM CAB + RPV: 92.5%
- 3-drug oral ART: 95.5%

HIV RNA ≥ 50 copies/mL at 48 weeks: 1.6% CAB-RPV, 1.0% 3-drug oral ART

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS Study: Results

There were also 4 virologic failures in the oral ART arm; new RAMs detected included one instance of G190S, one M184I, and one M230M/I.

Abbreviations: RAMs = resistance associated mutations

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype</th>
<th>Baseline INSTI RAMs</th>
<th>Baseline NNRTI RAMs</th>
<th>Viral Load at Confirmed Virologic Failure</th>
<th>INSTI RAMs at Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A/A1</td>
<td>L74I</td>
<td>E138E/A</td>
<td>25,745 copies/mL</td>
<td>L74I</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>None</td>
<td>V108V/I, E138K</td>
<td>258 copies/mL</td>
<td>None</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>L74I</td>
<td>None</td>
<td>1841 copies/mL</td>
<td>N155H, L74I</td>
</tr>
</tbody>
</table>

### Injection Site Reactions (ISRs)

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Baseline N = 308</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants who received injections, n</td>
<td>303</td>
</tr>
<tr>
<td>Any reaction, n (%)</td>
<td>250 (81)</td>
</tr>
<tr>
<td>Pain, n (%)</td>
<td>231 (75)</td>
</tr>
<tr>
<td>Grade 3 pain, n, (%)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Pain leading to withdrawal</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Nodule, n (%)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Induration, n (%)</td>
<td>30 (10)</td>
</tr>
<tr>
<td>Swelling, n (%)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Median duration of reaction, days</td>
<td>3</td>
</tr>
</tbody>
</table>

The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS-2M Study
Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance

ATLAS-2M Study: Design

**Study Design: ATLAS-2M**

**Background:** Phase 3, randomized, open-label trial assessing IM CAB-RPV q2 months after oral induction for adults taking 3-drug oral ART

**Inclusion Criteria**
- Adults from ATLAS receiving monthly IM CAB + RPV or oral ART with HIV RNA <50 copies/mL at 52 weeks
- Adults receiving standard oral ART outside of ATLAS with HIV RNA <50 copies/mL for ≥6 months; no prior virologic failure (K103N ok)

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**Lead-In**

**Maintenance**

**Week 4**

- Daily oral CAB + RPV (except if from ATLAS IM arm)

**Week 48**

- IM CAB + RPV Every 8 Weeks (n = 522)
- IM CAB + RPV Every 4 Weeks (n = 523)

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS-2M Study: Results

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)

HIV RNA < 50 copies/mL (%)

<table>
<thead>
<tr>
<th>48 weeks</th>
<th>Q8 Week</th>
<th>Q4 Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94.3</td>
<td>93.5</td>
</tr>
</tbody>
</table>

HIV RNA ≥ 50 copies/mL at 48 weeks: 1.7% Q8 week arm, 1.0% Q4 week arm

Long-Acting IM Cabotegravir and Rilpivirine for HIV Maintenance
ATLAS-2M Study: Results

<table>
<thead>
<tr>
<th>Virologic Failures and Resistance-Associated Mutations (RAMs)</th>
<th>Q8 Week (n = 522)</th>
<th>Q4 Week (n = 523)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed VF, n, %</td>
<td>8 (1.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Rilpivirine RAMs detected at VF, n</td>
<td>6/8</td>
<td>1/2</td>
</tr>
<tr>
<td>Specific rilpivirine RAMs detected at VF</td>
<td>K101E, E138E/K, E138A, Y188L</td>
<td>K101E, M230L</td>
</tr>
<tr>
<td>Pre-existing rilpivirine RAM’s detected, n</td>
<td>5/6</td>
<td>0/2</td>
</tr>
<tr>
<td>INSTI RAMs detected at VF, n</td>
<td>5/8</td>
<td>2/2</td>
</tr>
<tr>
<td>Specific INSTI RAMs detected at VF</td>
<td>Q148R, N155H</td>
<td>E138E/K, Q148R, N155N/H</td>
</tr>
<tr>
<td>Pre-existing INTI RAMs detected, n</td>
<td>1/5</td>
<td>0/2</td>
</tr>
</tbody>
</table>

5/8 in Q8 week arm had L74I polymorphism at baseline (3 subtype A)
9/10 VF’s in study re-suppressed on fully active oral ART; all 10 retained phenotypic susceptibility to DTG
Injection site reactions frequent but 98% grade 1/3; median duration 3 days

Reflections on Long-Acting CAB-RPV

• May be an excellent option for carefully selected individuals
  - No resistance, likely to adhere to regular injections, no hep B
  - Struggling with pill fatigue, swallowing pills, stigma, transitions out of hospital/corrections setting

• Many operational & clinical questions
  - Burden on clinic staff if injections must be given in clinic
  - Risk of missed doses
  - Optimal oral bridge for missed doses, tail for stopping
  - Role for persons with imperfect adherence/detectable VL
  - Injection site reaction fatigue over time
  - Metabolic/weight gain differences over standard oral ART

See also: Currier J. NEJM. March 2020;382(23)
Subcutaneous GS-6207 (Capsid Inhibitor)

Dose-Ranging Study
Dose Response Relationship of SubQ Capsid Inhibitor

- Novel mechanism of action; active with RAM’s to other ART
- SubQ dosing \( q \geq 12 \) weeks likely maintains adequate levels

Dose Response Relationship of SubQ Capsid Inhibitor

Subcutaneous GS-6207: Antiviral Activity

Dose Response Relationship of SubQ Capsid Inhibitor

Dose-response Relationship Between GS-6207 and Antiviral Activity: $E_{\text{max}}$ Model*

<table>
<thead>
<tr>
<th>GS-6207 SC Dose (mg)</th>
<th>Mean Day 10 Concentration, ng/mL (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO 20</td>
<td>2.6 (41.5)</td>
</tr>
<tr>
<td>50</td>
<td>4.4 (89.9)</td>
</tr>
<tr>
<td>150</td>
<td>13 (39.3)</td>
</tr>
<tr>
<td>450</td>
<td>38 (35.1)</td>
</tr>
<tr>
<td>750</td>
<td>79 (27.7)</td>
</tr>
</tbody>
</table>

*Each dot represents mean HIV-1 RNA reduction in each dosed group. CV, coefficient of variation; $E_{\text{max}}$, maximal effect.

Dose Response Relationship of SubQ Capsid Inhibitor
Investigator Conclusions

• Single subQ doses of GS-6207 had potent antiviral activity
• In a blinded safety review, GS-6207 was safe
• Most common AEs were self-limiting, mild to moderate injection-site reactions
• Results support further evaluation of GS-6207 as a long-acting ARV agent with a q6 month dosing interval
• Two clinical trials planned – treatment-naïve & experienced

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