Introducing Injectables: Behavior and Adherence Implications

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Disclosures

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Background

• Interest from PLHIV for LA therapy has been high for many years
  – 88% 13-24 y/o probably or definitely interested in using LA ART\(^1\)
  – Notably, provider surveys show more caution around LA use and populations
    • Largely anticipating use in patients with longstanding oral adherence issues, mental health, adolescents
  – This provider-patient interest gap highlights a number of interesting perspectives around LA therapy and HIV

What is driving patient interest?

• #1 – Stigma around an HIV diagnosis, both externally and internally derived, remains a very real fact

• #2 – Disclosure of HIV is perhaps the one area an individual retains the greatest control over their status
  – Fear of inadvertent disclosure

• #3 – Burden of disease, psychological challenges, can match actual physical manifestations

• #4 - Convenience
Why are providers more cautious around potential use of LA therapy?

• LA therapy introduces challenges patients may not always be considering
  – Unique safety concerns with LA, long PK tail, efficacy data still emerging
• Implementation challenges of a new treatment modality
• Why would a patient chose an IM shot over a simple small oral pill?
• Hard to fully quantify the psychological advantages patients may see around LA dosing vs daily oral Rx
CAB + RPV LA Background

- Cabotegravir (CAB) is an HIV-1 INI
  - Oral 30 mg tablet: $t_{1/2} \sim 40$ hours
  - Long-acting IM injection, 200 mg/mL: $t_{1/2} \sim 40$ days

- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25 mg tablet: $t_{1/2} \sim 50$ hours
  - Long-acting IM injection, 300 mg/mL: $t_{1/2} \sim 90$ days

- LATTE-2: CAB LA + RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years\(^1\)

- Two pivotal phase 3 studies (ATLAS and FLAIR\(^2\)) have reached their primary endpoints at 48 weeks

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CAB LA formulation allows for lower injection volumes

- Drug crystal suspended in aqueous vehicle\(^1,2\)
- Milled to nanometer size to increase surface area and drug dissolution rate\(^1,2\)
- Higher drug loading versus matrix approaches for lower injection volume\(^1,2\)

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### CAB LA 200 mg/mL\(^2\)

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB free acid (D50 ~200 nm)</td>
<td>Active drug</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant system</td>
<td>Wetting agent/stabiliser</td>
</tr>
<tr>
<td>Water for injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

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2. Spreen W et al. AIDS 2013. Abstract WEAB0103
CAB LA single injection provides detectable drug in plasma for 52 weeks

Mean CAB concentration–time profile

CAB LA apparent t½ ~40 days vs CAB oral t½ ~40 hours

Oral Dosing CAB + RPV complements LA dosing

• Oral Lead-in to assess individual patient tolerability prior to initiating LA
  – Studies underway to assess for optional use of the oral lead-in

• Oral bridging therapy to allow for planned missed LA injection visits
  – Vacation, travel, unexpected absences
Phase 3 FLAIR Study Design: Randomized, Multicenter, International, 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†
- Day 1 100 Week 4
- Oral CAB + RPV n=283
- CAB LA (400 mg) + RPV LA (600 mg)‡
- Oral daily n=283
- IM monthly n=278

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

**Extension Phase**
- Week 48
- N=629
- DTG/ABC/3TC
- Oral daily n=283
- CAB LA (400 mg) + RPV LA (600 mg)‡
- IM monthly n=278

**Study Week**
- −20
- −4
- Day 1
- 4§
- 96
- 100

**Confirm HIV-1 RNA <50 copies/mL**

**Randomization (1:1)**

**Primary endpoint**

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* NNRTI RAMS but not K103N were exclusionary.
† DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive
‡ Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up.
§ Participants received initial loading doses of CAB LA 600 mg and RPV LA 900 mg at Week 4. Beginning Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections every 4 wks.
FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

Virologic Outcomes

Primary endpoint:
LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48

Adjusted Treatment Difference (95% CI)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (%)</th>
<th>Adjusted Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB LA + RPV LA</td>
<td>-2.8</td>
<td>6% NI margin</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

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).

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

**Virologic Outcomes**

- Proportion of Participants (%)

| Virologic nonresponse (≥50 c/mL) | 2.1 | 2.5 |
| Virologic success (<50 c/mL) | 93.6 | 93.3 |
| No virologic data | 4.2 | 4.2 |

**Adjusted Treatment Difference (95% CI)**

- **Primary endpoint:** LA noninferior to DTG/ABC/3TC (≥50 c/mL) at Week 48
  - Difference (%)
    - CAB LA + RPV LA: 2.1
    - DTG/ABC/3TC: -2.8
  - Adjusted Treatment Difference: 6% NI margin

- **Key secondary endpoint:** LA noninferior to DTG/ABC/3TC (<50 c/mL) at Week 48
  - Difference (%)
    - CAB LA + RPV LA: 4.5
    - DTG/ABC/3TC: -3.7
  - 3 CVFs on LA
  - Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

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

Phase 3 ATLAS Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Adults with Virologic Suppression

**Screening Phase**
- N=705
- PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone*

**Maintenance Phase**
- PI, NNRTI or INSTI†
  - Current daily oral ART n=308
- Oral CAB + RPV n=308
- CAB LA (400 mg) + RPV LA (600 mg)§
  - IM monthly n=303

**Extension Phase‡**
- Extension Phase or transition to the ATLAS-2M study

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* Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2 × VL <50 c/mL ≤12 months
† INSTI-based regimen capped at 40% of enrolment; Triumeq excluded from study
‡ Optional switch to CAB LA + RPV LA at Week 52 for those on CAR
§ Participants who withdraw/complete IM CAB LA + RPV LA must complete 52 weeks of follow-up;
‖ Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks.
ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

Virologic Outcomes

Adjusted Treatment Difference (95% CI)*

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

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.

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

### Virologic Outcomes

| Virologic nonresponse (≥50 c/mL) | 1.6 | 1.0 |
| Virologic success (<50 c/mL) | 92.5 | 95.5 |
| No virologic data | 5.8 | 3.6 |

**CAB LA + RPV LA** (n=308)

- No virologic data:
  - CAB LA + RPV LA: 3.6%
  - CAR: 0.7%

- Virologic success:
  - CAB LA + RPV LA: 95.5%
  - CAR: 92.5%

- Virologic nonresponse:
  - CAB LA + RPV LA: 1.6%
  - CAR: 1.0%

### Adjusted Treatment Difference (95% CI)*

- **Primary endpoint:** LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48
  - Adjusted Treatment Difference: -1.2%
  - 6% NI margin

- **Key secondary endpoint:** LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48
  - Adjusted Treatment Difference: -6.7%
  - ~10% NI margin

- 3 CVFs on LA

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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.

The majority (99%, 1439/1460) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days.

**Participants with ISRs (%)**

**Event**

<table>
<thead>
<tr>
<th>Event</th>
<th>CAB LA + RPV LA N=308</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants receiving injections, n</td>
<td>303</td>
</tr>
<tr>
<td>Injections given, n</td>
<td>6978</td>
</tr>
<tr>
<td>ISR events, n (%)</td>
<td>1460 (20.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>1208 (82.7)</td>
</tr>
<tr>
<td>Nodule</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>Induration</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>Swelling</td>
<td>48 (3.3)</td>
</tr>
<tr>
<td>Grade 3 ISR pain</td>
<td>20 (1.7)</td>
</tr>
<tr>
<td>Median duration of ISRs, days</td>
<td>3</td>
</tr>
<tr>
<td>Participants with ISR leading to withdrawal, n (%)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

**Bars** represent incidence of onset ISRs relative to the most recent IM injection visit.

CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.
Timing of Injections Relative to Date of Projected Injection Visits – LATTE-2
ATLAS: High Participant Satisfaction (HIVTSQs)

**HIVTSQs Total Score**

<table>
<thead>
<tr>
<th>Week 24*</th>
<th>Week 44*</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

- **CAB LA + RPV LA**
- **CAR**

**Improvement**

<table>
<thead>
<tr>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.39 (4.17–6.60), p&lt;0.001</td>
</tr>
<tr>
<td>5.68 (4.37–6.98), p&lt;0.001</td>
</tr>
</tbody>
</table>

- The CAB + RPV group were more satisfied with the monthly injectable treatment compared with participants receiving CAR.

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CAB, cabotegravir; CAR, current antiretroviral; HIVTSQs, HIV Treatment Satisfaction Questionnaire (Status); ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

*Adjusted mean change from baseline; adjusted for baseline score, sex, age, race, and baseline third agent class. Error bars show 95% confidence interval. n=300 for CAB + RPV at Week 24 and n=300 at Week 48; n=288 for CAR at Week 24 and n=294 at Week 48.

"For the past 44 weeks you have received CAB LA + RPV LA injections every month. Today we would like you to compare your experience on the injections with the oral medication you received prior to entering the study. Which therapy do you prefer?"

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<table>
<thead>
<tr>
<th>Preference</th>
<th>Q4W IM (N=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Injection</td>
<td>266 (86.4%)</td>
</tr>
<tr>
<td>Daily Oral</td>
<td>7 (2.3%)</td>
</tr>
</tbody>
</table>

- Of 273 responses, 97% preferred monthly injection over daily oral.

<table>
<thead>
<tr>
<th>Preference</th>
<th>Q4W IM (N=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Injection</td>
<td>257 (90.8%)</td>
</tr>
<tr>
<td>Daily Oral</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>

- Of 259 responses, 99% preferred monthly injection over daily oral.
Structured qualitative Interviews with patients on CAB + RPV LA – LATTE-2 Study

• *One day is nothing...it’s as if you have a day with a headache. You take ibuprofen and that’s it. You put up with it. It’s temporary.*–Spain, Male trial participant

• *It might be painful, but it’s better than pills.*–U.S., Male trial participant

Worry and Stigma

It seems to me that it’s much better because you simply don’t have to worry about anything. If you go on a trip, you don’t have to bring your pills or take anything at all along. You follow your ‘normal life.’ You come once a month. You get the shot and it’s over. You don’t have to be thinking everyday ...oh I forgot to take the pill.....—Spain, Male trial participant

It's less and less stigmatized with the injection, because I don't feel like I'm reminding myself of [HIV]...with the injection you go through days and weeks...two months not having to worry about that, so it's less stigmatized.—U.S., Male trial participant

ACTG 5359: A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

• ~350 Patients with prior ART failure
• CAB + RPV fully active
• Intensive adherence support/payments 24 weeks
• LA vs SOC – superiority trial
Future direction of LA

- If approved, CAB + RPV LA will help establish future goal posts for future LA regimens
- Longer dosing intervals possible
  - Q2M under evaluation with CAB + RPV
  - bNAbs, Implants
- Other combinations – bNAbs, Capsid inhibitor, NRTTI, Maturation inhibitor
- Other approaches – microneedle patches, implants
Remaining Challenges

• Longer term data of efficacy and tolerability is desirable
  – LATTE-2 5 year data (2020)
  – FLAIR 96 week data (2019)

• Shifting burden of adherence/compliance from the patient to the provider
  – Infrastructure for patient reminders, follow up, clinic visit burden
  – Can alternative injectors be considered (pharmacists, home health, etc.)?

• Implementation research is needed to inform how to address the treatment paradigm shift and patient flow
  – Better understanding health care costs and utilization
Conclusions

• LA therapy in HIV has long been an aspirational goal for patients

• Work needs to be done on understanding who the most appropriate patients are for therapy, how to best meet the needs/desires of patients and how to implement in various clinical settings
Thank You