Long-Acting Antiretrovirals for Treatment

Tim Horn
June 26, 2019, FAPP Meeting
Potential Advantages of LA ART

- Address suboptimal adherence
- Ameliorate challenges associated with oral medications, including gastrointestinal, neurologic, or psychiatric disease
- Less frequent dosing & avoidance of pill fatigue
- Protection of health privacy
- Avoidance of HIV risk- and prevention-related stigma
LA Contraceptives

- Numerous products
  - IM and implantable progesterone analogs; hormone-imbedded intrauterine devices; etonogestrel and levonorgestrel implants (3–5 years)
- Most popular form of birth control in many parts of the world (60–80% of women using contraceptives in sub-Saharan Africa)\(^1\)

LA Antipsychotics

- Several long-acting products commercially available
- Indicated for schizophrenia, notably with risk factors for poor adherence
  - History of non-adherence
  - Substance use
  - Cognitive impairment
  - Ambivalence or negative attitudes toward
<table>
<thead>
<tr>
<th>ARV Class</th>
<th>Agent</th>
<th>Formulation</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>MK-8591</td>
<td>Implant</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>TAF</td>
<td>Implant</td>
<td>Preclinical (Px)</td>
</tr>
<tr>
<td></td>
<td>GS-9131</td>
<td>Implant</td>
<td>Preclinical</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Rilpivirine</td>
<td>Injectable</td>
<td>Phase III/NDA</td>
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<td></td>
<td>Elsulfavirine</td>
<td>Injectable</td>
<td>Preclinical</td>
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<tr>
<td>PI</td>
<td>Atazanavir</td>
<td>Injectable</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>Ritonavir</td>
<td>Injectable</td>
<td>Preclinical</td>
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<tr>
<td>INSTI</td>
<td>Cabotegravir</td>
<td>Injectable</td>
<td>Phase III/NDA,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Phase II/III (Px)</td>
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<tr>
<td></td>
<td>Raltegravir</td>
<td>Injectable</td>
<td>Preclinical</td>
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<tr>
<td>Entry Inhibitors</td>
<td>Ibalizumab</td>
<td>Intravenous</td>
<td>FDA Approved (Tx)</td>
</tr>
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<td></td>
<td>PRO 140</td>
<td>Intravenous and Injectable</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Albuvirtide</td>
<td>Intravenous and Injectable</td>
<td>Approved in China</td>
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<tr>
<td></td>
<td>bNAbs (e.g., VRC01)</td>
<td>Intravenous</td>
<td>Phase II/III</td>
</tr>
<tr>
<td></td>
<td>Combinectin</td>
<td>Intravenous</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Capsid Inhibitors</td>
<td>GS-CA1</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
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</table>
Long-Acting Cabotegravir/Rilpivirine (CARLA)

- **Cabotegravir**: Strand-transfer integrase inhibitor being developed for HIV Tx and Px; analog of dolutegravir
- **Rilpivirine**: Non-nucleoside reverse transcriptase inhibitor; first approved May 2011
- Formulated as a long-acting injectable nanosuspensions for intramuscular (IM) administration
- Also formulated/available as an immediate-release oral tablets for daily administration
- Possible FDA approval: Dec 2019 or Jan 2020
FLAIR: Randomized, Open-Label, Noninferiority Study in ART-Naïve Adults

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**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

**Extension Phase**
- Oral CAB + RPV n=283
- CAB LA (400 mg) + RPV LA (600 mg)

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

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

**Extension Phase**
- Oral CAB + RPV n=308
- CAB LA (400 mg) + RPV LA (600 mg)

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Noninferiority Achieved for Primary and Secondary Endpoints

**FLAIR Virologic Outcomes**

- Proportion of Participants (%)
- Virologic nonresponse (≥50 c/mL)
- CAB LA + RPV LA (n=283)
- DTG/ABC/3TC (n=283)
- Proportion of Participants (%)
- CAB LA + RPV LA (n=283)
- DTG/ABC/3TC (n=283)

- 2.1 2.5 93.6 93.3 4.2 4.2
- 1.6 1.0 92.5 95.5 5.8 3.6

**ATLAS Virologic Outcomes**

- PROPORTION OF PARTICIPANTS (%)
- Virologic nonresponse (≥50 c/mL)
- CAB LA + RPV LA (n=308)
- CAR (n=308)

- 1.6 1.0 92.5 95.5 5.8 3.6

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

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 139.
## FLAIR & ATLAS Injection Site Reactions

<table>
<thead>
<tr>
<th></th>
<th>FLAIR CAB+RPV (LA) N=283</th>
<th>ATLAS CAB+RPV (LA) N=308</th>
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</thead>
<tbody>
<tr>
<td>Participants receiving injections</td>
<td>278</td>
<td>303</td>
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<tr>
<td>Injections given</td>
<td>7,708</td>
<td>6,978</td>
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<tr>
<td>ISR events</td>
<td>2,203 (28.6)</td>
<td>1,460 (20.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>1,879 (85.3)</td>
<td>1,208 (82.7)</td>
</tr>
<tr>
<td>Nodule</td>
<td>86 (3.9)</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>Induration</td>
<td>82 (3.7)</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>Swelling</td>
<td>38 (1.7)</td>
<td>48 (3.3)</td>
</tr>
<tr>
<td>Warmth</td>
<td>38 (1.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Grade 3 ISR pain</td>
<td>12 (&lt;1)</td>
<td>20 (1.7)</td>
</tr>
<tr>
<td>Median duration of ISRs, days</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Participant with ISR leading to withdrawal</td>
<td>2 (&lt;1)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>
"They like not having to worry about taking their pills every day...they get their injection and they're good to go. They don't have to think about having HIV every day, they don't have to worry about co-workers or housemates seeing their pill bottles – there's maybe some relief of the stigma of HIV if they don't have to think about it every day."

– Dr. Susan Swindells, University of Nebraska, ATLAS Investigator

**FLAIR and ATLAS Participant Satisfaction**

- **FLAIR**: 99% preferred the LA regimen over induction phase treatment
- **ATLAS**: 97% preferred LA regimen over previous oral therapy
Dosing and Administration

- Dosing
  - Oral regimen to achieve virologic suppression – minimum of 20 weeks (FLAIR)?
  - Four-week oral lead-in dosing with cabotegravir and rilpivirine?
  - Loading CARLA doses: 2 injections of 3 mL
  - Maintenance CARLA doses every four weeks: 2 injections of 2 mL

- Cold-chain storage required (for rilpivirine)

- Scheduling, privacy/exam room space, provider availability, follow up, benefits determination/coordination
Intramuscular Administration

- May require staff training
- Not evaluated in people with buttock implants
- Need private space for administration

Gluteus Medius

Z-Tracking
Clinical Questions

- Will we see INSTI/NNRTI resistance for those who do not return for treatment?
- How will providers manage treatment-emergent drug-related toxicities?
- How will providers manage drug interactions, including for TB treatment?
- Will teratogenicity/birth defects be a problem? Example: neural tube defects?
  - ATLAS/FLAIR: Volunteers had to agree not to get pregnant for five years
Procurement

- Will only be available from specialty pharmacies/distributors
  - **Buy-and-bill**: Provider purchases drug/biologic product and bills primary payer
  - **White bagging**: Specialty pharmacy adjudicates claim and ships product to provider for administration
  - **Brown bagging**: Specialty pharmacy adjudicates claim; product acquired by patient and taken to provider for administration
Provider Administration

- Viiv Healthcare primarily focused on clinic and office administration
- Clients living with HIV usually seen every three to six months
- Capacity and staffing to support monthly injections – scheduling, exam rooms, wait times, MD/PA/NP/RN availability, drug product storage and inventory management
- Capacity and staffing to support monthly retention; client reminders and diligent missed-appointment follow up
- RWHAP provider network sufficiency to meet monthly administration needs of clients where they are (Pharmacy? Home health?)
- Pharmacies: state law/policy dependent; capacity/space, expertise, cultural competence
Payment: Medical vs. Pharmacy Benefit

- **Medical Benefit**
  - Providers purchase LA-ARV and bill payer for drug, administration, and any other associated office visit costs; mixed cost sharing

- **Pharmacy Benefit**
  - Prescription submitted to pharmacy and pharmacy ships drug to physician office (white bagging) or gives to patient (brown bagging)
  - Pharmacy bills for drug cost and charges drug cost sharing
  - Provider bills for administration and other associated office visit costs and charges medical cost sharing
<table>
<thead>
<tr>
<th>Drug coverage and transparency</th>
<th>Medicaid</th>
<th>Medicare</th>
<th>Commercial Insurance</th>
<th>RWHAP/ADAP</th>
</tr>
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<tr>
<th>Consumer cost sharing</th>
<th>Medicaid</th>
<th>Medicare</th>
<th>Commercial Insurance</th>
<th>RWHAP/ADAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/administration: Nominal copay</td>
<td>Part B: 20% of Medicare allowable cost (drug/admin bundled) Part D: separate drug and visit/admin cost sharing No manufacturer copay assistance</td>
<td>Drug/administration: copay/coinsurance Office visit” copay/coinsurance (sometimes bundled):</td>
<td>Separate processing of drug and medical copays</td>
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<thead>
<tr>
<th>Acquisition and distribution</th>
<th>Medicaid</th>
<th>Medicare</th>
<th>Commercial Insurance</th>
<th>RWHAP/ADAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Buy and bill” reimbursement; white/brown bagging sometimes prohibited</td>
<td>“Buy and bill” reimbursement if Part B; white/brown bagging if Part D</td>
<td>“Buy and bill” reimbursement OR white/brown bagging using specialty pharmacy (state and issuer variation)</td>
<td>“Buy and bill” reimbursement OR white/brown bagging through specialty pharmacy; pharmacist or home admin (e.g., VNA)?</td>
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Summary

- CARLA represent a game-changer for many people living with HIV and the health care and payer systems they depend on
- CARLA will be expensive – potential for high drug costs; office visit and administration fees
- Long-acting injectables frequently subject to prior authorization and step therapy in psychiatric and arthritis/inflammatory disease area
- How should we ensure ethical, clinically-based, and cost-effective medication access as the HIV treatment landscape becomes more competitive?
THANK YOU!