Long-Acting ART: What is on the Horizon? Are we Ready?
• Formulation & Delivery Fixes for Adherence Issues
• Long-Acting ART: What are the new Aspects?
• Long-Acting ART: What is coming?
• CAB-LA and RPV-LA: On the Near Horizon
  • The New Frontiers
• ART Implants: On the Far Horizon
• Are We Ready?
  • Gaps in Existing Technologies & Knowledge
  • What Are the Questions?
Delivery & Formulation Fixes for Adherence Issues

a. (x 1, on Day 1)

b. (x 2)

c. (swallowed x 1, on Day 1)

d. (Apply and remove, every 28 days)

e. Treatment Method

Time (days)

1 28 56

Healthwise, Inc.; drugs.com (A.D.A.M.); latimes.com; Gilead Sciences; dailymail.co.uk; brooksinfeta.com; Alkilani AZ, *Pharmaceutics 2015*, 7(4), 438-470
HIV pipeline 2020: targets in the HIV lifecycle

1. Entry inhibitors
   - Combinetin (GSK3732394)
   - NRTIs/NRTTIs (nukes)
     - Islatravir (EFdA)
     - MK-8504, MK-8583
   - NNRTIs (non-nukes)
     - Elsulfavirine
   - INIs (INSTIs)
     - Cabotegravir LA

2. Monoclonal antibodies (mAb)
   - UB-421 (CD4 receptor)
   - VRC01/LS and VRC07/LS
   - 3BNC117/LS and 10-1074/LS
   - PGDM1400, 10E8.4/mAb
   - PGT121 and elipivimab (GS-9722)
   - N6LS (gp120)
   - Jeronimab PRO-140 (CCRS)

3. HIV RNA
4. HIV DNA
5. Protease cuts new viral material
6. Maturation and budding

Targets in the HIV lifecycle
1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrate enables HIV to join the cell DNA.
5. Protease cuts and reassembles new HIV.
6. Final stages include maturation and budding as each cell produces hundreds of new virions.

Rev inhibitor
- ABX-464

Capsid inhibitors
- GS-6207
- GSK (pre-clinical)

Maturation inhibitors
- GSK'254 (oral)
- GSK 937 (LA)

HIV i-Base. March 2020 (www.i-Base.info)

= long-acting approach
*= as PrEP
Long-Acting ART¹ (LA-ART): What is Coming?

- Cabotegravir long-acting (CAB-LA) & Rilpivirine long-acting (RPV-LA)
- Islatravir (ISV; aka MK-8591, aka EfDA)
  - Implant: q 6-12 months
  - Oral: q day – q week (q Month as PrEP)
- Lenacapavir (aka GS-6207)
  - SC: q 6 months
  - PO: q week
- [Broadly neutralizing antibodies (bNAbs)]

LA-ART: What are the new aspects?

- Centering non-adherence, accommodating without blame
- DOT by definition (distinct from non-observed therapies)
  - De-linkage of individual behaviour from viral suppression
  - Until we investigate home self-injections
- Pay for Performance (P4P4P) ? easier than with daily oral strategies
  - Decrease in number of daily actions that need to be performed by PLWH
  - Adherence as a function of the number of daily actions needed is of interest
- Understanding real-world tolerability
  - Trade-off between frequency of dosing and acceptability of ISR, AEs
- Frequency of clinic visits higher (q Month) than with daily ART (q 6-12 months)
- What will the real-world frequency of missed injections/ resistance be?
- Pricing, availability, Ryan White/ ADAP, Administration/ personnel

Brantley AD et al., Public Health Rep 2018 Nov-Dec; 133(2 Suppl): 75S–86S. PMCID: PMC6262523

Rates of viral suppression after 6, 12, and 24 months of enrollment among patients enrolled in the Health Models pay-for-performance program at 3 urban HIV clinics, New Orleans and Baton Rouge, Louisiana, September 2013–September 2016
# Long Acting Cabotegravir & Rilpivirine

## Timeline & Important Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2017</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>FDA Submission Apr 2019</td>
</tr>
<tr>
<td>2019</td>
<td>FDA Declines Dec 2019</td>
</tr>
<tr>
<td>2020</td>
<td>FDA Resubmission Aug 2020</td>
</tr>
<tr>
<td>2021</td>
<td>EMA CHMP Positive Opinion Oct 2020</td>
</tr>
</tbody>
</table>

## Clinical Studies

### LATTE-1 LATTE-2

### FLAIR

- ATLAS

### ATLAS-2M POLAR

- EMA CHMP Positive Opinion Oct 2020

### CUSTOMIZE (U.S.) CARISEL (Europe)

## Importance

**FLAIR:** HIV VL<50 c/mL:
- 93.6% CAB/RPV LA
- 93.3% oral ART

**ATLAS:**
- Switch to qM LA CAB/RPV
- Non-inferior to oral ART

**ATLAS-2M POLAR:**
- q2M == q4wk
- 98% preferred LA-ART
- 94% preferred q2M to qM

First trials to explore implementation aspects of LA-ART:
- High acceptability
- Perceived barriers

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CUSTOMIZE study
N= 449 providers
Providing care during ATLAS-2M study
Europe, N. America, Asia, Africa, Latin America
• Primary outcome: overall feasibility of qmonth CAB-LA and RPV-LA
• Logistical barriers, benefits

Table 2. Provider Clinical Concerns With LA ART (Very/Somewhat Concerned):

<table>
<thead>
<tr>
<th>Concern</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not returning to clinic on time for injection appointments</td>
<td>224</td>
<td>79.7</td>
</tr>
<tr>
<td>Risk of resistance for patients not adherent to injections</td>
<td>195</td>
<td>69.4</td>
</tr>
<tr>
<td>Patients moving out of the area</td>
<td>182</td>
<td>64.8</td>
</tr>
<tr>
<td>Patients switching to a different provider</td>
<td>154</td>
<td>54.8</td>
</tr>
<tr>
<td>Drug interactions and comorbidities (e.g. TB, HCV)</td>
<td>138</td>
<td>49.1</td>
</tr>
<tr>
<td>Taking a patient off CAB LA + RPV LA and switching to oral ART</td>
<td>120</td>
<td>42.7</td>
</tr>
<tr>
<td>The oral lead-in phase before starting injections</td>
<td>68</td>
<td>24.2</td>
</tr>
</tbody>
</table>

Table 2 shows providers top concerns about patient management all focused on patients’ adhering to injection schedules:
• Patients not returning to the clinic on time for injection appointments (80%).
• Risk of resistance due to non-adherence to injection schedule (69%).
• Fear of patients moving out of area was mentioned by more than half (65%).
The New Frontiers for IM LA-CAB and LA-RPV

- Frequency of HIV RNA PCR checks?
  - Align with injections? Space out if remain suppressed?
- Therapeutic Drug Monitoring (TDM)
  - Check levels prior to injection? Individualized dosing frequency?
- Lower injection volume
- Identifying best candidates for LA-ART?
  - Patient-centered approaches
  - Eligibility scoring/ success predictors
- *Where* and *by whom* should injections be given?
  - Visiting health worker? RN? PLWH (*vastus lateralis*?)
Islatravir (ISL; EFdA; MK-8591)

- **Oral**
  - Linear PK for parent (plasma) and active triphosphate (TP) in PBMCs
    - Half-life of parent ISL: 50-60 hr
    - Half-life of active ISL-TP in PBMCs: 120-177 hr
  - Antiviral efficacy observed in monotherapy after single doses as low as 0.5 mg

PK-PD Modeling:
supports PrEP threshold 0.05 pmol/10^6 cells

Matthews R., TUAC0401LB, IAS 2019 (Mexico City).
Lenacapavir (LEN)

- FIC, Inhibits multiple capsid protein dependent functions
- Potent antiviral activity:
  - $T_{1/2} (SC) = 49-65$ days; $T_{1/2} (PO) = 11-13$ days
  - No food effect
  - Oral dosing: q 1 week
  - Subcutaneous dosing: q 6 months (oral lead-in 2/2 slow initial release)

## ART Implants on the Horizon

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swift/easy removal at the end of treatment or in setting of adverse effects</td>
<td>Specialized device with need for training/sterility/equipment/procedure for insertion &amp; removal</td>
</tr>
<tr>
<td>No oral lead-in required</td>
<td>Minor surgical procedure required to remove</td>
</tr>
<tr>
<td>No oral TDF/FTC needed to protect during subtherapeutic PK ‘tail’</td>
<td>Must be removed at the end of product lifespan</td>
</tr>
<tr>
<td>Lower dose/day</td>
<td>Impossible to discern from palpation how long the device has been in place</td>
</tr>
<tr>
<td>Can remain in place for years (require less interaction with healthcare system)</td>
<td>Can migrate from original insertion site to a place where palpation is difficult (esp. in beagles)</td>
</tr>
<tr>
<td>More consistent and predictable drug release kinetics</td>
<td>Regulated as both a drug and a device</td>
</tr>
<tr>
<td>PK properties may not depend on injection site</td>
<td>More complex uptake into generic marketplaces</td>
</tr>
<tr>
<td>Palpable under skin indicating its presence</td>
<td>Visibility (arm) &amp; possible stigma</td>
</tr>
<tr>
<td>Radio-opaque for visualization in case of unintended subcutaneous migration</td>
<td></td>
</tr>
<tr>
<td>Biodegradable versions also possible</td>
<td></td>
</tr>
<tr>
<td>Avoid high injection volumes</td>
<td></td>
</tr>
<tr>
<td>Implant type</td>
<td>Model</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Nonbiodegradable</td>
<td>Rats</td>
</tr>
<tr>
<td>Pure drug powder core, platinum microperforated silicone tubing, PVA coating</td>
<td>Beagle dogs</td>
</tr>
<tr>
<td>Releasable polymer nanochannel delivery implant (NDI)[1,5]</td>
<td>Rhesus macaques</td>
</tr>
<tr>
<td>- Titania drug reservoir</td>
<td></td>
</tr>
<tr>
<td>- Silicone nanochannel membrane</td>
<td></td>
</tr>
<tr>
<td>- Two sealable releasable silicone drug loading port</td>
<td></td>
</tr>
<tr>
<td>Silicone-based transdermal matrix-based [drug-in-adhesive] patch w polysorbate adhesives [5]</td>
<td>Dermatomed human cadaver skin</td>
</tr>
<tr>
<td>Biocompatible polymer blended with entecavir via hot melt extrudates and polymer coated tablets, both administered subcutaneously [16]</td>
<td>Rats (Wistar han)</td>
</tr>
<tr>
<td>- Titanium osmotic mini-pump system (Medici DDS™) [36]</td>
<td></td>
</tr>
</tbody>
</table>
| - Biodegradable and nonbiodegradable matrix-based polymer with islatravir [37] | Rats, NHP | Islatravir (ISL) aka Efda (MK-8591) | 2 mm x 40 mm | > 10 μg/mL/day for entire study | > 6 months (for 40 wt% and 60 wt% MK-8591 in PCL, and 50 wt% MK-8591 in EVA)  
> 12 months (for 60 wt% MK-8591 in PCL implants) |
| - Biodegradable and nonbiodegradable matrix-based polymer [29,39,40] (same polymer and applicator as Nexplanon) | Humans (healthy volunteers) | Islatravir (ISL) aka Efda (MK-8591) | 2 mm x 40 mm | 54 and 62 mg (0.17 mg/day) | 12 months+ |
| Birodegradable                                                               | Rhesus macaque | Doloregavir (DTG)            | 100 mg            |               |                             |
| - Ultralong-acting removable DTG/PGLA/NMP in 0.3:1:2 ratio [26] (formulation optimized for mice, not macaques) | Rhesus macaque | Doloregavir (DTG)            | 100 mg            |               |                             |
| - Ultralong-acting removable DTG/PGLA/NMP in 0.3:1:2 ratio [26] (formulation optimized for mice) | Humanized BLT mouse (prevention) | Doloregavir (DTG) | 1 cm | 250 mg/kg (0.7 mg/kg in DTG 50-80 μl) | > 5 months (flat shape of concentration: time curve at 140 days) |
| - Reservoir-style implant [26] (extruded tube of a biodegradable polymer, PCL, filled w TAF and castor oil excipient in 2:1 ratio) | In vitro | Tenofavir alafenamide (TAF) | 1.4 and 7 cm | Release rate: 0.28:0.06 mg/day (100 μm thickness) Range from 0.15 mg/day (for 200 μm thickness) to 0.91 mg/day (for 45 μm thickness) | 180 days (in vitro) |


**Islastravir**

**6-12 months**
Need for Multipurpose Implants

- ART plus...
  - Contraception
  - Opiate substitution therapy
  - Antipsychotic

<table>
<thead>
<tr>
<th>Drug and indication</th>
<th>Materials</th>
<th>Dose (mg/day)</th>
<th>Duration</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etonogestrel (Implanon; Nexplanon) Hormonal contraception</td>
<td>Ethylene vinyl acetate (EVA) copolymer, barium sulfate, magnesium stearate</td>
<td>65 mg (0.06 mg/day)</td>
<td>3 years</td>
<td>$2 \times 40$ mm (1 rod)</td>
</tr>
<tr>
<td>Levonorgestrel (Norplant; Jadelle) Hormonal contraception</td>
<td>Dimethylsiloxane/methylvinylsiloxane core in thin-walled silicone (provided w. disposable trocar)</td>
<td>150 mg (0.03–0.04 mg/day (p 12 months)</td>
<td>5 years</td>
<td>$2.5 \times 43$ mm (2 rods)</td>
</tr>
<tr>
<td>Buprenorphine (Probuphine) (subcutaneous) Matrix-style implant for maintenance treatment of opioid addiction</td>
<td>Drug released through four individual poly(ethylene-vinyl acetate) (EVA) rods</td>
<td>80 mg buprenorphine hydrochloride (0.44 mg/day)</td>
<td>6 months</td>
<td>$2.5 \times 26$ mm</td>
</tr>
<tr>
<td>Risperidone subcutaneous implant [32–34] Schizophrenia</td>
<td>Risperidone</td>
<td>375, 48, 720, or 960 mg (2, 2.7, 4, and 5.3 mg/day, respectively)</td>
<td>6 months</td>
<td>Not mentioned in primary publication</td>
</tr>
</tbody>
</table>

Gaps in Existing Technologies

• Multipurpose Treatment and Prevention (combined LA-ART & contraception)
• LA ART for prevention of vertical transmission (PMTCT); PrEP in pregnancy
• LA ART for Hepatitis B
• ISL, LCV, bNAbs, CAB/RPV: What are the partners? How well do the PK profiles need to match? How do you study DDIs? Are oral forms needed?
• TAF +/- FTC implants: local tissue necrosis issue  Su JT et al, AAC, 2020 Feb 21;64(3)
• First principles & modeling to predict which molecules and formulations will cause local toxicity
“Both the science and the art of medicine are advanced by **curiosity.**”
–Faith Fitzgerald, Ann Int Med 1999; 130:70-72

“What is the answer?”
--Gertrude Stein, on her deathbed. Then, when no answer came from Alice B. Toklas:
“In that case, **what is the question?**”
Different Domains of LA-ART Horizon

- Efficacy
- Safety
- Quality of Life
- Tolerability/ Acceptability
- Cost
- Logistics
- Monitoring
- Stigma
- Adherence
THANK YOU!

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IAPAC & Adherence 2020 Conference
Catherine Orrell
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Conference organizers
Jonathon Hess
Faculty & Attendees

Funders
- NIH/NIAID R24 AI118397 (Long-Acting/ Extended Release Antiretroviral Resource Program (LEAP))
- Johns Hopkins University Center for AIDS Research P30AI094189 (Adolescent and Young Adult Scientific Working Group micro-grant; Junior Faculty Retention Funding)
- Johns Hopkins Clinical Research Scholars KL2 Award
- Pearl M. Stetler Research Award for Women Physicians
- NIH T32 GM066691-11 & GM066691-12, NIGMS