Novel Approaches to HIV Treatment and Prevention using Long Acting Drug Delivery

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Dr. Flexner is disclosing the following potential conflicts:

- **Research grants and contracts**: Gilead
- **Consulting**: Cipla, Merck, Mylan, ViiV Healthcare
- **Stockholder and equity**: none to report
- **Patents and intellectual property**: 3 patent applications pending on long-acting drug delivery systems for HIV
Outline of presentation

- What is in the pipeline?
- What stands in the way of approval?
- What is the next generation of LA delivery systems for HIV treatment and prevention?
- How can long acting anti-HIV formulations and devices be made available in areas of greatest need?
LA/ER for HIV: What’s the attraction?

- Infrequent dosing
  - Long apparent $T_{1/2}$
- Lower daily drug dose needed (nanoformulation)
- Prevents poor adherence
- Possibility of directly observed therapy
- Tissue targeting (LN/macrophage uptake)
- Use in patients with pill fatigue
- Better protection of health privacy
- Avoids treatment-related HIV stigma
LA/ER for HIV: What’s the attraction?

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How close are LA injectable anti-HIV drugs to regulatory approval?
LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR MAINTENANCE THERAPY:
ATLAS WEEK 48 RESULTS

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M Masià,6 G Latiff,7 V Pokrovsky,8 JM Mrus,9 J Huang,10 KJ Hudson,9
DA Margolis,9 KY Smith,9 P Williams,11 WR Spreen9

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Africa; 8Central Research Institute of Epidemiology, Moscow, Russian Federation; 9ViiV Healthcare, Research Triangle Park, NC, United States;
10GlaxoSmithKline, Mississauga, ON, Canada; 11Janssen Research and Development, Beerse, Belgium

- Swindells S, et al. CROI 2019; Seattle, WA. Abstract 139.
ATLAS Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Study in Adults with Virologic Suppression (Ongoing)

Screening Phase

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

Maintenance Phase

Randomization 1:1

Oral CAB + RPV n=308

CAB LA (400 mg) + RPV LA (600 mg)§

1M monthly n=303

Primary Endpoint

Day 1 Baseline

Week 4§

Week 48

Week 52

Week 96

Extension Phase†

Extension Phase or transition to the ATLAS-2M study

PI, NNRTI or INSTI†

Current daily oral ART n=308

N=705

PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone*

*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 enrollment; 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.

ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside RTI; PI, protease inhibitor; RPV, rilpivirine; VL, viral load.

- Swindells S, et al. CROI 2019; Seattle, WA. Abstract 139.
ATLAS Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>Virologic Outcomes</th>
<th>Adjusted Treatment Difference (95% CI)*</th>
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<tr>
<td><strong>Proportion of Participants (%)</strong></td>
<td><strong>Primary endpoint:</strong></td>
</tr>
<tr>
<td>Virologic nonresponse (≥50 c/mL)</td>
<td>CAB LA + RPV LA (n=308)</td>
</tr>
<tr>
<td>1.6</td>
<td>92.5</td>
</tr>
<tr>
<td>0</td>
<td>95.5</td>
</tr>
<tr>
<td>Virologic success (&lt;50 c/mL)</td>
<td></td>
</tr>
<tr>
<td>5.8</td>
<td>0.6</td>
</tr>
<tr>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>No virologic data</td>
<td></td>
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</tbody>
</table>

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.
## ATLAS Confirmed Virologic Failure: CAB LA + RPV LA Arm

<table>
<thead>
<tr>
<th>Sex, Country, HIV-1 Subtype</th>
<th>Previous CAR</th>
<th>SVF Timepoint</th>
<th>Viral Load at SVF/CVF (c/mL)</th>
<th>SVF Timepoint RAMs (HIV-1 RNA)</th>
<th>Drug Sensitivity at SVF† (Fold Change)</th>
<th>Baseline RAMs (PBMC/HIV-1 DNA; Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, Russia, A/A1</td>
<td>3TC, AZT, LPV/r</td>
<td>Week 8</td>
<td>79,166 / 25,745</td>
<td>E138A</td>
<td>RPV (2.4) CAB (0.8) DTG (0.9)</td>
<td>E138E/A L74I</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>3TC, AZT, NVP to 3TC, ABC, NVP</td>
<td>Week 12</td>
<td>695 / 258</td>
<td>V108I E138K</td>
<td>RPV (3.7) CAB (1.2) DTG (1.0)</td>
<td>V108V/I E138K None</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>FTC, RAL, TDF to ABC, EFV, 3TC</td>
<td>Week 20</td>
<td>544 / 1841</td>
<td>E138E/K</td>
<td>RPV (6.5) CAB (2.7) DTG (1.2)</td>
<td>None L74I</td>
</tr>
</tbody>
</table>

- Plasma CAB and RPV concentrations at the time of failure were below the population means but within the range for the large majority of individuals who maintained virologic suppression

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3TC, lamivudine; ABC, abacavir; AZT, azidothymidine; CAB, cabotegravir; CAR, current antiretroviral; CVF, confirmed virologic failure; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; LA, long-acting; LPV, lopinavir; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; r, ritonavir; RAL, raltegravir; RAM, resistance-associated mutation; RPV, rilpivirine; RT, reverse transcriptase; SVF, suspected virologic failure; TDF, tenofovir disoproxil fumarate.

*L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity.

†Monogram biological/clinical cutoffs are: RPV=2.0, CAB=2.5, and DTG=4.0.
Patient satisfaction with injectable RPV and CBT

Margolis et al., *Lancet* 2017; 390: 1499-1510
Current status of regulatory approvals for cabotegravir and rilpivirine

- NDA filing in early 2019.
- Complete Response Letter (CRL) received on December 21, 2019, declining approval.
- Safety and efficacy of the combination was not questioned.
- Reasons given in the CRL were related to Chemistry Manufacturing and Controls (CMC), according to ViiV press release.
ViiV Healthcare receives complete response letter from US FDA for use of investigational cabotegravir and rilpivirine long-acting regimen in the treatment of HIV

London, 21 December 2019 – ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer Inc. and Shionogi Limited as shareholders, received a complete response letter (CRL) from the US Food and Drug Administration (FDA) regarding its application for cabotegravir and rilpivirine long-acting regimen for treatment of HIV-1 infection in virologically suppressed adults.

The reasons given in the CRL relate to Chemistry Manufacturing and Controls (CMC). There have been no reported safety issues related to CMC and there is no change to the safety profile of the products used in clinical trials to date. ViiV Healthcare will work closely with the FDA to determine the appropriate next steps for this New Drug Application.
What’s in the pipeline: Capsid Assembly Inhibitor–GS-6207
HIV Capsid Inhibitors

- Sager CROI 2019 Abstract #141
GS-6207: HIV Capsid Inhibitor

- Novel mechanism of action with unique resistance profile
- High antiviral potency (EC$_{50}$ = 50 pM)
- Resistant variants have low fitness
- Low in vivo clearance
- Half-life: 30-43 days
- Healthy volunteer PK consistent with long-acting potential
- Given as a subcutaneous suspension
- Oral formulation in development

- Sagar et al. CROI 2019: Abstract 141
GS-6207 pharmacokinetics following single S.C. administration may support ≥Q3m dosing

- At doses ≥100 mg, GS-6207 plasma concentrations at 12 weeks were above the paEC\textsubscript{95} of 3.87 ng/mL
- EC\textsubscript{95} determined in MT-4 T-Cell Line with WT HIV-1 (IIIB strain). C\textsubscript{w12}, GS-6207 plasma concentration on Day 84; IQ, inhibitory quotient; paEC\textsubscript{95}, protein adjusted EC\textsubscript{95}

<table>
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<tr>
<th>Dose</th>
<th>IQ at week 12</th>
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<tr>
<td>450 mg</td>
<td>4.7</td>
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<tr>
<td>300 mg</td>
<td>4.1</td>
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<tr>
<td>100 mg</td>
<td>1.3</td>
</tr>
<tr>
<td>30 mg</td>
<td>0.4</td>
</tr>
</tbody>
</table>

- Sagar et al. *CROI* 2019: Abstract 141
Capsid Inhibitor GS-6207 Antiviral Activity

- Daar E et al. *IAS* 2019; LBPEB13
What’s in the pipeline: Broadly-neutralizing Anti-HIV monoclonal antibodies
Broadly Neutralizing mAbs in Development to Key Sites of Neutralization-Sensitivity on HIV-1 gp160

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
Effect of VRC01 on Viral Rebound

PK profile of VRC01-LS and VRC07-LS


Broadly-neutralizing monoclonal antibodies

- **Questions for the future:**
  - How many bnAbs?
  - Breadth versus depth?
  - Can bnAbs be given by alternative routes of administration?
    - Subcutaneous
    - Intramuscular
    - Does it matter?
  - Can bnAbs be combined with small molecule LA formulations?
    - ACTG 5357 = VRC07 plus CBT maintenance study in development
  - Can bnAbs be delivered by device?
    - Implantable “pumps,” microneedles, etc.
  - Will bnAbs ever be affordable in LMICs?
What else is in the clinical pipeline: Implants
Long Acting ARV Implants

- Potential advantages over injectables
  - Removable (inert, or early bioerodable forms)
  - More consistent and predictable drug release
  - PK not dependent on injection site
  - May remain in place for years (inert, non-degradable subcutaneous versions)

- Potential disadvantages over injectables
  - Specialized device required for insertion
  - Minor surgical procedure to remove
  - Should be removed (if not bioerodable)
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace
Implants in clinical development: Tenofovir alafenamide (TAF) and Islatravir (EFdA)
FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the y-z (B) and x-y planes (C).
LA ARV Implants – Tenofovir Alafenamide

FIG 3 Subdermal implantation of TAF LA prototype device in beagle dogs maintains sustained drug levels with low systemic exposure to TAF and TFV with concomitant, efficient PBMC loading with TFV-DP. Pharmacokinetic profiles of plasma TAF (closed circles) and TFV (open circles) and PBMC TFV-DP (closed diamonds). Each data point represents the means ± standard deviations from four beagle dogs, and dotted lines correspond to the median concentrations for each analyte over the 40-day study. Note that TFV-DP levels were measured only after day 20.

M Gunawardana et al., Antimicrob Agents Chemother 2015; 59: 3913
Chemical structure of Islatravir (MK-8591; EFdA)

- Wu VH et al. *Antimicrob Agents Chemother* 2017
Chemical structure of Islatravir (MK-8591; EFDa)

- Wu VH et al. *Antimicrob Agents Chemother* 2017
4’-Ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)

Unique properties
- Unique mechanism of action (translocation inhibitor)
- Exceedingly potent (possible dose in humans of <5 mg/day)
- Lack of cross-resistance with most NRTI’s
- Minor impact of M184V
- More active against HIV-2 than other NRTI’s
- Long half-life of intracellular TP (>72 hours) in rhesus macaques
- Possibility of once-weekly oral dosing
- Possibility of implant formulation with dosing interval of >one year
Islatravir (EFdA) Implants Release Effective Drug Concentrations for >180 days in Humans

Intracellular ISL-TP PK Threshold of 0.05 pmol/10⁶ Cells Maintained Throughout Placement for Both Doses

- Matthews et al., IAS 2019; TUAC0401LB
Implants – A Note of Caution

European Journal of Pharmaceutical Sciences

Exploration of long-acting implant formulations of hepatitis B drug entecavir

Steven J. Henry\textsuperscript{a}, Stephanie E. Barrett\textsuperscript{a,}\textasteriskcentered, Seth P. Forster\textsuperscript{a}, Ryan S. Teller\textsuperscript{a}, Zhen Yang\textsuperscript{a}, Li Li\textsuperscript{a}, Megan A. Mackey\textsuperscript{a}, Gregory J. Doto\textsuperscript{b}, Michael P. Ruth\textsuperscript{b}, Takayuki Tsuchiya\textsuperscript{b}, Lee J. Klein\textsuperscript{a}, Marian E. Gindy\textsuperscript{a}

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Fig. 4. Histology of tissue around polyurethane (PU) coated tablet. Hematoxylin and Eosin stained sections revealed extensive necrosis around the implant and a connective tissue response in the subdermal layers. The necrotic and connective tissue surrounding the implant elevated the overlying ulcerative epidermis (A to C) causing implant expulsion. Scale bars: (A) 2 mm, (B) 100 μm, and (C) 500 μm. Asterisk denotes implant cavity.
Figure 1. Photos of representative Generation A TAF long-acting reservoir implants with lumen lengths of (a) 0.8 cm and (b) 1.6 cm and (c) a placebo implant that is empty except for a pellet of NaCl and magnesium stearate.

Figure 3. Dose-dependent PK was observed in our NZW rabbit experiments, with higher average TFV-DP levels leading to higher plasma levels of TFV-DP in circulating heterophils. TFV-DP levels increased within a week of implantation. BLQ values are plotted as 1/10th of the calculated LOQ value. Drug levels for all placebo implants were BLQ. The horizontal bar is mean TFV-DP. As per Table 1, in vitro release from Group 1: 0.13 mg/day; Group 2: 0.26 mg/day; Group 3: 0.52 mg/day, Group 4: 0.78 mg/day.
TAF Reservoir Implant – Local Inflammation and Tissue Necrosis in Rhesus Macaques

Figure 7. Representative histology slides from rhesus macaque FC48 after 12 weeks with a Generation B implant. Minimal inflammation and a distinct fibrous tissue capsule was observed for the placebo implant (c,d), however extensive inflammation was observed for implant containing active drug (a,b) despite a lower in vitro release rate of Generation B implants (0.13 mg/day in vitro release rate) versus the Generation A implants.

Other gaps in the LA ARV pipeline: Existing nucleoside reverse transcriptase inhibitors (NRTI’s)
“Extendification” of existing NRTI’s

“Extendification” of existing NRTI’s

Observed and simulated plasma concentrations of emtricitabine (FTC) after administration of prodrug solid drug nanoparticles (SDN’s)

How can long acting ARV formulations and devices be implemented in LMICs, and where are the greatest needs?
The Generic HIV Marketplace: Pills versus implants and injectables

- **Oral formulations:**
  - Modest up-front investment for manufacturing facilities
  - Rapid shift from one API to another
  - Little or no restriction on which products can be made in which facilities
  - Little or no market guarantee required

- **Parenteral LA formulations:**
  - Huge up-front investment for manufacturing facilities!
  - Slow shift from one delivery system to another
  - Cannot manufacture ARV and hormonal contraceptive delivery systems in the same facility (U.S. FDA Guidance)
  - Large market guarantee likely to be required
Use LA/ER injectable antimicrobials as a substitute for immunization in serious epidemics where a vaccine is unlikely to become available:

- HIV
- Tuberculosis
- Malaria
- Hepatitis C Virus
- Etc.
http://longactinghiv.org

Who We Are

Funded by an R24 grant from the National Institutes of Health, the mission of LEAP is 3-fold:

1. To support scientific innovation through investigator access to broad-based scientific expertise including the pharmaceutical industry.
2. To develop a communications and data hub to support investigators in this field
3. To provide a Modeling and Simulation Core Service that helps investigators identify the most promising approaches to the development of new products.

Funding Opportunities

Finding funds for research can be a challenge. The following resources are provided to help guide your
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<td>Bill and Melinda Gates Foundation</td>
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<td>Amer Al-Khouja</td>
<td>NIAID, R24 AI-118397 (LEAP)</td>
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<tr>
<td>David Meyers</td>
<td>NIAID, R01 AI-114405</td>
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<td>Caren Freel Meyers</td>
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