State of the LA-ART: New Drug Delivery Technologies in HIV Treatment and Prevention

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Dr. Flexner is disclosing the following potential conflicts as required by the organizers:

- **Research grants and contracts:** Gilead
- **Consulting:** Cipla, Merck, Mylan, Viiv Healthcare
- **Expert witness:** Gilead
- **Stockholder and equity:** none to report
- **Patents and intellectual property:** Two patents related to the development of long-acting formulations for delivery of antiretroviral drugs
<table>
<thead>
<tr>
<th>Phase 3</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI Entry Inhibitor</th>
<th>II Integrase Inhibitor</th>
<th>CI Capsid Inhibitor</th>
<th>MI Maturation Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>islatravir</td>
<td>MK-8507</td>
<td>PRO 140 (leronlimab) UB-421 Other bNAbs</td>
<td>cabotegravir</td>
<td>lenacapavir</td>
<td></td>
<td></td>
</tr>
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<td>Phase 2</td>
<td>censavudine (aka festinavir)</td>
<td>elsulfavirine</td>
<td>TMC 310911</td>
<td>albuvirtide cenicriviroc PF-232798</td>
<td></td>
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<td></td>
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<tr>
<td>Phase 1/2</td>
<td>elvucitabine</td>
<td></td>
<td>GS-1156</td>
<td></td>
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## Investigational ART Agents 2021

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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Other bNABs**
- lenacapavir
LA-Cabotegravir and LA-Rilpivirine
First complete long-acting HIV regimen

REGULATORY APPROVALS
- Canada – Mar 2020
- Europe (EMA) – Dec 2020
- United States – Jan 2021
- Australia – Feb 2021

- Co-Pack = Cabenuva
- Single Packs = Vocabria (CAB LA) and Rekambys (RPV LA)
- CAB tablets = Vocabria
- RPV tablets = Edurant
ATLAS and FLAIR

ATLAS (NCT02951052) and FLAIR (NCT02938520) are two randomized, open-label, international Phase 3 studies that demonstrated non-inferiority of switching to monthly intramuscular (IM) injections of CAB + RPV LA vs. current antiretroviral regimen (CAR).

Swindells et al. NEJM 2020; Orkin et al. NEJM 2020
ATLAS 2M: results

Summary of confirmed virologic failures

Q8W of CAB + RPV LA was:
- non-inferior to Q4W
- well tolerated (98% ISR grade 1-2)
- preferred by study participants

Overton et al. CROI 2020

CAB = cabotegravir; RPV = rilpivirine

International Workshop on Clinical Pharmacology of HIV, Hepatitis, and other Antiviral Drugs #AntiviralPK
ATLAS 2M: results

Summary of confirmed virologic failures

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CVFs</th>
<th>CVFs with RPV RAMs*</th>
<th>RPV RAMs Observed at Failure</th>
<th>CVFs with IN RAMs*</th>
<th>IN Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8W</td>
<td>522</td>
<td>8 (1.5)</td>
<td>6/8</td>
<td>K101E, E138E/K, E138A, Y188L</td>
<td>5/8</td>
<td>Q14</td>
</tr>
<tr>
<td>Q8W</td>
<td>523</td>
<td>2 (0.4)</td>
<td>1/2</td>
<td>K101E, M230L</td>
<td>2/2</td>
<td>E138E/K</td>
</tr>
</tbody>
</table>

Q8W of CAB + RPV LA was:

- non-inferior to Q4W
- well tolerated (98% ISR grade 1-2)
- preferred by study participants
### AB + RPV LA Phase 3 Studies – Extended Efficacy Outcomes

AB + RPV LA Q1M non-inferior to oral ART; Q2M non-inferior to Q1M dosing at Weeks 48 & 96; see ATLAS-2M Week 96 results - Science Spotlight presentation no. 1753 (H Jaeger, et al).

<table>
<thead>
<tr>
<th>Study (n, ITT-E)</th>
<th>Treatment</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HIV RNA</td>
<td>HIV RNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;= 50 c/mL</td>
<td>&lt;50 c/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;= 50 c/mL</td>
<td>&lt;50 c/mL</td>
</tr>
<tr>
<td>ATLAS 1 (n=308)</td>
<td>CARLA Q1M</td>
<td>1.6%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>Oral CAR</td>
<td>&lt;1%</td>
<td>95%</td>
</tr>
<tr>
<td>FLAIR 2 (n=283)</td>
<td>CARLA Q1M</td>
<td>2.1%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>Oral CAR</td>
<td>2.5%</td>
<td>93%</td>
</tr>
<tr>
<td>ATLAS-2M 3 (n=522)</td>
<td>CARLA Q2M</td>
<td>1.7%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>CARLA Q1M</td>
<td>1%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Most (88%) ATLAS participants Rolled-over to ATLAS-2M

<table>
<thead>
<tr>
<th>Week 96</th>
<th>HIV RNA</th>
<th>HIV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;= 50 c/mL</td>
<td>&lt;50 c/mL</td>
</tr>
<tr>
<td></td>
<td>&gt;= 50 c/mL</td>
<td>&lt;50 c/mL</td>
</tr>
<tr>
<td>0 CVF W48-W96</td>
<td>3.2%</td>
<td>87%</td>
</tr>
<tr>
<td>1 CVF W48-W96</td>
<td>3.2%</td>
<td>89%</td>
</tr>
<tr>
<td>0 CVF W48-W96</td>
<td>2.1%</td>
<td>91%</td>
</tr>
<tr>
<td>0 CVF W48-W96</td>
<td>1.1%</td>
<td>90%</td>
</tr>
</tbody>
</table>

CVF = confirmed virologic failure (consecutive HIV RNA ≥200 c/mL)

Injection site reactions (ISR), when reported, were generally mild and of several days duration. Monthly and 2-monthly ISR profiles are similar. ISRs or injection fatigue accounted for ~1% per year discontinuation rate.

The majority (3082/3100, 99%) of ISRs were Grade 1–2 and most (89%) resolved within ≤7 days (median duration, 3 days).

*Incidence is derived relative to the number of participants who received injections at each respective study visit.

Orkin et al. CROI 2020; Boston, MA. Poster 482LB.
Most participants preferred CAB + RPV LA Q8W dosing over daily oral ART and Q4W dosing in the ATLAS-2M study.

Participants on Q8W arm from oral ART (no prior Q4W experience)*

- Q8W CAB + RPV LA: 98%
- Daily oral ART: 1%
- No preference: 1%

N=306

Participants on Q8W arm with prior Q4W experience in ATLAS*

- Q8W CAB + RPV LA: 94%
- Q4W CAB + RPV LA: 3%
- Daily oral ART: 2%
- No preference: 1%

N=191

Towards Optional Oral lead-in (OLi) / direct to inject (dti)

Supportive safety data - no acute or severe ADRs reported across studies to-date
- CAB LA > 5800 study participant exposures; > 90,000 injections (includes PrEP trials)
- RPV LA > 2000 study participant exposures; > 60,000 injections

FLAIR ext. phase - switching directly to CAB + RPV LA gave comparable efficacy, safety and tolerability vs. oral lead-in

### FLAIR OLI: Snapshot Virologic Outcomes at Week 124

![Graph showing virologic outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DTI arm n=111</th>
<th>OLI arm n=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL</td>
<td>110 (99.1)</td>
<td>113 (93.4)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 copies/mL</td>
<td>1 (0.9)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Data in window not below threshold</td>
<td>0</td>
<td>1 (0.8)*</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>1 (0.9)†</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued for other reason while not below threshold</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Change in background therapy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No virologic data</td>
<td>0</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>0</td>
<td>2 (1.7)‡</td>
</tr>
<tr>
<td>Discontinued due to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued study for other reason</td>
<td>0</td>
<td>5 (4.1)§</td>
</tr>
<tr>
<td>On study but missing data in window</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Participant had HIV-1 RNA of 57 copies/mL at Week 124.
†Participant met the CVF criteria at Week 112.
‡Two participants discontinued due to AEs of injection site pain and weight gain.
§Five participants discontinued due to other reasons, which included burden of travel, prohibited medication use, participant relocation, burden of procedures/intolerability of injections and pregnancy.

Cabanuva Resistance: Four Factors Were Associated With an Increased Odds Ratio of CVF, Three Are Baseline Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Model OR (95% CI), p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM(s) at baseline†</td>
<td>37.24 (8.44–99), p&lt;0.001</td>
</tr>
<tr>
<td>Log$_2$ of post hoc Week 8 RPV trough concentration</td>
<td>4.17 (1.59–11.11), p=0.004</td>
</tr>
<tr>
<td>Baseline HIV-1 subtype A6/A1</td>
<td>6.59 (1.82–25.26), p=0.005</td>
</tr>
<tr>
<td>BMI (kg/m$^2$) at baseline</td>
<td>1.13 (1.03–1.25), p=0.014</td>
</tr>
<tr>
<td>Specified INSTI mutation (excluding L74I non-M mixture) at baseline†</td>
<td>0.11 (0.01–0.83), p=0.029</td>
</tr>
<tr>
<td>Log$_2$ of post hoc Week 8 CAB trough concentration</td>
<td>Not significant</td>
</tr>
<tr>
<td>Female at birth</td>
<td>Not significant</td>
</tr>
<tr>
<td>Q8W regimen</td>
<td>Not significant</td>
</tr>
<tr>
<td>(non-M mixture) INSTI polymorphism at baseline</td>
<td>Not significant</td>
</tr>
<tr>
<td>TI RAM(s) (excluding RPV RAMs) at baseline†</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Odds ratios (ORs), 95% penalised profile CIs and penalised likelihood ratio p-values are provided. Covariates with p<0.05 in the final backwards elimination model are presented. CAB and RPV PK parameters were log$_2$-transformed, therefore, the corresponding ORs are per halving of each variable.
†Identified per the IAS–USA 2019 list of mutations.
‡Identified per the IAS–USA list of mutations associated with resistance to bictegravir, CAB, dolutegravir, elvitegravir or raltegravir and observed mutations during in vitro passage of dolutegravir or seen in a previous dolutegravir study (NCT01328041) in INSTI-experienced subjects.


Margolis et al. HIV Glasgow 2020; Virtual.
LA Cabotegravir and Rilpivirine – Resistance

- Resistance to injectable LA-cabotegravir and LA-rilpivirine was rare in Phase 3 clinical trials, *but*:
  - Always seen in subtype A virus, (East and Central Africa and Eastern Europe).
  - Most DR patients had L74I in the integrase gene at baseline.
  - Most DR patients had CBT and RPV concentrations in lower quartile.
  - Relationship to BMI, pre-existing NNRTI and InSTI mutations.
  - More common with the Q8W regimen than the Q4W regimen.

- Can you predict who is at greatest risk of CBT and PRV resistance?
HPTN 083 Study: LA ART and one-pill once-per-day Go head-to-head For HIV prevention!
HPTN 083 Study Design

**STEP 1**
- Every day for 5 weeks
  - CAB

**STEP 2**
- Weeks 5 and 9
  - Every 2 months for approximately 3 years
  - TDF/FTC (Every day)

**STEP 3**
- Every day for 1 year
  - TDF/FTC

**Drug Administration**
- TDF/FTC pill
- Cabotegravir (CAB) injection
- Placebo for TDF/FTC pill
- Placebo for cabotegravir (CAB) injection (20% Intralipid solution)

Landovitz RJ et al. AIDS 2020, #OAXLB0101
HIV Incidence
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95% CI 0.61-1.07) per 100 PY

HIV Incidence
CAB vs. TDF/FTC

- 13 Infections, 3202 PY
- 39 Infections, 3187 PY

Hazard Ratio (95% CI)
Favors CAB Favors TDF/FTC

- CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB0101
**PrEP Study for Women in Sub-Saharan Africa**

Cabotegravir LA superior to oral TDF/FTC with 89% reduction in HIV acquisition

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CAB LA</th>
<th>TDF/FTC</th>
<th>Hazard Ratio (95% CI) CAB v TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Participants Enrolled</td>
<td>3223</td>
<td>1613</td>
<td>1610</td>
<td></td>
</tr>
<tr>
<td>No. HIV Events</td>
<td>38</td>
<td>4</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Person-Years</td>
<td>3808</td>
<td>1912</td>
<td>1896</td>
<td></td>
</tr>
<tr>
<td>Incidence Rate</td>
<td>1</td>
<td>0.21</td>
<td>1.79</td>
<td>0.11 (0.04, 0.32)</td>
</tr>
<tr>
<td>95% CI for incidence rate</td>
<td>[0.71, 1.37]</td>
<td>[0.06, 0.54]</td>
<td>[1.24, 2.51]</td>
<td></td>
</tr>
</tbody>
</table>

R4P 2020; ViiV and HPTN press releases Nov 9, 2020
HPTN 083 and 084 Implications

- One drug (CBT) was actually better than two drugs (TDF + FTC)!
- Unclear why:
  - Better PK profile over time
  - Consequences of non-adherence to daily oral PrEP
  - Higher barrier to resistance
  - Something else?
- Is LA-CBT more effective in women, and why?
- Clear demonstration of the benefits of an LA formulation as compared to standard one-pill-once-per-day ARVs.
What’s next for LA-cabotegravir?
Other CAB Long Acting Programs

- Microarray Patch (MAP) for Long-Acting HIV PrEP
  - CAB LA Reformulation: double-strength concentration (400mg/mL)
  - ViiV/GSK internal program
  - ClinicalTrials.gov NCT04484337

- CAB Implant: non-biodegradable, retrievable
- ViiV/GSK internal & external collaboration (Northwestern Univ. SLAP-HIV UM1 NIH grant)

Light microscopic image (x25) of MAP

Hope T, et al. HIV R4P Jan 2021 Virtual
https://doi.org/10.1093/ofid/ofz415.2491
Subcutaneous capsid inhibitor:
GS-6207 / Lenacapavir
HIV Capsid Inhibitors: Mechanism of Action

Yant et al., Nat Med 2019; 25:1377-1384
oral LEN PK

Half-life: approximately 12 days

Significant accumulation with multiple dose

Oral tablet can be used for:
- PK loading
- Lead-in

Oral 300 mg tablet

LEN, ng/mL

Weeks Post-dose

900 mg (3 tablets)
300 mg (1 tablet)
50 mg (1 tablet)

Inhibitory quotient; $\text{paEC}_{95}$, protein binding-adjusted 95% effective concentration.

Ryan R, et al. CROI 2020
Putting oral and SC together
Predicted LEN PK for Phase 2/3 LEN regimen

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CI, confidence interval.
Begley R, et al. AIDS 2020 (previously presented as SC 900 mg, but revised based on further data)
LEN is a Moderate Inhibitor of CYP3A:
3x (3.1–3.6x) Increase in MDZ AUC

- Caution is advised with LEN coadministration with sensitive CYP3A substrates.
- Minimal increase in TAF, ROS and PIT AUC indicates that LEN can be administered with sensitive P-gp, BCRP or OATP substrates.

* AUC↑:
  - TAF = 1.5x (1.4–1.7x);
  - ROS = 1.3x (1.2–1.4x);
  - PIT = 1.1x (1.0–1.2x)

Lutz J, CROI 2021; Abstract 89
Phenotype of HIV-1 encoding emergent variants

<table>
<thead>
<tr>
<th>All capside variants</th>
<th>WT</th>
<th>T107N&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Q67H</th>
<th>N74D</th>
<th>K70N</th>
<th>Q67H N74S</th>
<th>Q67H T107N</th>
<th>L56I</th>
<th>Q67H N74D</th>
<th>M66I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance to WT (%)</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>22</td>
<td>24</td>
<td>32</td>
<td>62</td>
<td>239</td>
<td>1,099</td>
<td>&gt;3,594</td>
</tr>
<tr>
<td>Activity in cells (%)</td>
<td>100</td>
<td>50</td>
<td>95</td>
<td>48</td>
<td>7</td>
<td>34</td>
<td>41</td>
<td>9</td>
<td>29</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup> mutant/WT mean EC<sub>50</sub> values determined 2 days post-infection with single-cycle reporter HIV-1 (NL4.3 strain) encoding firefly luciferase in MT-2 cells from 3 independent experiments in triplicate.

<sup>b</sup> Percentage values (percentage of WT) in MT-2 cells 2 days post-infection with p24-normalized inputs of single-cycle reporter HIV-1.

<sup>c</sup> Mutant observed only in combination with Q67H, not alone.

*Cosia (on demand) on Mon (08 March 2021) by Cihlar T
* Tapavir (GS-6207): first clinically active long-acting inhibitor of HIV capsid

*781 on Tue (09 March 2021) by VanderVeen L et al.
* Activity and resistance characterization of the HIV capsid inhibitor, lenacapavir

* Maximal effective concentration.
* Patil et al. Nature 2020
New LA-NRTIs:
Islatravir
Isavir (ISL, MK-8591), a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) with multiple mechanisms of action

Translocation inhibition due to the 4′-ethynyl group

- Translocation inhibition prevents the opening of the nucleotide binding site
- Additional nucleotides cannot bind or be incorporated into the viral DNA
- Viral replication is inhibited

Delayed chain termination due to the 4′-ethynyl and 3′-hydroxyl groups

- ISL incorporation changes the vDNA structure
- If translocation occurs and a nucleotide is added, the structural change prevents further nucleotide incorporation
- Viral replication is inhibited
- As such, ISL is not in the reverse transcriptase (RT) active site and is no longer susceptible to resistance-conferring mutations

ISL is in clinical development for the treatment and prevention of HIV-1 infection.
TP PK exhibited approximately linear dose proportionality

Mean (SD) ISL-TP concentration-time profile in PBMCs overlaid on population PK model-simulated median (95% PI) ISL-TP concentrations in PBMCs

Population PK simulations assessed the interim observed plasma and PBMC PK data\(^1\)

TP trough concentrations following 60 mg or 120 mg QM doses were all above the prespecified PK threshold of 0.05 pmol/10^6 PBMC cells.

Patel M et al., CROI 2021; Abstract 87

L, lisdexvir; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; PI, prediction interval; QM, once monthly; SD, standard deviation; TP, triphosphate.

Rudd DJ, et al. CROI 2020 (poster).
Study design: a Phase 2 study for once-monthly PrEP

Phase 2a, double-blind, randomized, parallel assignment, placebo-controlled, multicenter study in adults at low risk for HIV-1 acquisition

Key inclusion criteria
- 18-65 years
- Seronegative
- Risk for HIV acquisition < 250

Outcome measures
- Safety/tolerance
- PK (ISL/ISL-1)
- Exploratory
  - PBMC PK
  - Tissue PK
  - Hormonal

<table>
<thead>
<tr>
<th>Group 1 (n=100)</th>
<th>Group 2 (n=100)</th>
<th>Group 3 (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islatravir (60 mg) QM</td>
<td>Islatravir (120 mg) QM</td>
<td>Placebo QM</td>
</tr>
</tbody>
</table>

Timeline:
- 45-day screening period
- Day 1: Therapy
- Week 24: Follow-up
- Week 36: Extended follow-up
- Week 68

Randomization to study intervention at Day 1 and stratified by sex (female, male) and region (Africa, non-Africa). Sponsor unblinded at Week 24 to allow for an interim evaluation of safety. Participants and investigators/clinical site personnel remain blinded up to Week 36. After Week 36, only participants in the PBMC/PK bridging cohort who were randomly assigned to receive ISL will have an additional 32-week extended, unblinded PK follow-up through Week 68.

Patel M et al., CROI 2021; Abstract
New drug delivery platforms: Implants
Why 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
Implant Design Similar to Nexplanon®

- Implant based on Implanon®/Nexplanon®
- Made of same polymer
- Non-removable (not bioerodible)
- Does not use Nexplanon® applicator

- Clinical trial uses prototype implant

Polymer + ISL

- Matthews R et al. IAS 2019
A 56 mg implant projected to lead to concentrations above the threshold for 52 weeks.

- 56 mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for >52 weeks.

Matthews R et al., CROI 2021; Abstract 88.
Safety Summary
Globally Mild Local Tolerability Effects

A review of implant site adverse events (AEs) suggests that implants were generally well tolerated. 22/36 (61%) participants reported at least 1 implant site AE (not including hematoma). All AEs were mild or moderate in severity. No serious AEs and no discontinuations due to an AE. Types of AEs observed consistent with those observed with other implants.

<table>
<thead>
<tr>
<th>Number (percent) of individuals reporting AE during study</th>
<th>PBO</th>
<th>48 mg</th>
<th>52 mg</th>
<th>56 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>6 (50)</td>
<td>6 (75)</td>
<td>4 (50)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (25)</td>
<td>4 (50)</td>
<td>2 (25)</td>
<td>4 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/4 mod</td>
<td></td>
<td>1/4 mod</td>
</tr>
<tr>
<td>Tenderness/pain</td>
<td>4 (33)</td>
<td>2 (25)</td>
<td>4 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>3 (25)</td>
<td>5 (63)</td>
<td>2 (25)</td>
<td>6 (75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/5 mod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>2 (17)</td>
<td>4 (50)</td>
<td>4 (50)</td>
<td>4 (50)</td>
</tr>
</tbody>
</table>

No clear relationship between dose and AE frequency/severity. Most common AE not related to implant was headache, with no clear dose relationship. No effects on laboratory studies, ECGs, vital signs.

Matthews R et al., CROI 2021; Abstract 88
The Implant Quandry – Inert or Bioerodable?
Example of a Bioerodable Implant

Polymer-nanoparticle (PNP) hydrogels

Leuprolide acetate: a drug of diverse clinical applications

Andrea C Wilson, Sivan Vadakkadath Meethal, Richard L Bowen, Craig S Arwood†

†University of Wisconsin-Madison, Department of Medicine, and Geriatric Research, Education and Clinical Center, William S Middleton Memorial Veterans Administration Hospital, 2500 Overlook Terrace, Madison, WI 53705, USA

Leuprolide acetate is a synthetic nonapeptide that is a potent gonadotropin-releasing hormone receptor (GnRHR) agonist used for diverse clinical applications, including the treatment of prostate cancer, endometriosis, uterine fibroids, central precocious puberty and in vitro fertilization techniques. As its basic mechanism of action, leuprolide acetate suppresses gonadotrope secretion of luteinizing hormone and follicle-stimulating hormone that subsequently suppresses gonadal sex steroid production. In addition, leuprolide acetate is presently being tested for the treatment of Alzheimer’s disease, polycystic ovary syndrome, functional bowel disease, short stature, premenstrual syndrome and even as an alternative for contraception. Mounting evidence suggests that GnRH agonist suppression of serum gonadotropins may also be important in many of the clinical applications described above. Moreover, the presence of GnRHR in a multitude of non-reproductive tissues including the recent discovery of GnRHR expression in the hippocampi and cortex of the human brain...
LA Biologics:
Broadly-neutralizing antibodies (bnAbs)
Why bNAbS?

• Discovery and development is straightforward.
  • At least 9 anti-HIV bNAbS are in clinical development in 2021.

• They are human B-cell derived antibodies.
  • Low potential for anti-drug antibody (ADA) response

• A simple modification greatly extends their plasma half-life.
  • LS mutation in the Fc binding domain can increase plasma half-life to >3 months.
  • Does not seem to increase immunogenicity.

*Current Opin HIV/AIDS 2020; 15 (5)*
Antibody Potency and Breadth

Multi-clade virus panel (n=208)

Nicole Doria-Rose, Krisha McKee
Why bNAbs?

• Potency and breadth of activity vary greatly between antibodies.
  - As much as 1000-fold difference in potency, depending on the viral isolate being targeted.

• Combinations of antibodies are needed to cover most circulating HIV isolates in an infected individual.

*Current Opin HIV/AIDS 2020; 15 (5)*
Broadly Neutralizing mAbs in Clinical Development

- V1V2 Glycan
- CD4 Supersite
- N332 Glycan-V3 Supersite
- gp120-gp41 Interface
- Membrane-proximal external region (MPER)

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
Improved Pharmacokinetic Profile: VRC07-523LS and VRC01LS serum conc.

Trough at 12 weeks is 3-fold lower
Trough at 16 to 24 weeks is 5-fold lower

But overall, serum neut is better for VRC07-523LS vs VRC01LS

“Extendification” of bnAb half-life with the LS mutation

• The LS mutation reduces Fc binding and extends antibody half-life by 3-6 fold or more.
• The degree of change in half-life is variable, and not predicted based on antibody structure.
• Very similar antibodies can have a 3-5 fold difference in the extend of change in half-life.

Current Opin HIV/AIDS 2020; 15 (5)
bnAbs for HIV prevention:
The AMP Studies
## The AMP Studies: Study schema

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 (W0)</th>
<th>2 (W8)</th>
<th>3 (W16)</th>
<th>4 (W24)</th>
<th>5 (W32)</th>
<th>6 (W40)</th>
<th>7 (W48)</th>
<th>8 (W56)</th>
<th>9 (W64)</th>
<th>10 (W72)</th>
<th>W80*</th>
<th>W81</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*Week 80: last study visit to evaluate efficacy

**Week 104: final study visit to evaluate safety and tolerability
## HVTN 703/HPTN 081 enrollments

<table>
<thead>
<tr>
<th>Country</th>
<th>Screened</th>
<th>Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>206</td>
<td>150</td>
</tr>
<tr>
<td>Kenya</td>
<td>213</td>
<td>82</td>
</tr>
<tr>
<td>Malawi</td>
<td>237</td>
<td>180</td>
</tr>
<tr>
<td>Mozambique</td>
<td>59</td>
<td>26</td>
</tr>
<tr>
<td>South Africa</td>
<td>2041</td>
<td>1019</td>
</tr>
<tr>
<td>Tanzania</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>673</td>
<td>434</td>
</tr>
<tr>
<td><strong>Total Enrolled</strong></td>
<td>1924</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VRC01 10 mg/kg</th>
<th>n=642</th>
<th>VRC01 30 mg/kg</th>
<th>n=645</th>
<th>Placebo</th>
<th>n=637</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screening and enrollment data for Sub-Saharan Africa shows significant participation from countries including Zimbabwe, Malawi, Botswana, Tanzania, Mozambique, and South Africa.
<table>
<thead>
<tr>
<th>Country</th>
<th>Screened</th>
<th>Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>209</td>
<td>151</td>
</tr>
<tr>
<td>Peru</td>
<td>1659</td>
<td>1131</td>
</tr>
<tr>
<td>Switzerland</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>USA</td>
<td>1982</td>
<td>1381</td>
</tr>
<tr>
<td><strong>Total Enrolled</strong></td>
<td><strong>2699</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>N=899</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>N=897</td>
</tr>
<tr>
<td>Placebo</td>
<td>N=903</td>
</tr>
</tbody>
</table>
Prevention with VRC01: The AMP Studies

Estimated PE at the Week 80 visit = 27% for 704/085, 9% for 703/081, 18% pooled
Prevention efficacy at the Week 80 visit did not significantly differ from zero*
## Prevention with VRC01: The AMP Studies (Pooled Trials)

<table>
<thead>
<tr>
<th>Neutralization Resistance Level</th>
<th>Treatment arm</th>
<th>No. of HIV-1 Infections</th>
<th>No. of Person-Years</th>
<th>Rate per 100 Person-Years</th>
<th>PE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/ml</td>
<td>Control</td>
<td>19</td>
<td>2203</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>9</td>
<td>4427</td>
<td>0.20</td>
<td>75.4 (45.5, 88.9)</td>
</tr>
<tr>
<td></td>
<td>VRC01 10 mg/kg</td>
<td>4</td>
<td>2210</td>
<td>0.18</td>
<td>79.2 (39.1, 92.9)</td>
</tr>
<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>5</td>
<td>2217</td>
<td>0.23</td>
<td>71.5 (23.3, 89.4)</td>
</tr>
<tr>
<td>3 µg/ml</td>
<td>Control</td>
<td>10</td>
<td>2203</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>19</td>
<td>4427</td>
<td>0.43</td>
<td>4.2 (−108.7, 56.0)</td>
</tr>
<tr>
<td></td>
<td>VRC01 10 mg/kg</td>
<td>13</td>
<td>2210</td>
<td>0.59</td>
<td>−35.2 (−214.3, 41.8)</td>
</tr>
<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>6</td>
<td>2217</td>
<td>0.27</td>
<td>43.5 (−55.8, 79.5)</td>
</tr>
<tr>
<td>µg/ml</td>
<td>Control</td>
<td>35</td>
<td>2203</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>70</td>
<td>4427</td>
<td>1.58</td>
<td>3.3 (−48.0, 36.8)</td>
</tr>
<tr>
<td></td>
<td>VRC01 10 mg/kg</td>
<td>37</td>
<td>2210</td>
<td>1.67</td>
<td>0.9 (−59.7, 38.5)</td>
</tr>
<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>33</td>
<td>2217</td>
<td>1.49</td>
<td>5.8 (−55.1, 42.7)</td>
</tr>
</tbody>
</table>
The Future of bnAbs

Questions for the future:

• bnAbs for prevention (ever)?
• How many bnAbs? For treatment? For prevention?
• 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 progress
• Will bnAbs ever be affordable in LMICs?
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