The Adult Long-Acting Pipeline: What comes after Cabotegravir and Rilpivirine?

Charles Flexner, MD
Johns Hopkins University
Novel delivery: Subcutaneous ARV’s
Lenacapavir (GS-6207) PK Profile

- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor / oral and SC long-acting formulations
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants
- Supports 6 monthly dosing, maintained target concentrations for 26 weeks

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**Mean LEN Single-Dose Plasma Concentration-Time Profiles**

6 mos (26 wk)

- LEN 900 mg (3 x 1 mL; n = 8)
- LEN 300 mg (1 x 1 mL; n = 8)
- LEN 900 mg (2 x 1.5 mL; n = 8)

Mean LEN, ng/mL (SD)

- N = 30

*IQ: ratio of LEN plasma concentration to IC_{50}.*

Begley. AIDS 2020. Abstr PEB0265
CAPELLA: Phase 2/3 in heavily treatment-experienced PWH
Primary endpoint achieved (press release in Nov 2020)

% Achieving HIV-1 RNA Decline ≥ 0.5 \( \log_{10} \) copies/mL,

- LEN was generally safe and well-tolerated
- The study is ongoing

Oral 2228 on Tue (09 March 2021)
By Segal-Maurer S et al.
Potent antiviral activity of lenacapavir in phase 2/3 in heavily ART-experienced PWH

Segal-Maurer et al., CROI 2021. Abstr 2228
Novel delivery:
Intravenous ARV’s
Broadly Neutralizing mAbs in Development

Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014
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

### 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>
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<tr>
<td><strong>Total Enrolled</strong></td>
<td></td>
<td><strong>1924</strong></td>
</tr>
</tbody>
</table>

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

Screening and Enrollment (Sub Saharan Africa)
HVTN 704/HPTN 085 enrollments

<table>
<thead>
<tr>
<th>Country</th>
<th>Screened</th>
<th>Enrolled</th>
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<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>
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</tbody>
</table>

**Total Enrolled**: 2699

<table>
<thead>
<tr>
<th>Group</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>

Screening Enrollment (Americas, Switzerland)
# Prevention with VRC01: The AMP Studies

**Table 1:** Primary two-sided $\alpha = 0.05$ level Wald-based hypothesis test evaluating equality of the log cumulative hazard functions at $\tau$ in the VRC01 pooled vs. control groups.

<table>
<thead>
<tr>
<th>Total Primary Endpoints (VRC01 vs. Control)</th>
<th>$\tau$ (weeks)</th>
<th>Primary Endpoints through $\tau$ (VRC01 vs. Control)</th>
<th>Est. Cumulative PE($\tau$)</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HVTN 704/HPTN 085</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRC01 Pooled vs. Control</td>
<td>98 (60 vs. 38)</td>
<td>87.0</td>
<td>98 (60 vs. 38)</td>
<td>26.6%</td>
<td>(-11.7% to 51.8%)</td>
</tr>
<tr>
<td><strong>HVTN 703/HPTN 081</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRC01 Pooled vs. Control</td>
<td>77 (48 vs. 29)</td>
<td>85.9</td>
<td>76 (47 vs. 29)</td>
<td>8.8%</td>
<td>(-45.1% to 42.6%)</td>
</tr>
<tr>
<td><strong>Pooled AMP Trials</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>VRC01 Pooled vs. Control</td>
<td>175 (108 vs. 67)</td>
<td>85.9</td>
<td>174 (107 vs. 67)</td>
<td>18.1%</td>
<td>(-12.2% to 40.2%)</td>
</tr>
</tbody>
</table>

- 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>&lt;1 µg/ml</td>
<td>Control</td>
<td>19</td>
<td>2203</td>
<td>0.86</td>
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<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>1-3 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>&gt;3 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>

Novel delivery: Topical ARV’s
Dapivirine Vaginal Ring – Prevention only!

• Less effective than other prevention strategies in clinical trials
• Removable
  • Susceptible to nonadherence
  • Removal associated with reduced efficacy in clinical trials
• In development as a combination technology
  • Combined with topical hormonal contraception
  • May improve adherence
• Unconventional implementation strategy
  • Developed strictly in a not-for-profit setting
  • Regulated as both a drug and a device
Novel delivery: Implantable ARV’s
Ilatravir (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.
Intracellular ISL-TP PK threshold of 0.05 pmol/10^6 cells maintained throughout placement for two highest doses

- 56 mg implant ISL-TP concentrations comparable to 62 mg from previous study
- Half-life after removal of implant similar to half-life of orally dosed ISL (t½ for 56 mg is ~198 hr)
Novel delivery:
Long-acting Oral ARV’s
ISL-TP PK exhibited approximately linear dose proportionality

Population PK simulations assessed the interim observed plasma and PBMC PK data. ISL-TP trough concentrations following 60 mg or 120 mg QM doses were all above the prespecified PK threshold of 0.05 pmol/10^6 PBMCs.

1. ISL, islatravir; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; PI, prediction interval; QM, once monthly; SD, standard deviation; TP, tenofovir phosphate.
2. Rudd DD et al. CROI 2020 (poster).
Phase 2a, double-blind, randomized, parallel assignment, placebo-controlled, multicenter study in adults at low risk for HIV-1 acquisition

Key inclusion criteria
- Aged 18-65 years
- HIV seronegative
- Low risk for HIV acquisition
- N ≈ 250

Outcome measures
- Safety/tolerability
- PK (ISL/ISL-TP)
- Exploratory
  - PBMC PK
  - Tissue PK
  - Hormonal DDIs

*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 subset who were randomly assigned to receive ISL will have an additional 32-week extended, unblinded PK follow-up through Week 68.

DDI, drug-drug interaction; ISL, islatravir; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; QM, once monthly; TP, triphosphates. NCT04003103 (P016).

Patel M et al., CROI 2021; Abstract 87
MK-8507, a once-weekly NNRTI for HIV-1 treatment

- In vitro IC$_{50}$ (100% NHS)=51.3nM
- Mean plasma t$_{1/2}$ ~70 hours in humans supports once-weekly dosing
- Generally well tolerated with single doses up to 1200 mg and 3x weekly doses up to 400 mg
- Single oral doses of MK-8507 as low as 40 mg reduced mean plasma HIV-1 RNA levels >1 log for up to 7 days in treatment-naïve PLWH
- Phase 2 study of MK-8507 in combination with islatravir is planned (NCT04564547)

ISL/MK-8507 oral QW phase 2 dose-ranging study – dose selection framework

**ISL**
- Islatravir

**Benchmark ISL-TP**
- QD vs QW dosing population PK model

**HIV QW phase 2 doses**
- ISL 20 mg
- MK-8507 100, 200, 400 mg

**ISL+MK-8507**
- Viral dynamics modeling (VDM)
  - PK (variability); PD (clinical IC\textsubscript{50})
  - IC\textsubscript{50} shifts (resistance variants)
  - Adherence to regimen

**Simulations**
- Predict long-term efficacy
  (Percentage of participants with HIV-1 RNA below 50 copies/mL at 48 weeks)

**PK target**
- Population PK model

**MK-8507**
- 100 mg QW

Oral LEN PK

- Half-life: approximately 12 days
- Significant accumulation with multiple dose
- Oral tablet can be used for:
  - PK loading
  - Lead-in

IQ, inhibitory quotient; paEC<sub>95</sub>, protein binding-adjusted 95% effective concentration. Begley R, et al. CROI 2020
Novel delivery: What will the future hold???
The ARV Drug Delivery Pipeline
The ARV Drug Delivery Pipeline

- Microneedle patches
- New implant technologies
- Bioerodible implants
- Reduced volume injections
- Gastric reservoirs
- Combination technologies
# Acknowledgements

<table>
<thead>
<tr>
<th>Johns Hopkins University</th>
<th>Merck</th>
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<tbody>
<tr>
<td>Jane McKenzie-White</td>
<td>Jay Grobler</td>
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<td>ViiV Healthcare</td>
<td>Randy Matthews</td>
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<tr>
<td>William Spreen</td>
<td>Tracy Diamond</td>
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<td>Kimberly Smith</td>
<td>Bhargava Kandala</td>
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<td>Vaccine Research Center</td>
<td>Gilead</td>
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<td>Richard Koup</td>
<td>Martin Rhee</td>
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<td>UNC</td>
<td>James Rooney</td>
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<td>Myron Cohen</td>
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## FUNDING SOURCES

- Bill and Melinda Gates Foundation
- NIAID, R24 AI-118397 (LEAP)
- NIAID, R01 AI-114405
- longactinghiv.org