Long Acting ART for Treatment and PrEP

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Disclosures

I have received honoraria, travel sponsorship and research grants from:

• Gilead Sciences
• Janssen
• MSD
• ViiV Healthcare
TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

BUT... success depends on adherence.
Long Acting – What’s the attraction?

- Prevents poor adherence
- Infrequent dosing
- Use in patients with pill fatigue /aversion?
- Better protects health privacy
- Lower overall drug dose
## Yearly intake of ARV by regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Daily Dose (mg)</th>
<th>Yearly dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-Drug Regimens:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r + FTC/TDF</td>
<td>800/100 + 200/300</td>
<td>511.0</td>
</tr>
<tr>
<td>RAL + F/TAF</td>
<td>800 + 200/10</td>
<td>368.7</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>50/600/300</td>
<td>346.8</td>
</tr>
<tr>
<td>EVG/c/FTC/TAF</td>
<td>150/150/200/10</td>
<td>186.2</td>
</tr>
<tr>
<td><strong>2-Drug Regimens:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>50 + 300</td>
<td>127.8</td>
</tr>
<tr>
<td>DTG + RPV</td>
<td>50 + 25</td>
<td>27.4</td>
</tr>
<tr>
<td>CAB&lt;sub&gt;oral&lt;/sub&gt; + RPV&lt;sub&gt;oral&lt;/sub&gt;</td>
<td>30 + 25</td>
<td>20.1</td>
</tr>
<tr>
<td>CAB&lt;sub&gt;im&lt;/sub&gt; + RPV&lt;sub&gt;im&lt;/sub&gt;</td>
<td>400 + 600 (every 2 mo)</td>
<td>6g</td>
</tr>
</tbody>
</table>

50 years of tx
Will there be demand for long-acting formulations?

Lessons from the contraceptive pill

Women choose **multiple** modalities:

- Oral
- Long acting injectable
- Topical (Coil)
- Implantable
LA formulations: Pros and Cons

• PROS
  • – Allow monthly dosing
  • – Tolerated well to date
  • – More convenient
  • – Less stigma
  • – May promote adherence
  • – Potential for DOT?

• CONS
  • – Some require i.m. injection
  • – Long-term tolerability?
  • – Very long terminal ½-life
  • – Cannot be self-administered
  • – Potential for resistance in non-adherent patients
**Most advanced Long – Acting Formulations**

**CABOTEGRAVIR**
- UGT1A1 (minor 1A9) metabolism
- Low DDI potential as victim or perpetrator
- Animal studies support PreP
- Loading dose increased to 600mg im
- Treatment dose 400mg im q 4w

**RILPIVIRINE LA**
- Terminal T½ 30-90 days (G001)
- CYP3A4 substrate
- Low DDI potential as victim or perpetrator
- Animal studies support PreP
- Loading dose increased to 900mg im
- Treatment dose 600mg im q 4w

Spreen HIV-HEPPK 16 and 17

Crawels HIV-HEPPK 16 and 17
LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label, randomized phase IIb study
  - Cabotegravir: INSTI formulated as oral tablet and for long-acting IM injection

*Induction Phase*

- CAB 400 mg + RPV 600 mg IM Q4W† (n = 115)
- CAB 600 mg + RPV 900 mg IM Q8W‡ (n = 115)
- CAB 30 mg + ABC/3TC 600/300 mg PO QD Wk 20

*Maintenance Phase*

- Day 1
- Wk 32
- Wk 48
- Wk 96

- Wk 16: RPV 25 mg PO QD added

ART-naive HIV-infected pts
- > 18 yrs of age with CD4+ cell count
- > 200 cells/mm³ (N = 309)

*Pts with HIV-1 RNA < 50 copies/mL from Wks 16-20 continued to maintenance phase. †CAB loading dose at Day 1. ‡CAB loading doses at Day 1 and Wk 4.

- Injections were 2-3 mL, IM (gluteal region), provider administered

Switch to Long acting Injectables LATTE-2
HIV-1 RNA <50 c/mL at Week 48: ITT-ME (Snapshot)

Virologic outcomes

- **Virologic success**: 92, 91, 89%
- **Virologic non-response**: 7, <1, 2
- **No virologic data**: <1, 8, 9

Treatment differences (95% CI)

- **Oral** vs **Q8W IM**
  - Q8W (n=115)
  - Q4W (n=115)
  - CAB 744 (n=56)

Both Q8W and Q4W comparable to Oral CAB at Week 48

Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
99% of ISRs for pts receiving injectable therapy
grade 1 (82%) or 2 (17%); none grade 4

Most frequent ISRs: pain (67%), nodules (7%), swelling (6%)

2/230 pts (< 1%) withdrew for ISRs (both in Q8W arm)

AEs leading to withdrawal

Pooled Q4W/Q8W IM arms, 4%
PO arm, 2%
Sustainable response
LATTE-2: 96-Wk Results

Withdrawals between Wks 48 and 96:
- CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent)
- CAB PO arm, n = 3 (all withdrew consent)

No additional PDVF after Wk 48 in any arm

~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB

Phase III maintenance trials (ATLAS and FLAIR) assessing Q4W dose;

ATLAS-2M comparing Q4W and Q8W doses[^2-4]

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**Wk 96 Virologic Efficacy[^1]**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM CAB + RPV Q4W (n = 115)</td>
<td>94</td>
</tr>
<tr>
<td>IM CAB + RPV Q8W (n = 115)</td>
<td>84</td>
</tr>
<tr>
<td>PO CAB + ABC/3TC (n = 56)</td>
<td>87</td>
</tr>
</tbody>
</table>

Treatment difference (vs CAB PO):
- CAB IM Q4W: 3.0% (95% CI: -8.4% to 14.4%)
- CAB IM Q8W: 10.0% (95% CI: -0.6% to 20.5%)

[^1]: HIV-1 RNA < 50 copies/mL.
LATTE-2: Resistance data

• 3 participants met protocol-defined criteria for virological failure
  – 1 in oral dosing arm: no PR, RT or IN resistance mutations
  – 2 in Q8W injection arm:
    • One with R269R/G mixture in IN (no fold-change)
    • One with K103N, E138G, K238T in RT and Q148R in IN (resistant to NNRTIs, RAL, EVG, CAB but DTG sens)

Margolis DA et al Lancet 2017
# Long-Acting Cabotegravir for PrEP

<table>
<thead>
<tr>
<th>CAB Trial</th>
<th>Design and Findings</th>
</tr>
</thead>
</table>
| **ECLAIR**<sup>[1]</sup> | - Phase IIa (N = 127)  
  - **CAB LA IM (Q12W)** vs PBO IM for men at low risk for HIV infection  
  - Encouraging results in terms of pt satisfaction and safety |
| **HPTN 077**<sup>[2]</sup> | - Phase IIa (N = 199)  
  - **CAB LA IM (Q8W or Q12W)** vs PBO IM for men and women at low risk for HIV infection  
  - Q8W dosing consistently met prespecified PK targets |
| **HPTN 083/084**<sup>[3,4]</sup> | - Phase IIb/III (planned N = 4500/3200)  
  - **CAB LA IM (Q8W after 2 injections 4 wks apart)** vs TDF/FTC PO QD for MSM/TGW (083) or women (084) at high risk for HIV infection; trial now recruiting (estimated completion: 2022) |

Considerations: may remove need for QD tablets; however, less control of drug intake and same potential for subinhibitory concentrations if doses missed.

For all trials, an oral CAB phase preceded the injection phase.

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HIV-uninfected men and women at low risk for acquiring HIV infection, ages 18 to 65 (n=199)
Grade 2 or Higher AE’s Experienced by >5% of Any Arm

n=177
(CAB 134, PBO 43)

* Grade 2: < 90 to 60 ml/min or 10 to < 30% decrease from participant’s baseline.
Grade 3: < 60 to 30 ml/min or 30 to < 50% decrease from participant’s baseline.

<table>
<thead>
<tr>
<th>AE</th>
<th>CAB</th>
<th>PBO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>34%</td>
<td>2%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>25%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Lipase increased</td>
<td>7%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>2%</td>
<td>0.03</td>
</tr>
<tr>
<td>*Creatinine renal clearance decreased</td>
<td>46%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Blood glucose decreased</td>
<td>8%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>10%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>5%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>0%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Other clinically significant events

• Active Arm Discontinuations due to clinical AE, n=12
  • Gastrointestinal, n=1
  • Rash, n=3
  • Nervous system, n=8
    • Seizure, n=1

• Seroconversion, Active CAB (Cohort 1)
  • Detected Study W77 (48W after final injection)
  • CAB levels BLOQ at W53 and 77
  • Wild type virus
Percentage of Participants with ISR

Cohort 2

<table>
<thead>
<tr>
<th>Participants at Risk</th>
<th>CABLA</th>
<th>Placebo</th>
<th>CABLA</th>
<th>Placebo</th>
<th>CABLA</th>
<th>Placebo</th>
<th>CABLA</th>
<th>Placebo</th>
<th>CABLA</th>
<th>Placebo</th>
<th>CABLA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>60</td>
<td>18</td>
<td>60</td>
<td>18</td>
<td>59</td>
<td>18</td>
<td>58</td>
<td>17</td>
<td>58</td>
<td>17</td>
<td>55</td>
<td>16</td>
</tr>
<tr>
<td>Injection#1</td>
<td>88%</td>
<td>39%</td>
<td>78%</td>
<td>11%</td>
<td>75%</td>
<td>6%</td>
<td>78%</td>
<td>29%</td>
<td>64%</td>
<td>18%</td>
<td>60%</td>
<td>31%</td>
</tr>
<tr>
<td>Injectin#2</td>
<td></td>
<td></td>
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<tr>
<td>Injection#3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Injection#4</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Injection#5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Severity Grade: Mild, Moderate, Severe

## LA IM injectable ARVs for Treatment: Other Candidates

<table>
<thead>
<tr>
<th>Name</th>
<th>Man.</th>
<th>Status</th>
<th>Clinical trials</th>
<th>Results Exp.</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFDa, MK-8591</td>
<td>Merck</td>
<td>Phase 2b</td>
<td>Drive2SIMPLIFY</td>
<td>2020</td>
<td>Phase 2B study with DOR + 3TC</td>
</tr>
<tr>
<td>GS-9131</td>
<td>Gilead</td>
<td>No ongoing LA clinical activity</td>
<td>Preliminary data presented at CROI 2017</td>
<td></td>
<td>Favorable resistance profile</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Favorable synergistic effect when combined with other ARVs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Must overcome manufacturing challenges in order to bring down cost and allow for further study</td>
</tr>
<tr>
<td>GS-CA1</td>
<td>Gilead</td>
<td>Phase 2</td>
<td>Phase 1B studies</td>
<td></td>
<td>Capsid inhibitor with high potency, phase 1 studies suggested monthly or longer injections are possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Currently being developed as an injection for use in Phase 2</td>
</tr>
<tr>
<td>VRC01</td>
<td>NIAID VRC</td>
<td>Phase 1/2</td>
<td>VRC 601</td>
<td></td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VRC 602</td>
<td></td>
<td>Ongoing studies in adults and infants</td>
</tr>
<tr>
<td>Elsulfavirine or VM1500A</td>
<td>Viorim</td>
<td>Phase 2B</td>
<td>Currently under review for oral use</td>
<td></td>
<td>PK and Phase 2B studies show that this drug could be developed into a LA IM injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Similar profile to Efavirenz with fewer AEs in clinical trials</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>TaiMed Biologics</td>
<td>Phase 3</td>
<td>TMB-202</td>
<td></td>
<td>Monoclonal antibody, very high potency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMB-301</td>
<td></td>
<td>2017 results suggest drug resistance problems</td>
</tr>
</tbody>
</table>
Emerging LA PrEP Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting ARVs</td>
<td>▪ Cabotegravir LA IM injection Q12W well tolerated in phase IIa study (ÉCLAIR)[1]</td>
</tr>
<tr>
<td></td>
<td>▪ MK-8591 (EFdA) has extended half-life in early-phase studies[2]</td>
</tr>
<tr>
<td>HIV vaccines</td>
<td>▪ HVTN100 vaccine met immunogenic criteria required to move into phase IIb efficacy studies[3]</td>
</tr>
<tr>
<td></td>
<td>▪ Other vaccine concepts in earlier phases of study</td>
</tr>
<tr>
<td>Broadly neutralizing antibodies</td>
<td>▪ VRC01, 3BNC117 bNAbs have extended half-lives in early studies,[4,5] efficacy trials under way</td>
</tr>
</tbody>
</table>

Other LA drugs for treatment or PrEP
MK-8591 (EFdA) Nucleoside reverse transcriptase translocation inhibitor

MK-8591 is Effective in HIV patients when Dosed Once-Weekly: Results from ongoing Ph1b study

A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10

Friedman, et al., CROI 2016 Poster# 437LB

Potential for a drug in an implant

MK-8591 Parenteral Formulations
Release Effective Drug Levels for >180 days

Low dose amenable to extended-duration parenteral formulation

Grobler et al CROI 2016
GS-CA1 - Capsid Inhibitor
Mode of Action Summary

PRODUCER CELL

Gag
Gag-Pol

NUCLEUS

Gag-Pol

TARGET CELL

Reverse Transcription

Capsid Core Disassembly

Pre-integration complex

Nuclear Translocation

Integration

GS-CA1

Capsid Core Assembly

Maturation

GS-CA1

Integration
• Single subcutaneous injection maintains plasma concentrations well above paEC\textsubscript{95} for >10 wks
• Potential for a monthly dosing interval or longer in humans

\[
\text{paEC}_{95} = 11 \text{ nM}
\]
Monoclonal Antibody against CCR5

PRO-140 phase 1-2 trial results

<table>
<thead>
<tr>
<th>Study</th>
<th>Route</th>
<th>Treatment Groups</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO 140 1302</td>
<td>IV</td>
<td>- Placebo (n=9)</td>
<td>Jacobson et al., J. Infect. Dis. 198:1345, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 0.5 mg/kg single dose (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 mg/kg single dose (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5 mg/kg single dose (n=10)</td>
<td></td>
</tr>
<tr>
<td>PRO 140 2301</td>
<td>IV</td>
<td>- Placebo (n=11)</td>
<td>Jacobson et al., AAC, 54:4137, 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 5 mg/kg single dose (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 10 mg/kg single dose (n=10)</td>
<td></td>
</tr>
<tr>
<td>PRO 140 2101</td>
<td>SC</td>
<td>- Placebo (n=10)</td>
<td>Jacobson et al., J. Inf. Dis. 201:1481, 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 162 mg Days 1, 8, 15 (n=11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 324 mg Days 1, 15 (n=12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 324 mg Days 1, 8, 15 (n=11)</td>
<td></td>
</tr>
</tbody>
</table>
mAb against CCR5
Pro140 monotherapy in ART suppressed patients

• 39 HIV-infected patients on suppressive ART
• R5 virus by Monogram Trofile DNA assay
• 16 continued self-administration sc after week 13
• 15 eligible participants (median CD4 586 cells/mm³)
  • – 11 remained suppressed on PRO140 for >1 year
  • – 3 VF; one moved away from study site
  • – No change in co-receptor usage or susceptibility
• No anti-PRO140 antibodies detected

• Lalezari J et al CROI 2017
Ibalizumab – Long-Acting, Monoclonal Antibody

- Active against HIV-1 resistant to all approved ARV agents
- Binds to CD4 to prevent HIV attachment
- Initial development as IV infusion to be administered every 2 weeks

- In treatment-experienced patients (n=40) with resistance to approved ARV agents, After 24 weeks of treatment (with optimized background regimen):
  - Mean VL decrease of $1.6 \log_{10}$ from Baseline
    (55% with $\geq 1 \log_{10}$; 48% with $\geq 2 \log_{10}$)
  - 43% of patients had VL of <50 copies;
    50% with <200 copies
  - Adverse reactions were mild to moderate

Lewis et al. Croi 2017 Abstract #449LB
Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Single-arm, open-label phase III trial[1]
  - Primary endpoint: ≥ 0.5 log\textsubscript{10} HIV-1 RNA decrease at Day 14
  - **Ibalizumab**: humanized mAb to CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells; FDA breakthrough and orphan drug designations

\begin{itemize}
  \item Pts with HIV-1 RNA > 1000 copies/mL; on ART ≥ 6 mos, on stable ART ≥ 8 wks; resistant to ≥ 1 ARV from 3 classes, sensitive to ≥ 1 ARV for OBR (N = 40)
  \item 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance
  \item **TMB-311**: pts who completed Wk 24 of TMB-301 could continue to receive ibalizumab for an additional 24 wks (N = 27)[2]
\end{itemize}

## TMB-301/-311: Key Results

### Virologic Outcome With Ibalizumab

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TMB-301</th>
<th>TMB-311</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 14&lt;sup&gt;[1]&lt;/sup&gt; (N = 40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>83*</td>
<td>NR</td>
</tr>
<tr>
<td>≥ 1.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>≥ 2.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>NR</td>
<td>48</td>
</tr>
<tr>
<td>Mean log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>NR</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Wk 24&lt;sup&gt;[2]&lt;/sup&gt; (N = 40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>83*</td>
<td>NR</td>
</tr>
<tr>
<td>≥ 1.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
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<tr>
<td>≥ 2.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>NR</td>
<td>48</td>
</tr>
<tr>
<td>Mean log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>NR</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>NR</td>
<td>50</td>
</tr>
<tr>
<td>Wk 48&lt;sup&gt;[3]&lt;/sup&gt; (N = 27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>≥ 1.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>≥ 2.0 log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease, %</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mean log&lt;sub&gt;10&lt;/sub&gt; HIV-1 RNA decrease</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>43</td>
<td>59</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>50</td>
<td>63</td>
</tr>
</tbody>
</table>

*P < .0001 vs 3% at end of control period.

- Wk 24: 9 pts reported 17 serious AEs; 1 drug-related serious AE (IRIS) resulted in d/c
- Wk 48 TEAEs (all mild/moderate): upper respiratory tract infection, 15%; diarrhea, 11%; rashes, 7%

Broadly Neutralizing Antibodies (bNAbs) for HIV Prevention

- **VRC01**: monoclonal antibody directed against the HIV-1 CD4 binding site[1]
  - Terminal half-life in PK study: ~ 15 days; demonstrated antiviral activity in HIV-infected pts
  - Randomized phase II prevention trials now under way
    - Low-dose/high-dose IV VRC01 or placebo Q8W for adults at high risk for HIV infection
    - MSM/TGW (North/South America) and women (sub-Saharan Africa); planned overall enrollment: N = 4200

- Other bNAbs in development: **3BNC117, 10-1074**
Dapivirine Vaginal Ring for HIV Prevention

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<tbody>
<tr>
<td>Overall</td>
<td>27 (95% CI: 1-46; P = .05)</td>
<td>30.7 (95% CI: 0.90-51.5; P = .04)</td>
</tr>
<tr>
<td>Age &gt; 21 yrs</td>
<td>56 (95% CI: 31-71; P &lt; .001)</td>
<td>37.5 (95% CI: 3.49-59.5)</td>
</tr>
</tbody>
</table>

- HOPE (ASPIRE) and DREAM (IPM 027/Ring) programs implementing open-label extension dapivirine ring studies

Long Acting Implants

- Potential advantages over injectables
  - Removable
  - More consistent drug release
  - Could remain in place for years.

- Potential disadvantages over injectables.
  - Specialised device required for insertion
  - Removal?
  - Regulated as both a drug and device.
  - Generic marketplace?

Schlesinger E et al Pharm Res 2016; 33: 1649-1656;  Gunawardana M et al; AAC; 2015; 59: 3913-3919
Long Acting – Oral

Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy

Amaya R. Kirtane1, Omar Abouzid1,2, Daniel Minahan3, Taylor Beneke4, Alison L. Hill5, Christian Sellinger6, Anna Bershtein4, Morgan Craig3, Shirele S. Mo3, Hormoz Meridizam1, Cely Cleveland1,6, Jamie Rogner1, Young-Ah Lee1, Lucas Booth5, Farhad Javid, Sarah J. Wu6, Tyler Grant7, Andrew M. Bellerger1, Boris Nikolov1, Alison Hayward1, Lowell Wood4, Philip A. Eckhoff4, Martin A. Nowak1, Robert Langer1,2,5 & Giovanni Travorscag1,5

Nature Comms 2018; Jan 9th
Key Questions With Long-Acting ART

- Can we move away from daily oral therapy for HIV?
- Are emerging long-acting therapies as effective as oral therapies?
- What about toxicity?
- Is self-administration feasible? Is it desirable?
- What pts might be ideal candidates for long-acting therapy?
- How can resistance be prevented if pts miss doses?
- Can these agents be used as PrEP?