What We Know and What We Do Not Know About Long-acting PrEP

Raphael J. Landovitz, MD MSc
Professor of Medicine
UCLA Center for Clinical AIDS Research & Education
Equitable LAI PrEP Workshop, March 8, 2023
Raphael J. Landovitz has served on Scientific Advisory Boards for Merck.
EFFICACY
HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Primary blinded period, through May 2020

HIV Incidence

- **CAB**: n=2241
- **TDF/FTC**: n=2247

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
<th>CAB</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.44</td>
<td>1</td>
<td>1.29</td>
</tr>
</tbody>
</table>

- **41 Infections**: 3204 PY
- **14 Infections**: 3186 PY

Hazard Ratio (95% CI)

- **Favors CAB**: 0.44
- **Favors TDF/FTC**: 1.29

CI, confidence interval

- **0.18**
- **0.62**

Noninferiority

- **Superiority**: 0.75
- **Noninferiority**: 1.23

NI margin

- **0.34**

Primary Analysis

- **85-14-2020**
- **1 Year**

Year 1 Unblinded Analysis

- **05-14-2021**

Open to Enrollment

- **12-16-2016**

4.4 Years

Landovitz, R. HIV Glasgow 2022.
HPTN 083 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through May 2021

HIV Incidence

- CAB: 25 Infections, 4660 PY
- TDF/FTC: 73 Infections, 4596 PY

Hazard Ratio (95% CI)

- Favors CAB
  - Hazard Ratio: 0.54
  - 95% CI: 0.22 to 0.53

- Favors TDF/FTC
  - Hazard Ratio: 1.59
  - 95% CI: 1.23 to 2.00

HIV Incidence Rate/100 PY

- CAB: 0.00
- TDF/FTC: 0.50

CI, confidence interval

- 95% CI: 0.53

NI margin

- Favors CAB: 0.75
- Favors TDF/FTC: 1.23

Noninferiority: 

- 25 Infections

Superiority:

- 1.59

Landovitz, R. HIV Glasgow 2022.
HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Blinded period, through Nov 2020

HIV Incidence

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
<th>CAB (n=1614)</th>
<th>TDF/FTC (n=1610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>4 Infections</td>
<td>0.20 (1956 PY)</td>
</tr>
<tr>
<td>0.50</td>
<td></td>
<td>36 Infections</td>
</tr>
<tr>
<td>1.00</td>
<td></td>
<td>1.85</td>
</tr>
<tr>
<td>1.50</td>
<td></td>
<td>0.12 (1942 PY)</td>
</tr>
<tr>
<td>2.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval

Hazard Ratio (95% CI)

Favors TDF/FTC  Favors CAB

0.12 0.31

Superiority

0.05 0.75 1 2
HPTN 084 HIV Incidence: CAB vs. TDF/FTC

Combined blinded and unblinded period, through Dec 2021

HIV Incidence

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
</tr>
<tr>
<td>n=1613*</td>
</tr>
<tr>
<td>0.18</td>
</tr>
<tr>
<td>3334 PY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
</tr>
<tr>
<td>n=1610</td>
</tr>
<tr>
<td>1.70</td>
</tr>
<tr>
<td>3292 PY</td>
</tr>
</tbody>
</table>

56 Infections

CI, confidence interval

Hazard Ratio (95% CI)

Favors CAB Favors TDF/FTC

*Excludes 1 baseline infection from the blinded period
The Bottom Line: Efficacy

• Long-acting cabotegravir is very effective at preventing HIV in MSM, TGW, and cisgender women
  • 66% reduction in HIV infection when compared to MSM and TGW who were offered TDF/FTC
  • 89% reduction in HIV infection when compared to cisgender women who were offered TDF/FTC
# HPTN 083 HIV Incidence by Subgroup
## CAB vs. TDF/FTC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CAB Events/PY (IR%)</th>
<th>TDF/FTC Events/PY (IR%)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>11/2185 (0.50)</td>
<td>33/2114 (1.56)</td>
<td>0.32 (0.16, 0.63)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>2/1016 (0.20)</td>
<td>6/1071 (0.56)</td>
<td>0.33 (0.07, 1.61)</td>
</tr>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGW</td>
<td>2/368 (0.54)</td>
<td>7/383 (1.83)</td>
<td>0.29 (0.06, 1.41)</td>
</tr>
<tr>
<td>MSM</td>
<td>11/2829 (0.39)</td>
<td>32/2800 (1.14)</td>
<td>0.34 (0.17, 0.67)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African-American</td>
<td>4/686 (0.58)</td>
<td>15/711 (2.11)</td>
<td>0.28 (0.10, 0.83)</td>
</tr>
<tr>
<td>Non-Black/African-American</td>
<td>0/837 (0.00)</td>
<td>5/790 (0.63)</td>
<td>0.09 (0.00, 2.06)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>4/1523 (0.26)</td>
<td>20/1501 (1.33)</td>
<td>0.19 (0.07, 0.56)</td>
</tr>
<tr>
<td>Latin America</td>
<td>6/1016 (0.59)</td>
<td>11/1007 (1.09)</td>
<td>0.54 (0.20, 1.46)</td>
</tr>
<tr>
<td>Asia</td>
<td>2/569 (0.35)</td>
<td>6/580 (1.03)</td>
<td>0.34 (0.07, 1.66)</td>
</tr>
<tr>
<td>Africa</td>
<td>1/92 (1.08)</td>
<td>2/96 (2.08)</td>
<td>0.52 (0.05, 5.77)</td>
</tr>
</tbody>
</table>
## HPTN 084 HIV Incidence by Subgroup
### CAB vs. TDF/FTC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CAB Events/PY (IR%)</th>
<th>TDF/FTC Events/PY (IR%)</th>
<th>HR (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>4/1956 (0·20%)</td>
<td>36/1942 (1·85%)</td>
<td>0·12 (0·05–0·31)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>3/866 (0·35%)</td>
<td>20/851 (2·34%)</td>
<td>0·17 (0·05–0·54)</td>
</tr>
<tr>
<td>≥25 years</td>
<td>1/1090 (0·09%)</td>
<td>16/1091 (1·47%)</td>
<td>0·09 (0·02–0·49)</td>
</tr>
<tr>
<td><strong>Contraceptive Method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMPA</td>
<td>3/1009 (0·30%)</td>
<td>21/1000 (2·10%)</td>
<td>0·16 (0·05–0·53)</td>
</tr>
<tr>
<td>NET-EN</td>
<td>1/175 (0·57%)</td>
<td>6/182 (3·30%)</td>
<td>0·22 (0·03–1·48)</td>
</tr>
<tr>
<td>Implant</td>
<td>0</td>
<td>8/607 (1·32%)</td>
<td>0·06 (0·00–1·16)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1/152 (0·66%)</td>
<td>0·32 (0·01–9·89)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 kg/m²</td>
<td>4/1389 (0·29%)</td>
<td>27/1447 (1·87%)</td>
<td>0·16 (0·06–0·45)</td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>0</td>
<td>9/495 (1·82%)</td>
<td>0·05 (0·00–0·96)</td>
</tr>
</tbody>
</table>

### Hazard ratios (95% CI)

The Bottom Line: Efficacy in specific populations

- Long-acting cabotegravir is also very effective at preventing HIV in:
  - Young individuals
  - Black individuals
  - Transgender women
  - Individuals from various regions of the world
  - Individuals using various contraceptive methods
  - Individuals with higher BMIs
SAFETY
HPTN 083: Injection Site Reactions

Percentage of Participants Reporting an ISR

- Cabotegravir
  - Mild (Grade 1)
  - Moderate (Grade 2)
  - Severe (Grade 3)
- TDF/FTC
  - Mild (Grade 1)
  - Moderate (Grade 2)
  - Severe (Grade 3)

Injection Number

OVERALL

<table>
<thead>
<tr>
<th>Injection Number</th>
<th>Cabotegravir, n</th>
<th>TDF/FTC, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2117</td>
<td>2081</td>
</tr>
<tr>
<td>2</td>
<td>2117</td>
<td>2081</td>
</tr>
<tr>
<td>3</td>
<td>2037</td>
<td>1940</td>
</tr>
<tr>
<td>4</td>
<td>1938</td>
<td>1889</td>
</tr>
<tr>
<td>5</td>
<td>1872</td>
<td>1860</td>
</tr>
<tr>
<td>6</td>
<td>1761</td>
<td>1760</td>
</tr>
<tr>
<td>7</td>
<td>1620</td>
<td>1606</td>
</tr>
<tr>
<td>8</td>
<td>1464</td>
<td>1463</td>
</tr>
<tr>
<td>9</td>
<td>1360</td>
<td>1355</td>
</tr>
<tr>
<td>10</td>
<td>1200</td>
<td>1193</td>
</tr>
<tr>
<td>11</td>
<td>1034</td>
<td>1037</td>
</tr>
<tr>
<td>12</td>
<td>877</td>
<td>903</td>
</tr>
<tr>
<td>13</td>
<td>744</td>
<td>760</td>
</tr>
<tr>
<td>14</td>
<td>604</td>
<td>596</td>
</tr>
<tr>
<td>15</td>
<td>465</td>
<td>482</td>
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<tr>
<td>16</td>
<td>372</td>
<td>370</td>
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<td>17</td>
<td>298</td>
<td>288</td>
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<td>18</td>
<td>234</td>
<td>220</td>
</tr>
<tr>
<td>19</td>
<td>168</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>89</td>
</tr>
</tbody>
</table>

Landovitz RJ et al. NEJM 2021
HPTN 084: Injection Site Reactions

Any ISR, by injection number and arm

- 21% participants any ISR
  - 32% CAB vs. 9% TDF/FTC
- 4% participants Grade 2+ ISR
  - 7% CAB vs. 1% TDF/FTC
- Zero discontinuations d/t ISR
HPTN 083: Median Change in Weight (kg)

Landovitz RJ et al. NEJM 2021

Estimated mean weight change (kg/y)

**Week 0-40**
- CAB: +1.26 (95%CI 0.98, 1.54) kg/y
- TDF/FTC: -0.50 (95%CI -0.78, -0.22) kg/y
  - p=0.001

**Week 40-105**
- CAB: +1.11 (95%CI 0.82, 1.41) kg/y
- TDF/FTC: +1.19 (95%CI 0.90, 1.49) kg/y
  - p=0.70

**Visit week**

- W0
- W2
- W4
- W5
- W9
- W17
- W25
- W33
- W41
- W49
- W57
- W65
- W73
- W81
- W89
- W97
- W105

Study arm
- CAB
- TDF/FTC
HPTN 083: DXA BMD change over time

- BMD decreased in the TDF-FTC arm by 0.5-1.0%
- BMD increased in CAB-LA arm 0.5-1.5%
The Bottom Line: Safety

• Long-acting cabotegravir was safe and well tolerated
• The most common side effect was injection site reaction (ISR)
  • The majority were mild to moderate in severity
  • Reports of ISRs decreased over time
  • Very few ISRs led to the discontinuation of cabotegravir
• We’re all gaining weight, people on CAB-LA and TDF/FTC at about the same rate EXCEPT for the first year, where TDF/FTC people LOST weight (but then gained thereafter)
• By DXA measurement, CAB-LA had better outcomes than TDF-FTC over two years; no clinical differences
### HPTN 084 Cumulative Pregnancy Outcomes
#### CAB vs. TDF/FTC

<table>
<thead>
<tr>
<th></th>
<th>Total n=132</th>
<th>CAB n=63</th>
<th>TDF/FTC n=69</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td>57</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td><strong>Known pregnancy outcomes</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>61</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Pregnancy loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-36 weeks</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&lt;20 weeks**</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*includes multiple births
**includes ectopic pregnancy, elective and spontaneous abortion
The Bottom Line: Pregnancy

• Data are still being collected on the safety of cabotegravir during pregnancy and breastfeeding
• To date, data does not suggest there are any safety concerns
PHARMACOKINETICS
(That’s a Fancy word for ‘drug levels’)
CAB Subsequent to Final Injection (Log Scale)
Males

CAB Subsequent to Final Injection (Log Scale)
Females

Eshleman S et al. CROI 2022, #95

Schematic for Seroconversions

1\textsuperscript{st} HIV POS visit (Qual RNA, LLOD 30)

5-week oral lead-in

CAB-LA injection

1\textsuperscript{st} Site POS visit rapid and/or Ag/Ab test

CAB concentration

[CAB] 8xPAIC\textsubscript{90}

Weeks since enrollment

CAB (mcg/mL)

0 1 2 3 4 5 6 7 8 9 10

0 0.166 BLQ 0.664 1.33 2.00
Expected Pattern of CAB Concentrations

- **CAB concentration**
- **First HIV positive visit**
- **First site positive visit**
- **First HIV positive visit and first site positive visit**
- **CAB injection**
- **Time between first HIV positive visit and first site positive visit**
- **Time between last injection and first HIV positive visit**

**Chart Details:**
- **Y-axis:** CAB (mcg/mL)
- **X-axis:** Weeks since enrollment
- **Key Events:**
  - **0** weeks: BLQ
  - **10** weeks: 0.166 mcg/mL
  - **20** weeks: 0.664 mcg/mL
  - **100** weeks: 1.35 mcg/mL
  - **234 days:** TAF/FTC/BIC

**Legend:**
- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit
- Time between first HIV positive visit and first site positive visit
- Time between last injection and first HIV positive visit
Fast Elimination – One case so far
• **People born male**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 10.1 Months

• **People born female**: the median time from the last injection to the time when CAB concentration fell below the LLOQ was 1 year and 3.5 months

• Higher BMI associated with more prolonged period of exposure

• Rapid concentration decay in rare participants remains to be fully explained but likely is not a genetic “fast metabolizer” abnormality

Landovitz, R. Lancet HIV. 2020.
FAILURES
REMINDER: BOTH PrEP MEDICATIONS WORK EXTREMELY WELL

Combined blinded and unblinded period, through May 2021

HIV Incidence

- CAB n=2244
- 25 Infections
- 0.54
- 4660 PY

- TDF/FTC n=2248
- 73 Infections
- 1.59
- 4596 PY

Hazard Ratio (95% CI)

- Favors CAB
- Favors TDF/FTC

- CI, confidence interval

- 0
- 0.22
- 0.53
- 0.34
- 1.23
- 2

- Primary Analysis 05-14-2020
- Year 1 Unblinded Analysis 05-14-2021

- Landovitz, R. HIV Glasgow 2022.
FAILURE GROUPS IN HPTN 083

- **Group A cases**: HIV acquired at enrollment
- **Group B cases**: HIV acquired w/o recent CAB exposure
- **Group BR cases**: HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
- **Group C cases**: HIV acquired during oral lead-in
- **Group D cases**: HIV acquired in the setting of on-time CAB injections
- **Group DX cases**: HIV acquired while on CAB with at least one 10-week delayed injection
• **Group A cases:** HIV acquired at enrollment
• **Group B cases:** HIV acquired w/o recent CAB exposure
• **Group BR cases:** HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
• **Group C cases:** HIV acquired during oral lead-in
• **Group D cases:** HIV acquired in the setting of on-time CAB injections
• **Group DX cases:** HIV acquired while on CAB with at least one 10-week delayed injection
CAB arm, Group A

What we learned:

• If we do not diagnose HIV before PrEP agents start (acute or eclipse phase infection = very early infection), CAB can make it challenging to diagnose later

• Failure to diagnose HIV infection can lead to continued CAB administration, and even continued CAB injections
FAILURE GROUPS IN HPTN 083

• **Group A cases**: HIV acquired at enrollment
• **Group B cases**: HIV acquired w/o recent CAB exposure
• **Group BR cases**: HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
• **Group C cases**: HIV acquired during oral lead-in
• **Group D cases**: HIV acquired in the setting of on-time CAB injections
• **Group DX cases**: HIV acquired while on CAB with at least one 10-week delayed injection
What we learned:

• If you don’t take CAB, it doesn’t prevent HIV infection

• In 3 participants, exposure and HIV acquisition during the “tail” did not result in CAB resistance
  • This is reassuring, but DOES NOT RULE OUT THAT IT CAN HAPPEN WE NEED MORE DATA
  • When CAB is restarted after prolonged hiatus, failure to diagnose interim newly acquired HIV can lead to INSTI resistance, much as “A” cases can

• When people were provided open-label TDF/FTC to “cover they tail” they did not take it – this likely contributed to HIV acquisition
• **Group A cases:** HIV acquired at enrollment
• **Group B cases:** HIV acquired w/o recent CAB exposure
• **Group BR cases:** HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
• **Group C cases:** HIV acquired during oral lead-in
• **Group D cases:** HIV acquired in the setting of on-time CAB injections
• **Group DX cases:** HIV acquired while on CAB with at least one 10-week delayed injection
CAB arm, Group C

What we learned:

• If you don’t take CAB, it doesn’t prevent HIV infection
  • We don’t know how “forgiving” it is to missed doses

• There is likely a “time to onset” of protection with oral CAB
  • We don’t know how long

• If CAB delays new (incident) HIV detection by delaying testing, CAB injections can inadvertently be given

• As with the “A” Cases, viral “escape” at HIGH CAB levels can lead to CAB (and other integrase) resistance
FAILURE GROUPS IN HPTN 083

- **Group A cases**: HIV acquired at enrollment
- **Group B cases**: HIV acquired w/o recent CAB exposure
- **Group BR cases**: HIV acquired >6 months after the last CAB injection and an injection given at the time of the first positive visit
- **Group C cases**: HIV acquired during oral lead-in
- **Group D cases**: HIV acquired in the setting of on-time CAB injections
- **Group DX cases**: HIV acquired while on CAB with at least one 10-week delayed injection
CAB arm, Group D & DX

What we learned:

• Delays in HIV tests detecting “new” HIV infections

• CAB levels in the blood were as expected
  • It wasn’t “unexpectedly” low concentrations of CAB that explain the PrEP failure

• If HIV “smolders” after a PrEP failure, it can lead to CAB (and other integrase) resistance
  • That resistance can be often avoided by earlier detection
• When delays occur, CAB levels can drop, losing protection – but not leading to INSTI resistance to-date
## Bottom Line: Summary of HPTN 083 resistance

<table>
<thead>
<tr>
<th>CAB INITIATED OR RE-INITIATED WITH OCCULT HIV INFECTION</th>
<th>N (%)</th>
<th>Integrase Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated</td>
<td>1 (25)</td>
<td>Yes</td>
</tr>
<tr>
<td>Restarted</td>
<td>1 (50)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV ACQUISITION DURING OLI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>During OLI</td>
<td>2 (66)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV BREAKTHROUGH INFECTION WITH ON-TIME INJECTIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>On-time failure</td>
<td>6 (100)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV BREAKTHROUGH INFECTION WITH AT LEAST ONE 10+ WEEK DELAY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 delay</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV INFECTION 6+ MONTHS FROM LAST INJECTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail-phase*</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

*No result for one case
TESTING DELAYS
HIV RNA “spike” precedes production of detectable HIV antibodies
Diagnosing Acute HIV

- HIV-1 RNA (copies/ml)
- HIV-1 Antibody Titer

Detectable RNA Level
Detectable Antibody Level

Infection
Weeks/Months
The Bottom Line: Testing Delays

- RNA testing finds infections earlier, but is costly, may not be feasible in many settings, and may confuse patients and providers
  - This is being explored in HPTN 083 and 084 OLE’

- No delays seen in MSM/TGW when infection is acquired > 6 months after last injection
  - Likely a longer timeline for ciswomen/TGM
CLINICAL USE and IMPLEMENTATION
Making Good Decisions Absent Good Data

What to start?
- Whatever the patient will adhere/persist with best
- There is no ethical/moral “obligation” to use CAB

Onset of protection?
- PK suggests time from first injection (irrespective of OLI) to 8x PA-IC90 is median 2 days, 95% by 7 days
- Durability – incredibly interpatient variability (077 data), likely varies by sex (maybe BMI), wouldn’t assume more than 9-10 weeks for males, 12+ for females

Breakthroughs (nee: failures)
- Poorly understood to date
- Salvage with NNRTI or r/PI if infection likely to have occurred within 1 year, DTG/BIC-based ART >1 year?

Implementation
- Do we have the global, social, and political will to figure out how to use it?
Can CAB be given at other anatomic sites?

- 118 participants enrolled in a ATLAS-2M substudy to evaluate the pharmacokinetics, safety, tolerability, and efficacy of CAB+RPV LA following short-term repeat IM thigh administration.

- Across 704 thigh injections, 327 injection site reactions occurred:
  - Most were Grade 1 (55–76%) or 2 (19–38%)
  - 4–7% were grade 3

- The median duration of ISRs was 3–3.5 days
- One Grade 2 ISR led to withdrawal

- Only 28–33% preferred thigh injections
  - This was largely due to ease of access

How will it be paid for?

- Cabotegravir is currently priced at $22,200 per year
  - >185 times higher than the $60–$119 estimated cost-effectiveness threshold for middle-income countries (MICs)
- ViiV recently provided access to generic versions in 90 countries with the Medicines Patent Pool (MPP), including all African nations
  - Not applicable to all LMICS

Can we use it Equitably?

- **PrEP-to-need ratio**
  - Number of PrEP users divided by the number of new HIV diagnoses in that group in the same year
  - Equity metric, no "target" level
- **US prevention programs in all regions have demonstrated larger gaps in PrEP-to-need ratios by race/ethnicity**
  - Southern states lagged all other regions
- **Better programs are needed to provide PrEP to communities and people at greatest risk for HIV infection**

New Diagnoses of HIV Infection in the United States in 2020 (n=30,403)

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>MSM</th>
<th>Heterosexual</th>
<th>PWID</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>5126</td>
<td>6175</td>
<td>539</td>
</tr>
<tr>
<td>Black</td>
<td>8062</td>
<td>1240</td>
<td>422</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2674</td>
<td>858</td>
<td>422</td>
</tr>
</tbody>
</table>

PrEP-to-Need Ratio (2021)

<table>
<thead>
<tr>
<th>Region</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
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</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>47.0</td>
<td>19.5</td>
<td>26.3</td>
</tr>
<tr>
<td>South</td>
<td>4.5</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Midwest</td>
<td>4.9</td>
<td>5.5</td>
<td>7.3</td>
</tr>
<tr>
<td>West</td>
<td>3.2</td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

Concluding Thoughts

- Long-acting cabotegravir is **highly effective** for prevention of HIV in MSM, TGW, cisgender women and various subgroups
  - So is Tenofovir-based oral PrEP
- CAB is safe, generally well-tolerated, and data does not suggest there are safety concerns for use during pregnancy or breastfeeding
- The washout period after last CAB injection is longer in individuals born female compared to individuals born male
- RNA testing finds CAB breakthrough infections earlier, and often before resistance, but high cost and may not be feasible in many settings
- We need strong community advocacy to **demand** programmatic implication and rapid generic production to bring costs down
- If we don’t **demand** focus on making available biomedical prevention programs to most-affected communities, disparities will only widen
  - This is UNACCEPTABLE
Thank you!

Questions?
rlandovitz@mednet.ucla.edu