Long-acting injectable cabotegravir for HIV Pre-Exposure Prophylaxis

HPTN 083

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AIDS Institute Grand Rounds
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Disclosures

Raphael J. Landovitz has served as on scientific advisory boards for Gilead Sciences and Merck Inc, and has received honoraria from Roche, Inc and Janssen.
Today’s Agenda

- PrEP Background and Context
- HPTN 083 Study Design
- Statistical Methods
- Results
  - Population
  - HIV Incidence
  - Safety
  - Seroconversion events
  - Additional outcomes of interest
  - Update and PK, resistance in seroconversion
- Conclusions
Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials

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“PrEP 2.0”: Trials of Novel PrEP Agents

- **ASPIRE (Dapivirine)**: 27% incidence rate with CI: 1 – 46
- **Ring (Dapivirine)**: 31% incidence rate with CI: 1 – 51
- **DISCOVER (TDF/FTC)**: Incidence rate 0.30%
- **DISCOVER (TAF/FTC)**: Incidence rate 0.16%

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HPTN 083 Study Design

- Phase 2b/3 randomized, double-blind, double-dummy @ 43 sites globally
  - MSM/TGW age 18+
  - Risk: any nCRAI, >5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 months; or SexPro Score ≤16 (US only)
  - Generally good health
  - No HBV or HCV
  - No contraindication to gluteal injections, seizures, gluteal tattoos/skin conditions

- Planned enrollment 5000
  - ≥ 50% under age 30
  - ≥ 10% TGW
  - ≥ 50% of US enrollment Black

- Primary efficacy endpoint: Incident HIV infections during blinded comparison
- Primary safety endpoint: G2 or higher clinical and laboratory AEs
Statistical Design: Efficacy

- **Non-inferiority design**
  - Non-inferiority margin 1.23
  - Alternative hypothesis of HR 0.75
  - Target background HIV Incidence ~4.5%
  - Anticipated TDF/FTC adherence by TFV plasma detectable ~57%

- Endpoint-driven (172 events) with pre-specified interim analyses at 25%, 50%, and 75% of endpoints
  - O’Brien-Fleming stopping boundaries for interim data analysis used to determine early stopping metrics

- DSMB recommended termination of blinded study after interim analysis on May 14, 2020 (25% endpoints accrued) for crossing pre-specified stopping bound

- Results include events occurring through May 14, 2020; participants unblinded, continuing on study
  - All to be offered CAB as soon as available at sites

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Participant Disposition

4570 Randomized

2287 Randomized to FTC/TDF
- 3 inappropriately enrolled

2284 Eligible FTC/TDF
- 3 HIV-1 infected at enrollment
- Retained:
  - 6m 1925/2127 (90.5%)
  - 12m 1476/1706 (86.5%)
  - 18m 888/1096 (81.0%)
  - 24m 413/550 (75.1%)
- 34 had no follow-up visits with HIV status determined

2283 Randomized to CAB
- 1 inappropriately enrolled

2282 Eligible CAB
- 2 HIV-1 infected at enrollment
- Retained:
  - 6m 1935/2124 (91.1%)
  - 12m 1464/1999 (76.2%)
  - 18m 865/1078 (80.2%)
  - 24m 423/557 (75.9%)
- 37 had no follow-up visits with HIV status determined

ITT cohort

Primary efficacy cohort

2247 in analysis

2243 in analysis
<table>
<thead>
<tr>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL (n=4566)</strong></td>
</tr>
<tr>
<td><strong>Gender Identity, n (%)</strong></td>
</tr>
<tr>
<td>MSM</td>
</tr>
<tr>
<td>TGW</td>
</tr>
<tr>
<td><strong>Age, median (IQR)</strong></td>
</tr>
<tr>
<td>26 (22, 32)</td>
</tr>
<tr>
<td><strong>Age, n (%)</strong></td>
</tr>
<tr>
<td>18-29</td>
</tr>
<tr>
<td>30-39</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>50-59</td>
</tr>
<tr>
<td>≥60</td>
</tr>
<tr>
<td><strong>Region, n (%)</strong></td>
</tr>
<tr>
<td>United States</td>
</tr>
<tr>
<td>Latin America</td>
</tr>
<tr>
<td>Asia</td>
</tr>
<tr>
<td>Africa</td>
</tr>
<tr>
<td><strong>Education, n (%)</strong></td>
</tr>
<tr>
<td>Post-Secondary (YES)</td>
</tr>
<tr>
<td><strong>Relationship Status, n (%)</strong></td>
</tr>
<tr>
<td>Single (YES)</td>
</tr>
</tbody>
</table>
# Study Population

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>844 (49.7)</td>
<td>433 (51.0)</td>
<td>411 (48.9)</td>
</tr>
<tr>
<td>White/Asian/Native/Other</td>
<td>854 (50.4)</td>
<td>416 (49.0)</td>
<td>438 (51.1)</td>
</tr>
<tr>
<td><strong>Latin America</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/Afro-Carribean</td>
<td>395 (20.1)</td>
<td>196 (19.9)</td>
<td>199 (20.3)</td>
</tr>
<tr>
<td>Native</td>
<td>858 (43.7)</td>
<td>425 (43.2)</td>
<td>433 (44.2)</td>
</tr>
<tr>
<td>White/Asian/Other</td>
<td>711 (39.6)</td>
<td>363 (36.8)</td>
<td>348 (35.5)</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>749 (99.6)</td>
<td>375 (99.5)</td>
<td>374 (99.7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.4)</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>119 (78.3)</td>
<td>57 (77.0)</td>
<td>62 (79.5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.3)</td>
<td>3 (4.1)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States: Latinx</td>
<td>303 (17.8)</td>
<td>154 (18.1)</td>
<td>149 (17.6)</td>
</tr>
<tr>
<td>Latin America: Latinx</td>
<td>1805 (91.9)</td>
<td>912 (92.7)</td>
<td>893 (91.1)</td>
</tr>
</tbody>
</table>
N: 1,698 (37.2%)
Median age: 27 (IQR 24-34)
Age ≤30: 61%
TGW: 7.4%
Black/African-American: 49.7%
LA
N: 1,964 (43.0%)
Median age: 26
Age ≤30: 67.7%
TGW: 10.3%
South Africa
N: 152 (3.3%)
Median age: 23
Age ≤30: 75.0%
TGW: 9.9%
Asia
N: 752 (16.5%)
Median age: 24
Age ≤30: 79.8%
TGW: 29.8%
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 Rate /100 PY

N=2244
N=2250

CI, confidence interval

HIV Incidence

Hazard Ratio (95% CI)

Favors CAB
Favors TDF/FTC

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Number Needed to Treat
CAB vs. TDF/FTC

NNT is 123 (95% CI 100-215) to prevent one additional HIV infection using CAB vs. TDF/FTC with adherence seen in HPTN 083

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HIV Incidence – ITT

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>Cabotegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>2247</td>
<td>2243</td>
</tr>
<tr>
<td>2 years</td>
<td>2133</td>
<td>2081</td>
</tr>
<tr>
<td>3 years</td>
<td>2019</td>
<td>1913</td>
</tr>
</tbody>
</table>

Cumulative number of events

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>Cabotegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>1965</td>
<td>185</td>
</tr>
<tr>
<td>2 years</td>
<td>1776</td>
<td>1624</td>
</tr>
<tr>
<td>3 years</td>
<td>1632</td>
<td>1494</td>
</tr>
</tbody>
</table>

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HR 0.34 (0.18, 0.62)  
p=0.0005
## Results: HIV incidence in key populations

<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>
13 Incident HIV Infections
Cabotegravir

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13 Incident HIV Infections
Cabotegravir

Infection prior to administration of study product

- A1: 93%
- A2: 93%

B1: 78%
B2: ?
B3: 100%
B4: 95%
B5: 3%

C1: 96%
C2: 98%
C3: 93%

D1: 100%
D2: 97%
D3: 97%
D4: 87%
D5: 90%

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13 Incident HIV Infections
Cabotegravir

Infection after prolonged hiatus from CAB

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13 Incident HIV Infections
Cabotegravir

Infection during oral lead-in phase

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13 Incident HIV Infections
Cabotegravir

Infection despite continuous, on-time CAB injections
Infection prior to administration of study product

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Randomly selected “adherence” subset

<table>
<thead>
<tr>
<th>Visit Week</th>
<th>Overall</th>
<th>Week 4</th>
<th>Week 9</th>
<th>Week 17</th>
<th>Week 33</th>
<th>Week 57</th>
<th>Week 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1256</td>
<td>10.9%</td>
<td>1.5%</td>
<td>1%</td>
<td>2.5%</td>
<td>3.5%</td>
<td>2.5%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Number of samples assayed: 1256</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 7 doses/week (≥1250 fmol/punch): 34.2%
- 4 – 7 doses/week: 41.8%
- 2 – 4 doses/week (350 - <700 fmol/punch): 29.3%
- <2 doses/week (LLOQ - <350 fmol/punch): 25.6%
- No detectable drug (BLQ): 10.9%

Plasma TFV
- 87% >0.3 ng/mL
- 75% >40 ng/mL

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Each participant selected for adherence testing may have up to 8 samples included in this summary.

* Category values for Week 4 adjusted for days on therapy, as steady state not yet achieved
Results: TDF/FTC Adherence

TFV-DP ≥ 700fmol/punch in DBS

1 ≥ 700fmol/punch consistent with 4+ TDF/FTC doses per week.
2 Random sample (N=372). Each participant selected for adherence testing may have up to 10 samples. PK testing is performed on samples taken at week 4, 9, 17, 33, 57, 81, 105, 129, 153, and 177.
47 (2.2%) CAB participants permanently discontinued injectable product due to an injection-related AE

Severity of ISR was strongly associated with odds of permanent discontinuation

Cabotegravir
Moderate (Grade 2)
Severe (Grade 3)
TDF/FTC
Moderate (Grade 2)
Severe (Grade 3)
Grade 2+ Adverse Events Reported in ≥5%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with grade 2+ AEs, n (%)</td>
<td>4202 (92.1%)</td>
<td>2106 (92.3%)</td>
<td>2096 (91.9%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance decreased</td>
<td>3204 (70.2%)</td>
<td>1642 (72.0%)</td>
<td>1562 (68.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CPK increased</td>
<td>937 (20.5%)</td>
<td>460 (20.2%)</td>
<td>477 (20.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>828 (18.1%)</td>
<td>388 (17.0%)</td>
<td>440 (19.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>775 (17.0%)</td>
<td>412 (18.1%)</td>
<td>363 (15.9%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>510 (11.2%)</td>
<td>255 (11.2%)</td>
<td>255 (11.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Musculoskeletal discomfort</td>
<td>507 (11.1%)</td>
<td>253 (11.1%)</td>
<td>254 (11.1%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>495 (10.9%)</td>
<td>252 (11.0%)</td>
<td>243 (10.7%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Headache</td>
<td>448 (9.8%)</td>
<td>216 (9.5%)</td>
<td>232 (10.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>382 (8.4%)</td>
<td>197 (8.6%)</td>
<td>185 (8.1%)</td>
<td>0.53</td>
</tr>
<tr>
<td>ALT/SGPT increased</td>
<td>347 (7.6%)</td>
<td>191 (8.4%)</td>
<td>156 (6.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>323 (7.1%)</td>
<td>117 (5.1%)</td>
<td>206 (9.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>316 (6.9%)</td>
<td>166 (7.3%)</td>
<td>150 (6.6%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>306 (6.7%)</td>
<td>158 (6.9%)</td>
<td>148 (6.5%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Rash</td>
<td>253 (5.5%)</td>
<td>139 (6.1%)</td>
<td>114 (5.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>241 (5.3%)</td>
<td>123 (5.4%)</td>
<td>118 (5.2%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>181 (4.0%)</td>
<td>60 (2.6%)</td>
<td>121 (5.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*70% of pyrexia events in CAB were within 7 days of an injection (event probability 0.65%)
16% of pyrexia events in TDF/FTC were within 7 days of an injection (event probability 0.05%)

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## Adverse Events: Grade 3+
### Reported in ≥2%

<table>
<thead>
<tr>
<th>Event</th>
<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with grade 3+ AEs, n (%)</td>
<td>1490 (32.7%)</td>
<td>766/2282 (33.6%)</td>
<td>724/2280 (31.8%)</td>
<td></td>
</tr>
<tr>
<td>CPK increased</td>
<td>633 (13.9%)</td>
<td>309 (13.5%)</td>
<td>324 (14.2%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Creatinine clearance decreased</td>
<td>348 (7.6%)</td>
<td>190 (8.3%)</td>
<td>158 (6.9%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>152 (3.3%)</td>
<td>76 (3.3%)</td>
<td>76 (3.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>152 (3.3%)</td>
<td>75 (3.3%)</td>
<td>77 (3.4%)</td>
<td>0.87</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>122 (2.7%)</td>
<td>69 (3.0%)</td>
<td>53 (2.3%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

| Participants with EAEs and SAEs, n (%) | 240 (5.3%) | 122 (5.4%) | 118 (5.2%) |         |

| Participant deaths, n (%)           | 11 (0.24%)  | 7 (0.3%)   | 4 (0.2%)   |         |

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# Prevalent and Incident STIs

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalent at baseline, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>241 (5.3)</td>
<td>115 (5.1)</td>
<td>126 (5.5)</td>
</tr>
<tr>
<td>Gonorrhea\text{urine}</td>
<td>29 (0.6)</td>
<td>17 (5.1)</td>
<td>12 (0.5)</td>
</tr>
<tr>
<td>Gonorrhea\text{rectal}</td>
<td>297 (6.5)</td>
<td>150 (6.6)</td>
<td>147 (6.5)</td>
</tr>
<tr>
<td>Chlamydia\text{urine}</td>
<td>122 (2.7)</td>
<td>57 (2.5)</td>
<td>65 (2.9)</td>
</tr>
<tr>
<td>Chlamydia\text{rectal}</td>
<td>502 (11)</td>
<td>255 (11.2)</td>
<td>247 (10.9)</td>
</tr>
<tr>
<td><strong>Incidence, n (rate per 100 py)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>908 (16.5)</td>
<td>451 (16.4)</td>
<td>457 (16.5)</td>
</tr>
<tr>
<td>Gonorrhea\text{urine}</td>
<td>128 (2.4)</td>
<td>57 (2.1)</td>
<td>71 (2.6)</td>
</tr>
<tr>
<td>Gonorrhea\text{rectal}</td>
<td>592 (10.9)</td>
<td>295 (10.9)</td>
<td>297 (11)</td>
</tr>
<tr>
<td>Chlamydia\text{urine}</td>
<td>241(4.4)</td>
<td>124 (4.6)</td>
<td>117 (4.3)</td>
</tr>
<tr>
<td>Chlamydia\text{rectal}</td>
<td>906 (16.7)</td>
<td>481 (17.8)</td>
<td>425 (15.7)</td>
</tr>
</tbody>
</table>
Changes in Weight
Median of changes from baseline (IQR)

Landovitz RJ et al. AIDS 2020, #OAXLB0101

HPTN 077: Over 41 weeks

CAB +1.48 (95%CI 0.15, 2.8) kg/y
PBO +1.57 (95%CI -1.35, 4.49) kg/y
p=0.95

Landovitz RJ et al. CID 2019.
Changes in Weight
Median of changes from baseline

Median Body Weight Change from Enrollment, kg (IQR)

**Week 0-40**
- CAB: +1.54 (95%CI 1.0, 2.0) kg/y
- TDF/FTC: -0.51 (95%CI -0.80, -0.22) kg/y
  - p<0.001

**Week 40-105**
- CAB: +1.07 (95%CI 0.61-1.5) kg/y
- TDF/FTC: +1.06 (95%CI 0.79,1.3) kg/y
  - p=0.93

HPTN 077: Over 41 weeks
- CAB: +1.48 (95%CI 0.15, 2.8) kg/y
- PBO: +1.57 (95%CI -1.35, 4.49) kg/y
  - p=0.95

Landovitz RJ et al. CID 2019.
And then we observed something unexpected...
HIV Incidence: CAB vs. TDF/FTC

**HIV Incidence**

<table>
<thead>
<tr>
<th></th>
<th>CAB n=2243</th>
<th>TDF/FTC n=2247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (/100 PY)</td>
<td>0.41</td>
<td>1.22</td>
</tr>
<tr>
<td>Infections</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>PY</td>
<td>3205</td>
<td>3187</td>
</tr>
</tbody>
</table>

**Hazard Ratio (95% CI)**

- Favors TDF/FTC: 1.23
- Favors CAB: 0.75
- CI, confidence interval

Marzinke et al, Journal of Inf Dis, 2021 in Press
Pre-specified HIV Testing

**Real-time site testing**
- **Screening**
  - POC Ab
  - Ag Ab
  - VL

**Enrollment**
- POC Ab
- Ag Ab
- Ab / VL

**Follow-up visits**
- POC Ab
- Ag Ab
- Ab / VL / DNA

**HPTN Laboratory Center testing (retrospective)**
- Visits with reactive/positive site tests
  - Ag Ab
  - qual RNA
  - Ab

**Back-testing**
- quant RNA

**Blinded adjudication of study endpoints**

**Site testing**
- **Point-of-care antibody test**
  - Ab

- **Instrumented antigen/antibody test**
  - Ag Ab

- **Viral load test**
  - VL

- **Confirmatory/discriminatory antibody test**
  - Ab

- **Ultrasensitive DNA test**
  - DNA

**HPTN LC testing**
- **ARCHITECT antigen/antibody test**
  - Ag Ab

- **APTIMA qualitative RNA test**
  - qual RNA

- **Geenius discriminatory antibody test**
  - Ab

*Selected cases

Marzinke et al, Journal of Inf Dis, 2021 in Press
### Extended HPTN LC Testing

**HIV testing**

**Back-testing**

<table>
<thead>
<tr>
<th>CAB arm: All visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC arm: Enrollment, weeks 2, 4, 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CAB arm: Enrollment plus three visits prior to the first RNA pos visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC arm: Enrollment plus one visit prior to the first RNA pos visit</td>
</tr>
</tbody>
</table>

- If Ag/Ab test reactive
- If qualitative RNA test reactive
- Selected cases/visits

**HIV genotyping (VL >500 c/mL)**

**CAB arm**

- All study visits

**TDF/FTC arm**

- First HIV positive visit
- First site positive visit

**Pharmacology testing**

**CAB concentrations**

- Plasma [CAB]: all study visits
- Plasma [TFV]: baseline infections, step 3 infections
- DBS [TFV-DP]: step 3 infections

**TDF/FTC concentrations**

- Plasma [TFV]: first site pos, first HIV pos, 3 prior visits
- DBS [TFV-DP]: first site pos, 1 prior visit

**Tests**

- ARCHITECT antigen/antibody test
- APTIMA qualitative RNA test
- Geenius discriminatory antibody test
- Viral load test
- Single copy RNA test

Marzinke et al, Journal of Inf Dis, 2021 in Press
13 Incident, 2 baseline Infections: Cabotegravir

Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC dispensed
Step 3: Overdue TDF/FTC dispensation
Annual follow-up

Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
* First site positive HIV test

Marzinke et al, Journal of Inf Dis, 2021 in Press
13 Incident, 2 baseline Infections: Cabotegravir

Marzinke et al, Journal of Inf Dis, 2021 in Press
13 Incident, 3 baseline Infections: Cabotegravir

Marzinke et al, Journal of Inf Dis, 2021 in Press
12 Incident, 4 baseline Infections: Cabotegravir

Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: CAB LA injection > 2 week overdue
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up

Percent adherence to oral lead-in
CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test

Marzinke et al, Journal of Inf Dis, 2021 in Press
HIV Incidence: CAB vs. TDF/FTC

Marzinke et al, Journal of Inf Dis, 2021 in Press
HIV Incidence: CAB vs. TDF/FTC

**HIV Incidence**

- **CAB**
  - n=2241
  - 12 Infections
  - 3204 PY
- **TDF/FTC**
  - n=2247
  - 39 Infections
  - 3187 PY

HIV Incidence Rate/100 PY

- **HIV Incidence Rate**
  - CAB: 0.37
  - TDF/FTC: 1.22

CI, confidence interval

**Hazard Ratio (95% CI)**

- **Favors CAB**
  - 0.32
- **Favors TDF/FTC**
  - 1.23

Marzinke et al, Journal of Inf Dis, 2021 in Press
CAB arm, Group A
HIV positive at study enrollment
NRTI: K65R, M184V
NNRTI: L100I, K103N, P225H

Viral load
Confirmatory Ab test
Qualitative RNA test
Ag/Ab test

BLQ
0.166
0.664
1.33
3
20
0
1
2
3
4
5
6
CAB (mcg/mL)

Viral load
Confirmatory Ab test
Qualitative RNA test
Ag/Ab test

BLQ
0.166
0.664
1.33
3
20
0
1
2
3
4
5
6
CAB (mcg/mL)

Viral load
Confirmatory Ab test
Qualitative RNA test
Ag/Ab test

BLQ
0.166
0.664
1.33
3
20
0
1
2
3
4
5
6
CAB (mcg/mL)

Viral load
Confirmatory Ab test
Qualitative RNA test
Ag/Ab test

BLQ
0.166
0.664
1.33
3
20
0
1
2
3
4
5
6
CAB (mcg/mL)

The x-axis represents weeks since enrollment. The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press
CAB arm, Group B
No recent CAB exposure
The x-axis represents weeks since enrollment. The shaded area represents time on ART.

Suppressed on boosted-PI regimen

Undetectable on EFV (now RPV)-based ART

Suppressed on TDF/FTC/EFV

Suppressed on TAF/FTC/BIC

CAB concentration  CAB injection  First HIV positive visit

First site positive visit  First HIV positive visit and first site positive visit

#  Weeks between last injection and the first HIV positive test

Marzinke et al, Journal of Inf Dis, 2021 in Press
CAB arm, Group C
Infected during the CAB oral lead-in period
The x-axis represents weeks since enrollment. The shaded area represents time on ART.
CAB arm, Group D
Infected in the setting of on-time CAB injections
The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press
The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press
The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press
A Cautionary Tale

The shaded area represents time on ART.

Marzinke et al, Journal of Inf Dis, 2021 in Press
<table>
<thead>
<tr>
<th>Case</th>
<th>Sample type</th>
<th>Visit type</th>
<th>Subtype</th>
<th>Drug resistance mutations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>INSTI Phenotype&lt;sup&gt;b&lt;/sup&gt; (Fold change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NRTI</td>
<td>NNRTI</td>
</tr>
<tr>
<td>A1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Enrollment</td>
<td>B</td>
<td>K65R, M184V</td>
<td>L100I, K103N, I135T, P225H</td>
</tr>
<tr>
<td>A2</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Enrollment</td>
<td>C</td>
<td>I135T, Q207E</td>
<td>I13V, M36I, L89M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (60 days later)</td>
<td>Week 6</td>
<td>I135T, Q207E</td>
<td>I13V, M36I, L89M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (69 days later)</td>
<td>Week 6</td>
<td>I135T, Q207E</td>
<td>I13V, M36I, L89M</td>
</tr>
<tr>
<td>B1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Yearly 1</td>
<td>B</td>
<td>I135T, V179T, Y181C, H221Y</td>
<td>I62V</td>
</tr>
<tr>
<td>C1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Week 9</td>
<td>B</td>
<td>L10I, L13V, M36I</td>
<td>L10I, L13V, M36I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (10 days later)</td>
<td>Week 10</td>
<td>L10I, L13V, M36I</td>
<td>L74I, E138K/Q148R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (14 days later)</td>
<td>Week 10</td>
<td>L10I, L13V, M36I</td>
<td>L74I, E138K/Q148R</td>
</tr>
<tr>
<td>C3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Week 9</td>
<td>B</td>
<td>V118I</td>
<td>M36I, I62V, A71T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (1 day later)</td>
<td>Interim visit</td>
<td>V118I</td>
<td>M36I, I62V, A71T</td>
</tr>
<tr>
<td>D3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>Week 17</td>
<td>BF</td>
<td>K103N, I135T</td>
<td>L10V, M36I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (112 days later)</td>
<td>Week 33</td>
<td>K103N, I135T</td>
<td>L10V, M36I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up (117 days later)</td>
<td>Week 33</td>
<td>K103N, I135T</td>
<td>L10V, M36I</td>
</tr>
<tr>
<td>D4</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; viremic</td>
<td>F/U Week 12</td>
<td>C</td>
<td>K20R, E35D, M36I, L89M</td>
<td>I62V</td>
</tr>
</tbody>
</table>

Marzinke et al, Journal of Inf Dis, 2021 in Press
Key virology findings - CAB arm

- Extended testing identified earlier infection dates in many cases
- Virus loads were often low at the first HIV positive visit
- There was often a prolonged period of viral suppression after infection
- Antibody expression was diminished / delayed in many cases
- In some cases, RNA and Ab tests reverted to negative/non-reactive early in infection
TDF/FTC arm
39 Incident, 3 Baseline Infections: TDF/FTC

Marzinke et al, Journal of Inf Dis, 2021 in Press
TDF/FTC arm – infected despite good adherence

Marzinke et al, Journal of Inf Dis, 2021 in Press
Key Observations & Conclusions

Key observations:

• 4 incident infections in the CAB arm occurred despite target plasma CAB concentrations; evaluation of correlates of protection is ongoing
• CAB-LA can delay detection of infection using standard HIV testing algorithms
• INI resistance seen when viremic “escape” occurs at higher CAB concentrations
• INI resistance was not seen in 3 tail-phase infections or 1 tail “escape” case
• 37/39 in the TDF/FTC arm with incident infection had suboptimal or non-adherence

Conclusions:

• Oral lead-in will be optional in 083 OLE
• Use of VL testing as a primary screen for HIV infection will be assessed in 083 OLE
• In the setting of CAB-LA, prompt diagnosis and ART initiation are needed to avoid resistance

In HPTN 083, CAB-LA and TDF/FTC were both highly effective for HIV prevention. CAB-LA was superior to daily oral TDF/FTC for HIV PrEP in HPTN 083
HIV Incidence
Counterfactual Placebo Incidence

Adherence subset: TFV plasma detectable 86.5%

Meta-regression of PBO-controlled TDF/FTC PrEP trials anticipates 74.7% risk reduction for adherence based 86.5% plasma TFV > 0.3 ng/mL

Caveat: If higher risk associated with higher adherence

**TDF/FTC** arm 1.22% HIV incidence
Risk reduced by 74.7% based on TDF/FTC use
Background HIV incidence is estimated to be 4.82% (95% CI 2.32-10.50%)

**CAB** risk reduction (incidence 0.41%) compared to a counterfactual placebo would be estimated to be 91.5% (95% CI 82-96%)

Landovitz RJ et al. AIDS 2020, #OAXLB0101
Sinead Delaney-Moretlwe and Mina Hosseinipour, Protocol Chairs

- **Primary Objective:** Reduce HIV Incidence (superiority, double blind, double dummy design)
- **Endpoint-driven trial (HIV infection)** – monitored by NIAID DSMB every 6 months
- **Est. study duration:** enrollment 24 months; follow-up up to 4.5 years
- **N=3200 at 20 sites in Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe**

Start Nov 2017

Blinded Study halted by DSMB November 2020
Primary outcome: HIV incidence

40 infections over 3892 person-years
Pooled HIV incidence 1.03 (0.73, 1.4) per 100 person-years

<table>
<thead>
<tr>
<th></th>
<th>CAB</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infections</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Person-years</td>
<td>1,953</td>
<td>1,939</td>
</tr>
<tr>
<td>HIV incidence (95% CI)</td>
<td>0.2 (0.06, 0.52)</td>
<td>1.86 (1.3, 2.57)</td>
</tr>
</tbody>
</table>

Wald test z statistic – 4.20, efficacy stopping bound (z scale) – 3.61

Women in the CAB group had an 89% lower risk of HIV infection, compared to TDF/FTC group.
“PrEP 3.0”: Trials of Novel PrEP Agents

**ASPIRE**
(Dapivirine)

- Incidence rate: 0.30%
- CI: 1 – 46

**Ring**
(Dapivirine)

- Incidence rate: 0.16%
- CI: 1 – 51

**DISCOVER**
(TDF/FTC)

- Incidence rate: 1.22%

**HPTN 083**
(TDF/FTC)

- Incidence rate: 0.41%

**HPTN 084**
(CAB)

- Incidence rate: 1.79%

**DISCOVER**
(TAF/FTC)

- Incidence rate: 0.16%

**HPTN 084**
(CAB)

- Incidence rate: 0.21%
Conclusions

- Both CAB and TDF/FTC highly effective for HIV prevention

- The PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083 and HPTN 084

- CAB-LA was generally well tolerated despite injection site reactions

- 1/4, 0/5, 2/3, and 2/4 Acute (Prevalent), Distant from CAB, Oral-lead-in, and On-time injection participants developed INSTI resistance
  - Tail phase seroconversion did not result in INSTI resistance
  - Breakthrough at high and expected CAB concentrations resulted in INSTI resistance

- CAB is the first long-acting injectable agent to demonstrate robust HIV prevention efficacy
Acknowledgements

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• Additional funding from ViiV Healthcare

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• Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutchinson Cancer Research Center
• Leadership and Operations Center, FHI 360
• HPTN Leadership

Pharmaceutical Support
• ViiV Healthcare
• Gilead Sciences, Inc.

HPTN 083 Study Team
Community Program Managers
Community Educators & Recruiters, CAB Members

Our 43 Sites in 7 countries

...and our Study Participants!

Questions? Email rlandovitz@mednet.ucla.edu or @doc_in_a_box