Cabotegravir Pharmacology in the Background of Delayed Injections in HPTN 084


Presenting Author
Mark A. Marzinke, PhD

Johns Hopkins University School of Medicine
Baltimore, MD, USA

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Overall Study Findings: HPTN 084

• HPTN 084 is an ongoing Phase 3 randomized controlled trial that demonstrated the superiority of long-acting injectable cabotegravir (CAB) compared to daily oral F/TDF for HIV prevention in individuals assigned female at birth.
  – HIV incidence CAB 0.20 vs F/TDF 1.85 per 100 py, HR 0.12; 95% CI 0.05 - 0.31

• The blinded portion of the trial was stopped at a planned interim review on 05Nov2020.

• Participants were subsequently unblinded and continued on their original randomized study regimen pending a protocol amendment to offer open-label CAB.
HPTN 084 Study Design

- Oral Lead-In: 30 mg CAB or oral F/TDF, placebo
- Injection Phase: 600 mg CAB-LA or oral F/TDF, placebo
- PK Tail Phase: Open-Label F/TDF

- The CAB-LA regimen was targeted to achieve concentrations >4x PA-IC$_{90}$ (0.664 mcg/mL) in 80% of individuals, and >8x PA-IC$_{90}$ (1.33 mcg/mL) in 50% of individuals.
Evaluation of Delayed Injections in HPTN 084

- Interrogate the impact of delayed injections on CAB concentrations
  - Sampling was limited to participants randomized to the CAB study arm during the blinded phase of the trial
  - Sampling was limited to the following:
    - Type 1 Delay: If the second injection (week 9) took place 8-14 weeks after the first injection (week 5)
    - Type 2 Delay: If any subsequent injection took place 12-18 weeks after the last injection
Characteristics of Participants Who Received Delayed Injections

• 194/1614 participants (12%) had at least one delayed injection during blinded phase of HPTN 084; 224 total delays observed
  – 19 Type 1 Delays
  – 205 Type 2 Delays

<table>
<thead>
<tr>
<th>Country</th>
<th>Participants (n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>8</td>
<td>4.1</td>
</tr>
<tr>
<td>Eswatini</td>
<td>7</td>
<td>3.6</td>
</tr>
<tr>
<td>Kenya</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Malawi</td>
<td>10</td>
<td>5.2</td>
</tr>
<tr>
<td>South Africa</td>
<td>108</td>
<td>55.7</td>
</tr>
<tr>
<td>Uganda</td>
<td>26</td>
<td>13.4</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>29</td>
<td>15.0</td>
</tr>
</tbody>
</table>

• Participant Profile
  – Age (median): 25 years (18-44 years)
  – BMI (median): 26.3 (16.9-54.3)
  – Weight (median): 68 kg (40-146)
Injection Delays Between 1\textsuperscript{st} and 2\textsuperscript{nd} Injections (Type 1 Delays)

<table>
<thead>
<tr>
<th>[CAB] Trough</th>
<th>8-10 weeks Between Injections</th>
<th>10-12 weeks Between Injections</th>
<th>12-14 weeks Between Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=11</td>
<td>N=4</td>
<td>N=4</td>
<td></td>
</tr>
<tr>
<td>&gt;8x PA-IC\textsubscript{90}</td>
<td>10 (91%)</td>
<td>2 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&gt;4-8x PA-IC\textsubscript{90}</td>
<td>1 (9%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>1-4x PA-IC\textsubscript{90}</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>&lt;1x PA-IC\textsubscript{90}</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Type 1 Delay

![Graph showing injection delays between 1\textsuperscript{st} and 2\textsuperscript{nd} injections with different categories and percentages.](image-url)
Injection Delays *After* the 2\textsuperscript{nd} Injection (Type 2 Delays)

<table>
<thead>
<tr>
<th>[CAB] Trough</th>
<th>12-14 weeks Before Injections</th>
<th>14-16 weeks Between Injections</th>
<th>16-18 weeks Between Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=109</td>
<td>N=57</td>
<td>N=39</td>
</tr>
<tr>
<td>&gt;8x PA-IC\textsubscript{90}</td>
<td>95 (87%)</td>
<td>48 (84%)</td>
<td>24 (62%)</td>
</tr>
<tr>
<td>&gt;4-8x PA-IC\textsubscript{90}</td>
<td>12 (11%)</td>
<td>6 (11%)</td>
<td>11 (28%)</td>
</tr>
<tr>
<td>1-4x PA-IC\textsubscript{90}</td>
<td>1 (1%)</td>
<td>2 (4%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>&lt;1x PA-IC\textsubscript{90}</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>
HIV Infections in Participant with Delayed Injections

• During blinded phase of HPTN 084, one participant acquired HIV in the background of late injections
  – 3/9 injections occurred late (8.5, 15.1, 16.1 weeks)
  – CAB concentration at first HIV positive visit: 0.416 mcg/mL (<4x PA-IC₉₀)

Delany-Moretlwe et al. Lancet. 2022; 399
Eshleman et al. J Infect Dis. 2022; 225(10)
CAB Population Pharmacokinetic (popPK) Model and Significant Co-variates

Han et al. Br J Clin Pharm. 2022; 88(10)
CAB Population Pharmacokinetic (popPK) Model and Significant Co-variates

Han et al. Br J Clin Pharm. 2022; 88(10)
Conclusions

• HPTN 084 participants on a CAB-LA 600 mg Q2M regimen who received late injections maintained CAB concentrations >4x PA-IC$_{90}$ and >8x PA-IC$_{90}$ 98% and 87% of the time, respectively, following a 6 week delay (12-14 weeks between injections).

• Data from HPTN 084 suggest that there may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed CAB injections.
Future Considerations

- While data suggest injection forgiveness in persons assigned female at birth, adoption of quarterly dosing (CAB-LA 600 mg Q3M) has not been evaluated for prevention
  - Q3M dosing should not be pursued in persons assigned male at birth
  - Empiric evidence to ensure target concentrations are achieved with alternative dosing regimens is needed
Acknowledgments

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• Gilead Sciences

HIV Prevention Trials Network
• Leadership and Operations Centre, FHI360
• Laboratory Centre (Johns Hopkins)
• Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
• HPTN Leadership

HPTN 084 Study team
• 20 sites in 7 countries in sub-Saharan Africa
• Community advisory boards and partners

… and our study participants!

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