Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: results from HPTN 084

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on behalf of the HPTN 084 study team
Authors


on behalf of the HPTN 084 study team
Disclosures

- I have served on MSD advisory boards
- I have received drug donations for research from Gilead Sciences
Background

- Antiretroviral-based pre-exposure prophylaxis can reduce HIV acquisition

- Women are disproportionately affected by HIV, esp. in sub-Saharan Africa where women experience individual and social barriers to consistent daily oral PrEP use

- Novel long-acting products e.g., CAB LA administered less frequently may simplify PrEP use and provide much needed HIV protection

Primary Objectives

• To evaluate the relative efficacy of oral CAB/CAB LA vs. daily oral TDF/FTC for HIV prevention.

• To evaluate the relative safety of oral CAB/CAB LA vs. daily oral TDF/FTC for HIV prevention.
Study population

- Planned enrolment n=3200 at 20 sites
- Cisgender women aged 18-45 years
- HIV negative
- Sexually active
- Modified VOICE Risk Score $\geq 3^*$
  - Age, partner characteristics, alcohol use
  - Increased to $\geq 5$
- No contraindications to either agent
  - No hepatic or renal insufficiency, seizures, allergy
- Not pregnant or breastfeeding
- Use reliable form of modern contraception
  - From May 2018, only LARC with <1% failure rate
HIV, pregnancy testing and safety assessments at each product administration visit; additional post injection safety visits
Real-world adherence counselling support aligned with national guidelines
Statistical analysis

• Endpoint-driven trial (n=114)
  – Background HIV incidence in absence of PrEP 3.5% pa
  – CAB adherence 80-85%, TDF/FTC adherence 45-50%, LTFU 5% pa
  – 90% power, $\alpha = 0.05$ to detect RR 0.48-0.54

• Superiority analysis
  – HIV incidence during steps 1 and 2
  – Intent to treat, Cox proportional hazards model, stratified by site

• Interim reviews at 22%, 39%, 59%, 78% of information planned
  – Early stopping using an O’Brien-Fleming boundary for efficacy
  – Pre-specified stopping boundary crossed during planned interim review Nov 5, 2020
Screening, enrolment and follow-up

- **4,882 Screened**
- **3,224 Randomised**
- **1,658 excluded**

- **Allocated to CAB LA n=1,614**
  - Follow-up
    - M6 1358/1441 (94.2%)
    - M12 901/999 (90.2%)
    - M18 321/377 (85.1%)
    - M24 71/84 (84.5%)
  - Analysed n=1,614
    - 1,953 person-years

- **Allocated to TDF/FTC n=1,610**
  - Follow-up
    - M6 1346/1442 (93.3%)
    - M12 905/1002 (90.3%)
    - M18 332/378 (87.8%)
    - M24 77/88 (87.5%)
  - Analysed n=1,610
    - 1,939 person-years

20 no post randomisation HIV results
22 no post randomisation HIV results
<table>
<thead>
<tr>
<th></th>
<th>Total (n=3224)</th>
<th>CAB (n=1614)</th>
<th>TDF/FTC (n=1610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>25 (22, 30)</td>
<td>25 (22, 30)</td>
<td>25 (22, 20)</td>
</tr>
<tr>
<td>≤ 25 years</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Not living with partner</td>
<td>82%</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>In the past month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner HIV positive or unknown*</td>
<td>34%</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>≥ 2 sex partners*</td>
<td>54%</td>
<td>54%</td>
<td>55%</td>
</tr>
<tr>
<td>Transactional sex*</td>
<td>41%</td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td>Anal sex*</td>
<td>6%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Median VOICE risk score (IQR)</td>
<td>6 (5,7)</td>
<td>6 (5,7)</td>
<td>6 (5,7)</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>17%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td>55%</td>
<td>55%</td>
<td>56%</td>
</tr>
</tbody>
</table>

*Responses for 3210 participants, CAB n=1610 and TDF/FTC N=1600
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.

Cumulative HIV incidence – ITT

HR: 0.11 (0.01, 0.31)
P = 0.00027
Overall, 62% detectable TFV and 46% >40ng/ml
Injection coverage, 6-month intervals - all

Injection coverage: injections administered as a proportion of total expected injection visits
Cabotegravir - 4 incident HIV Infections
Cabotegravir - 4 incident HIV Infections

Infection in the absence of recent CAB exposure

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
First site positive HIV test
Cabotegravir - 4 incident HIV Infections
TDF/FTC - 36 Incident HIV Infections

Step 1: Oral TDF/FTC lead-in
Step 2: Blinded TDF/FTC
Step 2: Blinded TDF/FTC overdue
Blinded TDF/FTC dispensed
First site test positive for HIV
Additional testing among seroconverters, in progress

- **HIV**
  - Timing of first infection

- **Drug concentrations**
  - CAB all visits
  - TDF/FTC selected visits peri-infection

- **Resistance profiles**
  - HIV infection at time of first detection
Safety: Injection site reactions (ISR)

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
Safety: Grade 2+ adverse events - reported in ≥ 5%

<table>
<thead>
<tr>
<th>Participants with ≥ Grade 2 events</th>
<th>Total (n=3224)</th>
<th>CAB (n=1614)</th>
<th>TDF/FTC (n=1610)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Any Grade 2+ events</td>
<td>2956</td>
<td>92%</td>
<td>1477</td>
</tr>
<tr>
<td>Creatinine clearance decreased</td>
<td>2359</td>
<td>73%</td>
<td>1166</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>664</td>
<td>21%</td>
<td>337</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>650</td>
<td>20%</td>
<td>309</td>
</tr>
<tr>
<td>Chlamydia infection</td>
<td>528</td>
<td>16%</td>
<td>253</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>509</td>
<td>16%</td>
<td>236</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>409</td>
<td>13%</td>
<td>210</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>320</td>
<td>10%</td>
<td>172</td>
</tr>
<tr>
<td>Blood glucose decreased</td>
<td>292</td>
<td>9%</td>
<td>146</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>267</td>
<td>8%</td>
<td>145</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>230</td>
<td>7%</td>
<td>123</td>
</tr>
<tr>
<td>Back pain</td>
<td>188</td>
<td>6%</td>
<td>89</td>
</tr>
<tr>
<td>Abnormal loss of weight</td>
<td>177</td>
<td>5%</td>
<td>76</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>166</td>
<td>5%</td>
<td>81</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>159</td>
<td>5%</td>
<td>86</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>155</td>
<td>5%</td>
<td>79</td>
</tr>
<tr>
<td>Any SAE/EAE</td>
<td>73</td>
<td>2%</td>
<td>32</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
<td>0,1%</td>
<td>3</td>
</tr>
</tbody>
</table>
CT/GC incidence - ITT (n=3,224)

- Chlamydia
  - CAB (n=1614): 18.4
  - TDF/FTC (n=1610): 20.5

- Gonorrhoea
  - CAB (n=1614): 7.2
  - TDF/FTC (n=1610): 8
Changes in weight, kg – ITT (n=3,224)

- Initial immediate increase in weight on CAB: +0.42 kg CAB, (95% CI 0.30, 0.54), p <0.001
- Overall, increase in weight in both arms:
  - CAB +2.4 (95% CI 2.1, 2.7) kg/year
  - TDF/FTC +2.2 (95% CI 2.0, 2.4) kg/year
  - p=0.12
## Pregnancy incidence and outcomes - ITT

<table>
<thead>
<tr>
<th></th>
<th>Total n=3224</th>
<th>CAB n=1614</th>
<th>TDF/FTC n=1610</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. confirmed pregnancies</td>
<td>50</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Person-years</td>
<td>3829.7</td>
<td>1914.5</td>
<td>1915.2</td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>1.3 (1.0, 1.7)</td>
<td>1.5 (1.0, 2.2)</td>
<td>1.1 (0.7, 1.7)</td>
</tr>
</tbody>
</table>
# Pregnancy outcomes - ITT

<table>
<thead>
<tr>
<th></th>
<th>Total n=50</th>
<th>CAB n=29</th>
<th>TDF/FTC n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td>23</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td><strong>Known pregnancy outcomes n=27</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Pregnancy loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=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>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ectopic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Congenital anomalies n=27</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*includes elective terminations
Conclusions

• Both agents highly effective in preventing HIV
  – Pooled incidence 1.03 (0.73, 1.4) per 100 py

• CAB was superior to daily oral TDF/FTC in preventing HIV in cisgender women
  – 89% lower risk of HIV infection in participants receiving CAB compared to TDF/FTC
  – CAB LA 8-weekly likely provided an adherence advantage over daily oral TDF/FTC
  – Ongoing testing to fully understand reasons for breakthrough infections

• Both products were safe and well tolerated with few differences in Grade 2+ adverse events by arm, apart from ISR
  – ISR were generally mild, associated with pain, and generally occurred at 1\textsuperscript{st} injection
  – No discontinuations due to ISR

• Results complement data from HPTN 083, and confirm CAB as first safe and effective injectable PrEP agent for cisgender women
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