Laboratory Analysis of HIV Infections in HPTN 083: Injectable CAB for PrEP

HPTN 083 Study Design

**STEP 1**
- Group A: Every day for 5 weeks
- Group B: CAB

**STEP 2**
- Weeks 5 and 9
- Every 2 months for approximately 3 years
- TDF/FTC (Every day)

**STEP 3**
- Every day for 1 year
- Group A: TDF/FTC
- Group B: CAB

**Drug Administration**
- TDF/FTC pill
- Cabotegravir (CAB) injection
- Placebo for TDF/FTC pill
- Placebo for cabotegravir (CAB) pill
### HIV Incidence: CAB vs. TDF/FTC

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>HIV Incidence Rate/100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
<td>TDF/FTC</td>
</tr>
<tr>
<td>n=2243</td>
<td>n=2247</td>
</tr>
<tr>
<td>0.41</td>
<td>1.22</td>
</tr>
<tr>
<td>3205 PY</td>
<td>3187 PY</td>
</tr>
<tr>
<td>13 Infections</td>
<td>39 Infections</td>
</tr>
</tbody>
</table>

CI, confidence interval
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

Site testing

POC
Ab
Point-of-care antibody test

Ag
Ab
Instrumented antigen/antibody test

VL
Viral load test

Confirmatory/discriminatory antibody test

DNA
Ultrasensitive DNA test (centralized at JHU)

HPTN LC testing

Ag
Ab
ARCHITECT antigen/antibody test

qual RNA
APTIMA qualitative RNA test

Ab
Geenius discriminatory antibody test

Blinded adjudication of study endpoints

*Selected cases
**Extended HPTN LC Testing**

### HIV testing

**Back-testing**

- **CAB arm:** All visits
- **TDF/FTC arm:** Enrollment, weeks 2, 4, 5

**Ag Ab**

- **CAB arm:** Enrollment plus three visits prior to the first RNA pos visit
- **TDF/FTC arm:** Enrollment plus one visit prior to the first RNA pos visit

**If Ag/Ab test reactive**

- **Ab**

**If qualitative RNA test reactive**

- **VL**

**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

- **CAB arm**
  - 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

**ARCHITECT antigen/antibody test**

**APTIMA qualitative RNA test**

**Geenius discriminatory antibody test**

**Viral load test**

**Single copy RNA test**
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
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
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* First site positive HIV test
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- **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
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* First site positive HIV test
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HIV-infection
* First site positive HIV test
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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
13 Incident, 3 baseline Infections: Cabotegravir
13 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
HIV Incidence: CAB vs. TDF/FTC

**HIV Incidence**

- **CAB**:
  - n=2243
  - 13 Infections
  - 3205 PY
  - HIV Incidence Rate: 0.41

- **TDF/FTC**:
  - n=2247
  - 39 Infections
  - 3187 PY
  - HIV Incidence Rate: 1.22

**Hazard Ratio (95% CI)**

- **Favors CAB**
- **Favors TDF/FTC**

**CI, confidence interval**

Noninferiority margin: [0.18, 0.62]
Superiority margin: [1.23, 2.00]
HIV Incidence: CAB vs. TDF/FTC

HIV Incidence

<table>
<thead>
<tr>
<th>Rate /100 PY</th>
<th>CAB (n=2241)</th>
<th>TDF/FTC (n=2247)</th>
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<tr>
<td>0.37</td>
<td>3204 PY</td>
<td>3187 PY</td>
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39 Infections

30 Infections

Hazard Ratio (95% CI)

Favors CAB

Favors TDF/FTC

CI, confidence interval
CAB arm, Group A
HIV positive at study enrollment
The x-axis represents weeks since enrollment. The shaded area represents time on ART.
CAB arm, Group B
No recent CAB exposure
The x-axis represents weeks since enrollment. The shaded area represents time on ART.
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.
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A Cautionary Tale
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
TDF/FTC arm – infected despite good adherence

K65R, Y181C, G190A, H221Y

E16

E34

TFV concentration
TFV-DP concentration
First HIV positive visit
First site positive visit
First HIV positive visit and first site positive visit

Weeks since enrollment

TFV (ng/mL)

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

TFV (fmol/punch)

K65R, Y181C, G190A, H221Y

TDF/FTC arm – infected despite good adherence
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
Acknowledgements

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• HPTN Leadership

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• 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