Laboratory Analysis of HIV Infections in the Year 1 Unblinded Period of HPTN 083 Injectable Cabotegravir for PrEP in MSM and TGW

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Background

- HPTN 083: Phase 2b/3 randomized controlled trial of increased-risk, HIV-uninfected MSM and TGW at 43 sites in 7 countries
- HPTN 083 consistently demonstrated a 66% reduction in HIV incidence in MSM/TGW assigned to cabotegravir injections vs. daily oral TDF/FTC for pre-exposure prophylaxis.¹
- Virology and pharmacology of 58 HIV infections from the blinded study period were previously characterized¹⁻⁴
- We now present virology and pharmacology findings for 52 additional cases that occurred up to one year after study unblinding

2. Landovitz RJ et al, AIDS 2020, Abstract OAXLB0101
HPTN 083 Study Design

**STEP 1**
Every day for 5 weeks

**STEP 2**
- Weeks 5 and 9
- Every 2 months for approximately 3 years

**STEP 3**
Every day for 1 year

**STEP 4**
- **OPTIONAL** Every day for 5 weeks
  - 2 shots, 4 weeks apart then every 2 months

**STEP 5**
- Daily

**Group A**
- Screening day and informed consent
- Every day for 5 weeks
- TDF/FTC
- CAB

**Group B**
- Screening day and informed consent
- Every day for 5 weeks
- TDF/FTC
- CAB
Methods

• New HIV infections detected at sites through November 15, 2021 for which first evidence of HIV infection was before May 15, 2021

• Concentrations of CAB and TFV in plasma and TFV-DP in DBS were quantified by LC-MS/MS

• Timing of HIV infection was assessed using an Ag/Ab test, a discriminatory test and RNA assays

• Drug resistance testing was performed using a commercial assay (viral load [VL] >500 c/mL) and a low VL integrase genotyping assay (VL <500 c/mL)¹

¹Eshleman SE, JID 2022
HIV Incidence: CAB vs. TDF/FTC

HIV Incidence

- CAB: 25 Infections (0.54/4660 PY)
  - 73 Infections (1.59/4596 PY)
- TDF/FTC: 1.59

Hazard Ratio (95% CI)

- Favors CAB
  - Hazard Ratio: 0.54
  - 95% CI: (0.22, 0.53)
- Favors TDF/FTC
  - Hazard Ratio: 1.59
  - 95% CI: (1.0, 2.1)

CI, confidence interval

- Open to Enrollment: DEC-2016 to JUN-2017
- 4.4 Years
- Primary Analysis: DEC-2020 to JUN-2021
- Year 1 Unblinded Analysis: DEC-2021
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 2: Lapse in CAB LA injection coverage
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Oral lead-in

NEW Blinded Period case

Cabotegravir Arm Infections

D5

0 10w 20w 30w 40w 50w
Step 1: Oral CAB lead-in
Step 1: Lapse in oral CAB coverage
Step 2: CAB LA 600 mg IM
Step 2: Lapse in CAB LA injection coverage
Step 3: Open-label TDF/FTC
Step 3: Overdue TDF/FTC dispensation
Annual follow-up
Oral lead-in

CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test

Cabotegravir Arm Infections

New Year 1 Cases (Unblinded)
<6m after last (D, Dx)
>6m after last (B, BR)
Step 1: Oral CAB lead-in
Step 2: CAB LA 600 mg IM
Step 3: Open-label TDF/FTC dispensation
Annual follow-up
Oral lead-in

CAB LA 600 mg IM
Open-label TDF/FTC dispensed
HIV-infection
First site positive HIV test

New Year 1 Cases (Unblinded)

<6m after last (D, Dx)
>6m after last (B, BR)
**Cabotegravir Arm Infections**

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**New Year 1 Cases (Unblinded)**

- <6m after last (D, Dx)
- >6m after last (B, BR)

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- **Step 1:** Oral CAB lead-in
- **Step 2:** CAB LA 600 mg IM
- **Step 2:** Lapse in CAB LA injection coverage
- **Step 3:** Open-label TDF/FTC
- **Step 3:** Overdue TDF/FTC dispensation
- **Annual follow-up**
- **Oral lead-in**
- **CAB LA 600 mg IM**
- **Open-label TDF/FTC dispensed**
- **HIV-infection**
- **First site positive HIV test**
**Cabotegravir Arm Infections**

**New Year 1 Cases (Unblinded)**

- **<6m after last** (D, Dx)
- **>6m after last** (B, BR)

**Step 1:** Oral CAB lead-in
**Step 2:** CAB LA 600 mg IM injection
**Step 3:** Open-label TDF/FTC dispensation

- CAB LA 600 mg IM injection
- Open-label TDF/FTC dispensed
- HIV-infection
- First site positive HIV test

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**Table:**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>D5</th>
<th>D6</th>
<th>Dx1</th>
<th>Dx2</th>
<th>Dx3</th>
<th>BR1</th>
<th>BR2</th>
<th>B6</th>
<th>B7</th>
<th>B8</th>
<th>B9</th>
<th>B10</th>
<th>B11</th>
<th>B12</th>
</tr>
</thead>
</table>
Cabotegravir Arm Infections

New Year 1 Cases (Unblinded)

>6m after last AND >3 years from enrollment (B)
Cabotegravir Arm Infections

**D5**
- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit

**D6**
- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit

<table>
<thead>
<tr>
<th>CAB (mcg/mL)</th>
<th>0</th>
<th>0.664</th>
<th>1.35</th>
<th>2.020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks since enrollment</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

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

**Viral load**
- BLQ
- 0.166
- 0.664
- 1.35
- 20

**Confirmatory Ab test**
- WT
- G148R

**Qualitative RNA test**
- +

**Ag/Ab test**
- +

**With on-time**
Cabotegravir Arm Infections

**DX1**
- Ag/Ab test: Qualitative RNA test
- Confirmatory Ab test: Viral load
- CAB concentration
- First HIV positive visit: 2.9 months
- First site positive visit: IND (2) 1,212,690 202,620 ND <40 ND
- CAB injection
- PI: M46L
- WT: ND

**DX2**
- Ag/Ab test: Qualitative RNA test
- Confirmatory Ab test: Viral load
- CAB concentration
- 5.6 months
- NNRTI: E138I/A x2
- IND: 73,360
- IND: 56
- IND: 550 ND <40

**DX3**
- Ag/Ab test: Qualitative RNA test
- Confirmatory Ab test: Viral load
- CAB concentration
- 5.6 months
- WT: 48,000
- WT: 42,270
- WT: <40 <40 <40
- CAB injection
- WITH at least one 10-week delayed injection

**Legend**
- CAB concentration
- CAB injection
- First HIV positive visit
- First site positive visit
- First HIV positive visit and first site positive visit
**Cabotegravir Arm Infections**

**BR1**
- First HIV positive visit:
  - 14 months after Last injection
- First site positive visit:
  - 81 days after CAB injection

**BR2**
- First HIV positive visit and first site positive visit:
  - 14.2 months after last injection

>6m after last injection AND an injection given at time of first positive visit

**CAB concentration**
- Plasma TFV: 102 ng/mL
# Summary of HPTN 083 Major INSTI RAMs

## CAB INITIATED OR RE-INITIATED WITH OCCULT HIV INFECTION

<table>
<thead>
<tr>
<th>RAMs</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>E138E/K, Q148K/R</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Q148R</td>
<td>1 (50)</td>
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</tbody>
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## HIV ACQUISITION DURING OLI

<table>
<thead>
<tr>
<th>HIV ACQUISITION DURING OLI</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>E138E/A/K, G140G/S, Q148R</td>
<td>2 (66)</td>
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</table>

## HIV BREAKTHROUGH INFECTION WITH ON-TIME INJECTIONS

<table>
<thead>
<tr>
<th>HIV BREAKTHROUGH INFECTION WITH ON-TIME INJECTIONS</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>E138K, G140A, Q148R, N155H, R263K</td>
<td>6 (100)</td>
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## HIV BREAKTHROUGH INFECTION WITH AT LEAST ONE 10+ WEEK DELAY

<table>
<thead>
<tr>
<th>HIV BREAKTHROUGH INFECTION WITH AT LEAST ONE 10+ WEEK DELAY</th>
<th>N (%)</th>
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<tbody>
<tr>
<td></td>
<td>0 (0)</td>
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## HIV INFECTION 6+ MONTHS FROM LAST INJECTION

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<th>HIV INFECTION 6+ MONTHS FROM LAST INJECTION</th>
<th>N (%)</th>
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<tr>
<td></td>
<td>0 (0)</td>
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*No result for B4

GenoSure PRIme (Monogram Biosciences) | Low VL INSTI Genotyping
TDF/FTC Arm Infections in Year 1 Unblinded Phase

2 of 34 cases not explained by adherence

Weeks since enrollment

First HIV positive visit and first site positive visit
First HIV positive visit
First site positive visit
TFV-DP ≥1250 fmol/punch
TFV-DP ≥700 - <1250 fmol/punch
TFV-DP ≥350 - <700 fmol/punch
TFV-DP >LLOQ - <350 fmol/punch
TFV-DP BLO
Conclusions

• Plasma CAB concentrations were generally as expected
  • Cases of rapid CAB clearance require additional investigation

• INSTI mutations were observed in 3 new cases
  • All CAB arm infections with on-time injections to-date had INSTI RAMs
  • Initiation of CAB PrEP with undiagnosed infection can select for INSTI mutations

• HIV acquisition 6+ months after last CAB-LA did not have significant diagnostic delays nor INSTI resistance
  • The timeline may be different for individuals born female

• With additional experience, CAB efficacy advantage persisted; ongoing demonstration projects will further inform real-world implementation of CAB-LA PrEP
Acknowledgements

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Our Sites and Site Staff
and OUR PARTICIPANTS!

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