CROI 2022 Update: HIV Prevention

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No conflicts of interests or relationships to disclose.
Data presented in this presentation offer a limited glimpse of health inequities that exist within a larger social context. Racism, not race, creates and perpetuates health disparities.

The MWAETC, in alignment with the American Medical Association, encourages characterizing race as a social construct, rather than an inherent biological trait, and supports ending the practice of using race as a proxy for biology in medical education, research and clinical practice.

January 2022
HIV Prevention At CROI

New Data on CAB-LA PrEP

• HPTN 083 Updates
• Early detection of HIV infection and INSTI resistance risk in CAB-LA PrEP

Other Prevention Modalities

• Islatravir updates
• Dapivirine vaginal ring
CAB-LA as PrEP: HPTN 083 Updates
**HPTN 083**: Phase 2b/3 randomized controlled trial of MSM + TGW at increased risk of HIV at 43 sites in 7 countries

- Demonstrated CAB-LA superiority over daily oral TDF/FTC for HIV PrEP
- CAB-LA FDA approved for PrEP 12/2021

Landovitz RJ et al. CROI 2022. Abstr 96.; Landovitz et al. NEJM 2021
Data for updated blinded + unblinded year of follow up (“Year 1 Unblinded”)

Incidence rates of infection higher (x1.5) than in the blinded period

Combined efficacy stayed the same

Why higher rates in unblinded?
- Study product adherence
- Increased contribution of person-time from high incidence areas

### Updated Efficacy, Safety, and Case Studies in HPTN 083: CAB-LA vs TDF/FTC for PrEP

**UPATED PRIMARY BLINDED PERIOD**

<table>
<thead>
<tr>
<th>HIV Incidence and relative effectiveness</th>
<th>CAB</th>
<th>TDF/FTC</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident HIV infections, n</td>
<td>14</td>
<td>41</td>
<td>0.34 (0.18, 0.62)</td>
</tr>
<tr>
<td>Accrued person-time, pyrs</td>
<td>3204</td>
<td>3186</td>
<td></td>
</tr>
<tr>
<td>Incidence, events/100pyrs (95% CI)</td>
<td>0.44</td>
<td>1.29</td>
<td>(0.24, 0.73)</td>
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<tr>
<td></td>
<td></td>
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<td>(0.92, 1.75)</td>
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</tbody>
</table>

**Study product adherence**

| CAB injection person-years covered*, % | 2183 (91.5%) |
| Detectable plasma TFV samples, n (%)   | 1763 (86.0%) |

| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | 1522 (74.2%) |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | 1472 (72.4%) |

**YEAR ONE UNBLINDED PERIOD**

<table>
<thead>
<tr>
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<th>CAB</th>
<th>TDF/FTC</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident HIV infections, n</td>
<td>11</td>
<td>31</td>
<td>0.33 (0.17, 0.67)</td>
</tr>
<tr>
<td>Accrued person-time, pyrs</td>
<td>1455</td>
<td>1410</td>
<td></td>
</tr>
<tr>
<td>Incidence, events/100pyrs (95% CI)</td>
<td>0.76</td>
<td>2.20</td>
<td>(0.38, 1.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.49, 3.12)</td>
</tr>
</tbody>
</table>

**Study product adherence**

| CAB injection person-years covered*, % | 79.9% |
| Detectable plasma TFV samples, n (%)   | 369 (76.1%) |

| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | 308 (63.5%) |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | 281 (59.4%) |

**ALL DATA COMBINED**

<table>
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<th>CAB</th>
<th>TDF/FTC</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident HIV infections, n</td>
<td>25</td>
<td>72</td>
<td>0.34 (0.21, 0.54)</td>
</tr>
<tr>
<td>Accrued person-time, pyrs</td>
<td>4660</td>
<td>4596</td>
<td></td>
</tr>
<tr>
<td>Incidence, events/100pyrs (95% CI)</td>
<td>0.54</td>
<td>1.57</td>
<td>(0.35, 0.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.23, 1.97)</td>
</tr>
</tbody>
</table>

**Study product adherence**

| CAB injection person-years covered*, % | 87.9% |
| Detectable plasma TFV samples, n (%)   | 2141 (83.6%) |

| Plasma TFV concentration samples ≥ 40 ng/ml, n (%) | 1835 (71.7%) |
| DBS TFV–DP concentration samples ≥700 fmol/punch, n (%) | 1657 (66.4%) |

Characterization of Incident Infections

- **Blinded Data**: (4) baseline/prevalent; (5) > 6 months after last CAB exposure; (3) during oral lead in period, **(4) despite on time CAB injection**

- **Updated Blinded Data**: (2) despite on time CAB injection

- **Year 1 Unblinded**: (1) **despite on time CAB injection**; (3) “mostly” on time injection; (7) >6 months after last CAB exposure

- **Not included**: (6) >=3 years after enrollment

Advantage of CAB-LA for HIV PrEP in MSM/TGW persists with 1 additional year of follow up, unblinded
- Increased HIV incidence in both arms may be attributable to attenuation of adherence/persistence and increased contribution from high-incidence regions
- No new safety concerns

CAB-LA PrEP breakthrough infections remain very rare, but unexplained
- HPTN 083 now reports a total of 7 cases of breakthrough despite on-time injections in 4660 person years of CAB-LA participant follow-up (0.15 per 100 PY)
CAB-LA as PrEP: Early Detection of HIV may reduce INSTI Resistance Risk
CAB-LA PrEP: Early detection of HIV infection may reduce INSTI-R

- Breakthrough HIV infection difficult to detect while on CAB-LA
- Prior HPTN 083 data: 5 with INSTI RAMs, 2 unable to perform genotypic testing (VL < 500 c/mL)
- Goal: Assess whether earlier detection of HIV using RNA assay for screening reduces INSTI resistance risk
- Among 21 samples from 7 participants:
  - Retrospective qualitative RNA testing (VL < 500 c/mL)
  - For each case, 1st HIV positive visit retrospectively identified by qualitative RNA temporally compared to 1st site identified HIV positive visit (by Ag/Ab test)
  - INSTI RAM data collected on both standard genotype resistance assay and low VL INSTI resistance assay (SGS, University of Pittsburgh)
CAB-LA PrEP: Early detection of HIV infection may reduce INSTI-R

- Major INSTI RAMs were retrospectively detected in low VL samples in 5/7 cases

- RNA assay for HIV screening would have detected infection before a major INSTI RAM was detected (4 cases) or before an additional major INSTI RAM(s) accumulated (2 cases)

- In 6/7 cases, INSTI RAMs detected late; in the one case with major mutation at first positive visit, more developed later

Eshleman et al. CROI 2022. Abstr. 95.
CAB-LA PrEP: Early detection of HIV infection may reduce INSTI resistance risk

- HIV screening with sensitive RNA assay in those on CAB-LA PrEP can identify earlier infection
  - May allow for earlier ART initiation → reduced risk of INSTI resistance
  - Should be performed using the most sensitive RNA assay available

- Findings support the language in the US package insert and recent guidance from the US CDC for HIV testing in the setting of CAB-LA PrEP

- No participants were started on INSTI-based ART; data not yet available on use in infections in the setting of CAB PrEP

**in the context of proven high efficacy, CAB-LA should also be considered for HIV PrEP in settings where HIV RNA screening is not readily available**

Eshleman et al. CROI 2022. Abstr. 95.
Other Prevention Modalities
Islatravir (ISL)

• Nucleoside reverse transcriptase translocation inhibitor (NRTTI) under development for treatment and prevention

• Two formulations under study for PrEP:
  - Once monthly oral
  - Once yearly subdermal implant

• “Based on changes in lymphocytes observed in clinical trials of ISL, the PrEP program has been placed on clinical hold by the US FDA.”
Week 24 Metabolic and Renal Outcomes:
- No discontinuations for metabolic or renal reasons
- Small, non-significant changes from baseline in weight, peripheral and trunk fat
  - Slight increases in higher dose group
- No changes in Cr or eGFR across all treatment groups; similar decreases in P/Cr
- At week 24, no clinically meaningful differences from placebo in metabolic and renal parameters were observed with ISL 60 mg or ISL 120 mg after 6 QM doses

ISL Distribution in Mucosal Tissues, PBMC, and Plasma after Monthly Oral Dosing:
- Exploratory tissue PK sub-study; tissue and blood samples collected after first and last doses in 6 months
- Comparable levels of drug concentrations across tissue types in women and men
- High correlation between plasma ISL and tissue ISL-TP levels
- Can use systemic ISL PK as a surrogate for tissue exposure
Choice and Adherence to Dapivirine Ring or Oral PrEP by Young African Women in REACH

- **US**: Voluntary removal of DPV approval consideration to FDA

- WHO now recommends monthly dapivirine (DPV) ring as PrEP option for women
  - Previous data: well tolerated, no difference in NNRTI resistance rates
  - Efficacy dependent on adherence

- REACH: Randomized crossover trial in adolescent girls and young women (AGYW) 16-21 years
  - Monthly DPV vaginal ring or daily oral TDF/FTC with three 6-month periods, last being “choice”
  - Previous data from first two study periods with higher ring acceptability and compliance over oral PrEP

- Updates: in the choice period, **2/3 opted for ring**; drug levels indicated partial to high adherence

Conclusions

- CAB-LA for HIV PrEP in MSM/TGW remains superior to daily oral PrEP in HPTN083 in the unblinded period

- Breakthrough HIV infection on CAB-LA PrEP remains rare but unexplained
  - Screening with sensitive RNA assay for infection can mitigate INSTI resistance risk development

- Other PrEP formulations
  - ISL (on clinical hold), future pending
  - DPV-VR not being reviewed in US, but promising option for AGYW in Africa

- **Choice** is critical in PrEP adherence and efficacy
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