AETC AIDS Education & Training Center Program Mountain West

CROI 2022 Update: HIV Prevention

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Disclosures

No conflicts of interests or relationships to disclose.

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

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CAB-LA as PrEP: HPTN 083 Updates

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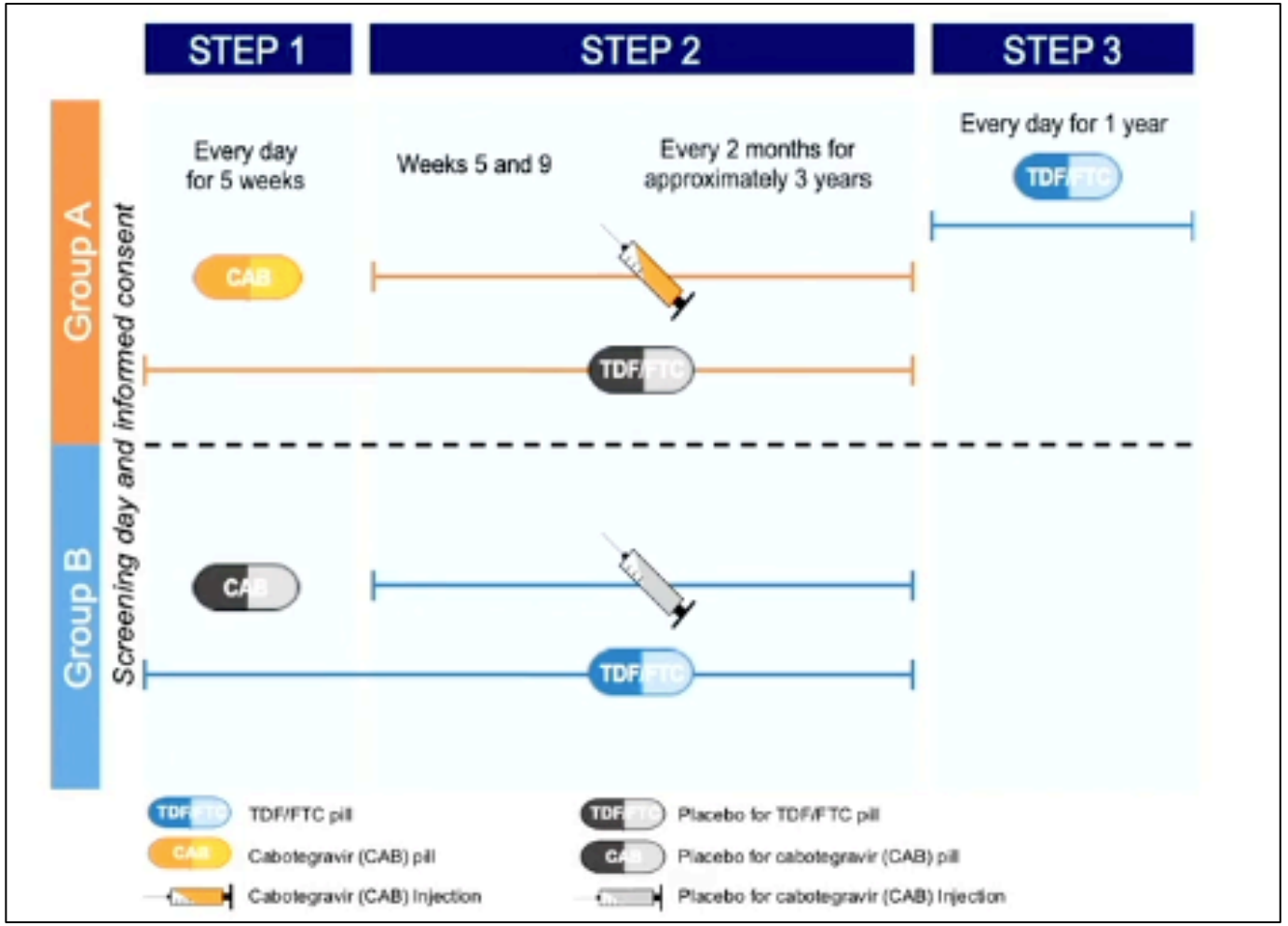
Updated Efficacy, Safety, and Case Studies in HPTN 083: CAB-LA vs TDF/FTC for PrEP

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

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

- 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

	CAB	TDF/FTC	HR (95% CI)
UPDATED PRIMARY BLINDED PERIOD			
HIV incidence and relative effectiveness			
Incident HIV infections, n	14	41	0.34 (0.18, 0.62)
Accrued person-time, pyrs	3204	3186	
Incidence, events/100pyrs (95% CI)	0.44 (0.24, 0.73)	1.29 (0.92, 1.75)	
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			
HIV incidence and relative effectiveness			
Incident HIV infections, n	11	31	0.33 (0.17, 0.67)
Accrued person-time, pyrs	1455	1410	
Incidence, events/100pyrs (95% CI)	0.76 (0.38, 1.35)	2.20 (1.49, 3.12)	
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			
HIV incidence and relative effectiveness			
Incident HIV infections, n	25	72	0.34 (0.21, 0.54)
Accrued person-time, pyrs	4660	4596	
Incidence, events/100pyrs (95% CI)	0.54 (0.35, 0.79)	1.57 (1.23, 1.97)	
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%)	

Landovitz RJ et al. CROI 2022. Abstr 96.

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

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*

Landovitz RJ et al. CROI 2022. Abstr 96.

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

- 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)

Landovitz RJ et al. CROI 2022. Abstr. 96.

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CAB-LA as PrEP: Early Detection of HIV may reduce INSTI Resistance Risk

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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 (HIV-1 RNA < 500 copies/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 (HIV-1 RNA < 500 copies/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 HIV-1 RNA INSTI resistance assay (SGS, University of Pittsburgh)

Marzinke et al. JID 2021:224; Eshleman et al. CROI 2022. Abstr. 95.

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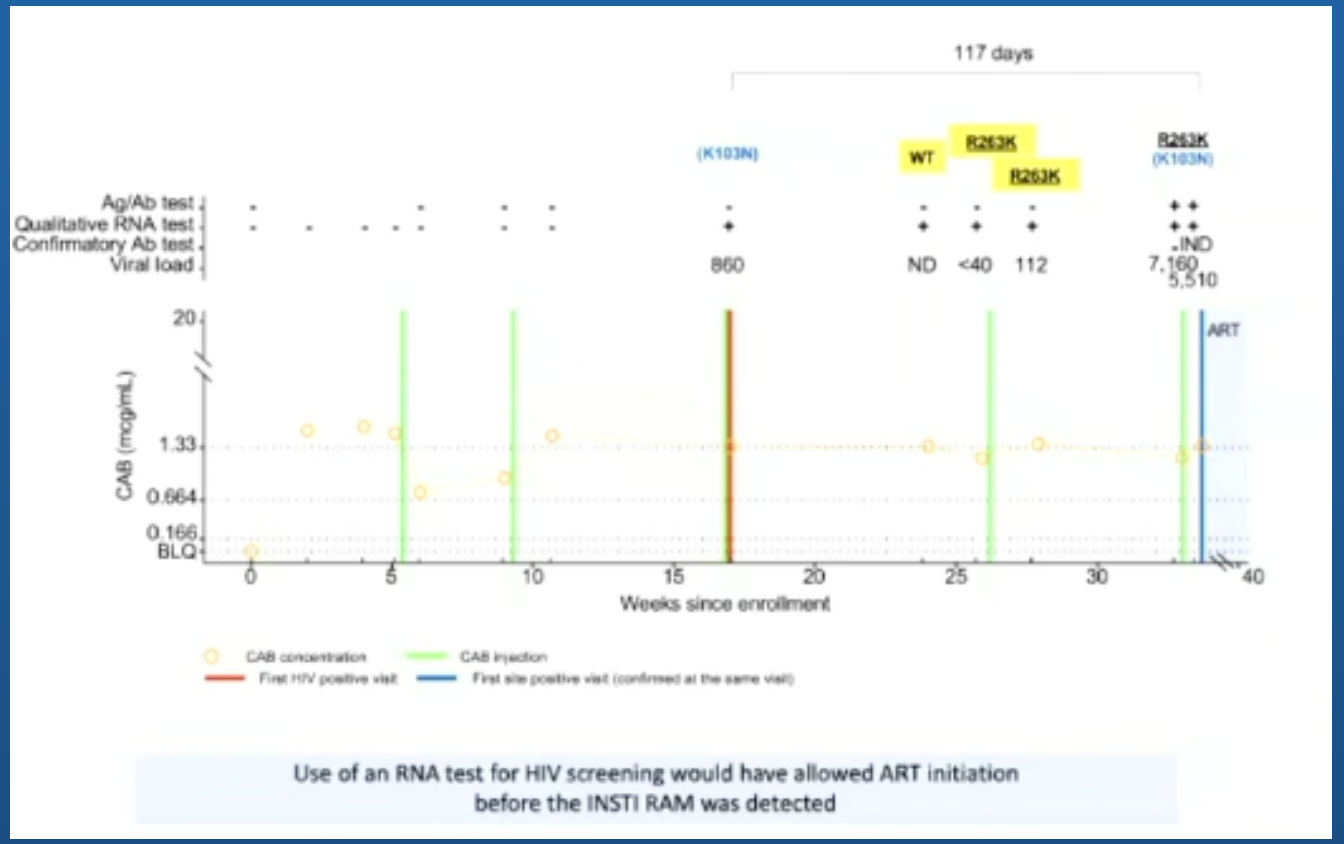
CAB-LA PrEP: Early detection of HIV infection may reduce INSTI-R

- 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.

Eshleman et al.

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CAB-LA PrEP: Early detection of HIV infection may reduce INSTI-R

- 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/recent CDC guidance for HIV testing in the setting of CAB-LA PrEP
- Data not yet available on use of INSTI based ART 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.

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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.”**

Hiller et al. IAS 2021 OALCO1LB03

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Phase IIA Trial of Islatravir QM for HIV PrEP

Week 24 Metabolic and Renal Outcomes[1]

- No discontinuations for metabolic or renal reasons
- Small, non-significant changes from baseline in weight, peripheral and trunk fat
- 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[2]

- 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**

1 MacDonald et al. CROI 2022. Abstr 85
2 Hendrix et al. CROI 2022. Abstr 83

Choice and Adherence to Dapivirine Ring or Oral PrEP by Young African Women in REACH

- **US: FDA no longer considering dapivirine vaginal ring (DPV-VR) for approval**

- WHO now recommends monthly dapivirine ring as PrEP option for women
  - Previous data: well tolerated, no difference in NNRTI resistance rates[1,2]
  - Efficacy dependent on adherence

- REACH: Randomized crossover trial in adolescent girls & young women (AGYW)16-21 years
  - Monthly DPV-VR or daily oral TDF/FTC with three 6-month periods, last being “choice”
  - Previous data from first 2 study periods with higher ring acceptability and compliance over oral PrEP[3]

- Updates: in the choice period**, 2/3 opted for ring**; drug levels indicated partial to high adherence[4]

[1] Baeten et al. Lancet HIV. 2021; [2] Nel et al. Lancet HIV. 2021
[3] Nair et al. IAS 2021; [4] Ngure et al. CROI 2022. Abstr 88.

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Conclusions

- CAB-LA for HIV PrEP in MSM/TGW remains superior to daily oral PrEP in HPTN083
- Breakthrough HIV infection on CAB-LA PrEP remains rare but unexplained
  - Screening with sensitive RNA assay for HIV can mitigate INSTI resistance risk
- 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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