

CROI 2022 Update: HIV Prevention

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Last Updated: March 2, 2022

Disclosures

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.

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

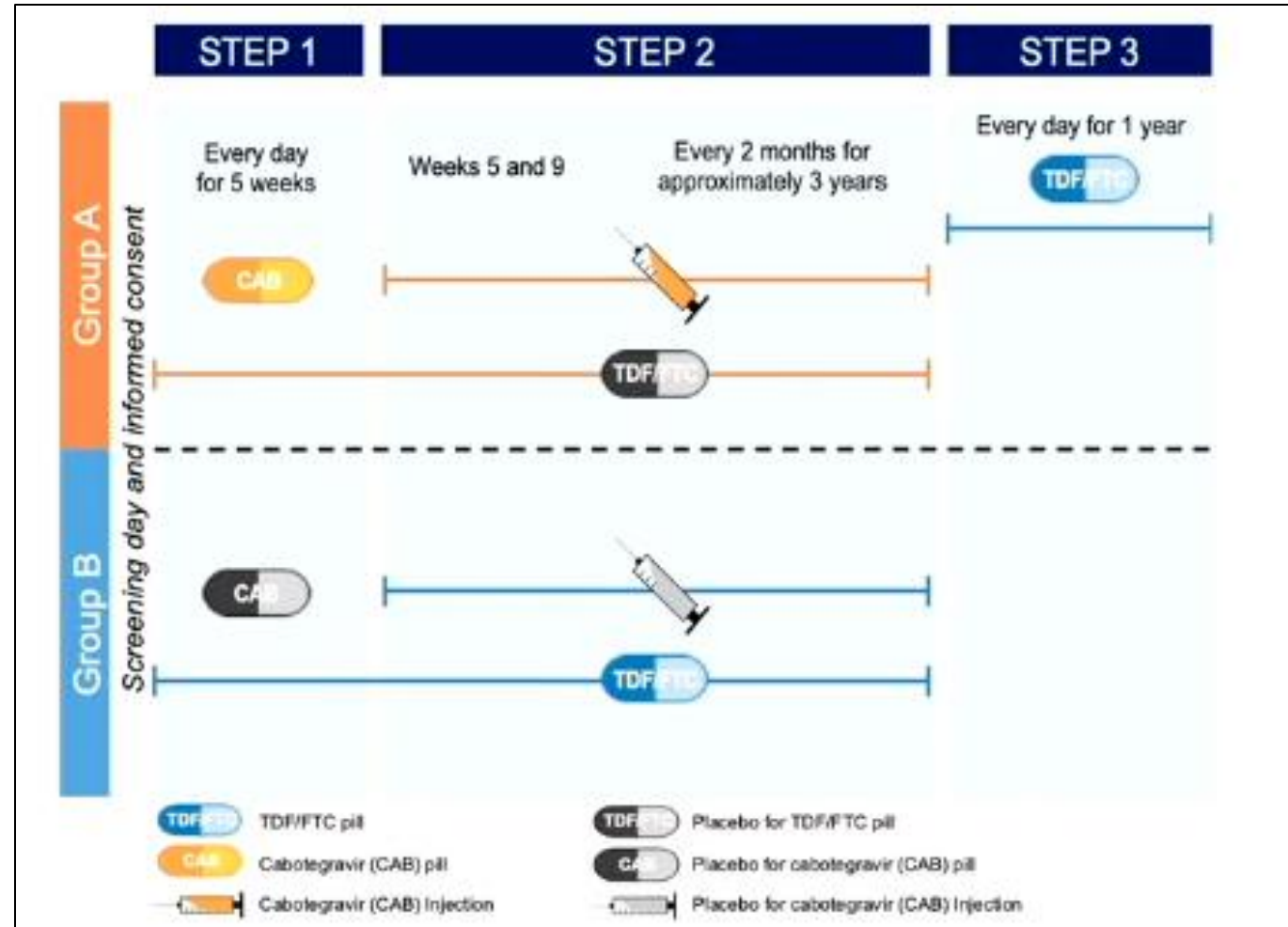
- Islatravir updates
- Dapivirine vaginal ring

CAB-LA as PrEP: HPTN 083 Updates

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



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%)	

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*

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)

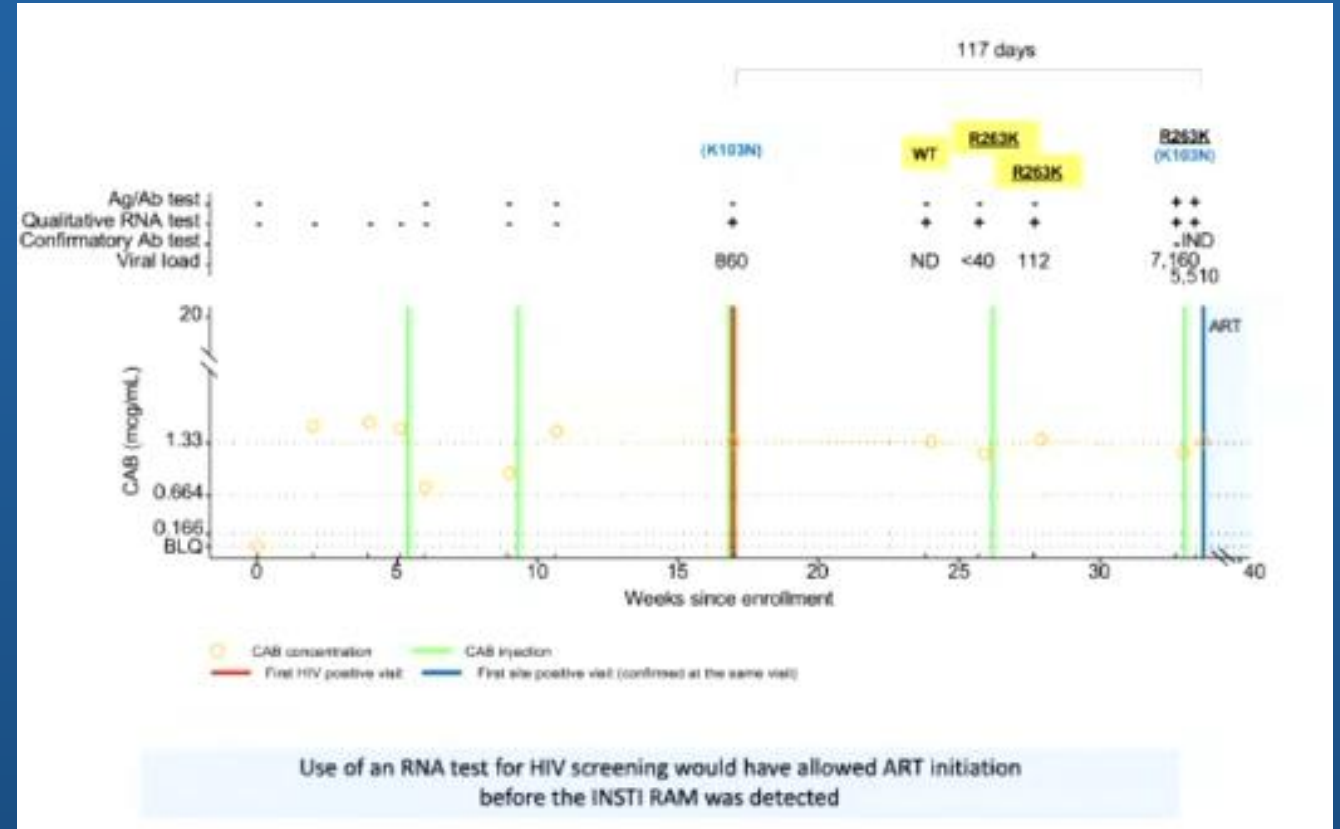
CAB-LA as PrEP: Early Detection of HIV may reduce INSTI Resistance Risk

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



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****

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.”**

Phase IIA Trial of Islatravir QM for HIV PrEP

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

Acknowledgment

The Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling \$2,908,478 with 0% financed with non-governmental sources.

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