Long-acting injectable PrEP in women: laboratory analysis of HIV infections in HPTN 084

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BACKGROUND

HPTN 084 is a Phase 3 randomized, double-blind, double-dummy superiority trial that showed that long-acting injectable cabotegravir (CAB) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and were highly effective for HIV prevention in women in sub-Saharan Africa. Participants were randomized 1:1 to active CAB + TDF/FTC placebo or active TDF/FTC + CAB placebo. The blinded trial was stopped at a planned interim Data Safety Monitoring Board review in November 2020. CAB was superior, with an 89% lower risk of infection compared to TDF/FTC. We characterized the 40 observed infections in HPTN 084 (4 CAB, 36 TDF/FTC) using virology and pharmacology assays.

METHODS

HIV testing at study sites was performed in real-time using locally available tests

- Sites performed 1-2 HIV rapid tests and a laboratory-based Ag/Ab test (FDA-cleared)
- If any test was reactive, sites consulted the HIV alias committee and performed confirmatory testing
- If recommended by the committee, an ultra-sensitive assay HIV DNA test was performed at Johns Hopkins University

Retrospective testing was performed at the HPTN Laboratory Center to confirm and characterise HIV infections

- Ag/Ab testing (Architect HIV Ag/Ab Combo test)
- Ab testing (Geenius HIV 1/2 Confirmatory Assay)
- Qualitative RNA testing (Aptima HIV RNA Qualitative assay; LOD 30 copies/ml)
- Viral load testing (RealTime HIV Viral Load Assay; LOQ 40 copies/ml)
- Single copy RNA testing (selected samples) (University of Pittsburgh)
- HIV genotyping (viremic samples >500 copies/ml GenoSure; PRIme; Monogram Biosciences)

Drug concentrations were determined by liquid chromatography-tandem mass spectrometry (plasma CAB LOQ 0.025 mcg/mL), plasma tenofovir [TFV] LOQ 0.31 ng/ml); and intraerythrocytic TFV-diphosphate [TFV-DP] LOQ 31.3 fmol/punch).

For CAB cases, plasma CAB concentrations were measured at all study visits in the CAB arm. The protein-adjusted in vitro 90% CAB inhibitory concentration (PA-IC_{90}) is 0.166 mcg/mL. Concentrations ≥8x PA-IC_{90} were expected to be protective. (*Overton, Lancet HIV 2020; Marzinke, JID 2021 in press*)

For TDF/FTC cases, plasma TFV was quantified at the first HIV positive visit, the first site positive visit, and up to three prior visits; TFV-DP was quantified at two visits, when available: 1) the first HIV positive visit or the next visit with a DBS sample, and 2) the closest visit prior to the first HIV positive visit.

Adherence to daily oral TDF/FTC was categorised as: **poor** adherence (< 2 doses/week) TFV <40ng/ml, TFV-DP <350 fmol/punch at the closest visit following first HIV positive visit; **inconsistent** adherence (2-4 doses/week) TFV >40 ng/mL, TFV-DP 350-500 fmol/punch (4-8 weeks) or 350-700 fmol/punch (≥8 weeks) at the closest visit following first HIV positive visit; or **partial** adherence (>4 doses/week) TFV >40 ng/mL and TFV-DP >500 fmol/punch (4-8 weeks) or >700 fmol/punch (≥8 weeks).

RESULTS

IDENTIFICATION OF HIV INFECTIONS

HIV infection was confirmed in four CAB arm participants including one who was found to have HIV infection at enrollment prior to CAB administration; this case was re-classified as a baseline infection (Case A1). (Figure 1 and 2). Two participants with incident infection received no CAB injections and had no recent CAB exposure (Cases B1 and B2). B1 completed the oral lead in but as late for her first injection visit. B2 transitioned to open-label TDF/FTC due to pregnancy prior to the injection phase. The third incident infection occurred during the injection phase of the study in a participant with delayed injection visits (Case DX) (Figure 1 and 3). All 36 infections in the TDF/FTC arm were incident infections. When prevalent infections were excluded, the unadjusted hazard ratio for CAB vs. TDF/FTC was 0.08 (95%CI 0.03, 0.27) (Table 1).

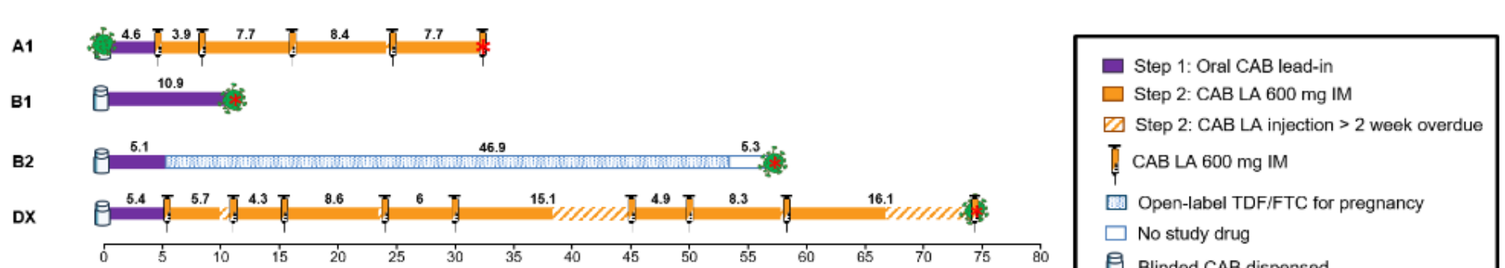

FIGURE 1. Cabotegravir: 3 incident, one baseline infection

	CAB	TDF/FTC
HIV infections	3	36
Person-years	1,956	1,942
HIV incidence (95% CI)	0.15 (0.03, 0.45)	1.85 (1.3, 2.57)

TABLE 1. HIV incidence, excluding prevalent cases based on retrospective testing

STUDY DRUG EXPOSURES, DRUG CONCENTRATIONS AND HIV RESISTANCE

Cabotegravir cases

(A) Case A1

Visit type	Diagnosis visit type	Site Testing: Rapid 1 test	Rapid 2 test	Ag/Ab test	DNA test	Viral load	HPTN LC Testing: Ag/Ab test	Qualitative RNA test	Confirmatory Ab test	Viral load	Resistance
	1st HIV POS	NR		NR						<40	
Enrollment*							NR	R		SCA 21.4	
Week 2		NR		NR			NR	R		500	WT
Week 4		NR		NR			NR	R		1,740	WT
Week 5 (Inj 1)		NR		NR			NR	R		6,300	WT
Week 8		NR		NR			R	R	IND	87	
Week 9 (Inj 2)		NR		NR			NR	NR		SCA NEG	
Week 13		NR		NR			NR	NR		SCA NEG	
Week 17 (Inj 3)		NR		NR			NR	NR		SCA NEG	
Week 21		NR		NR			NR	NR		SCA NEG	
Week 25 (Inj 4)		NR		NR			NR	NR		SCA NEG	
Week 33 (Inj 5)	1st SITE POS	NR		R		ND	R	NR	IND	SCA NEG	
Interim Visit		NR		NR	<4.09	ND	R	NR	IND	SCA NEG	
Interim Visit		NR		R	4.6	ND	R	NR	IND	SCA NEG	
Interim Visit		NR	R	NR	4.4	ND	R	NR	IND	SCA NEG	
Week 57		NR	NR	NR		33	R	NR	IND	SCA NEG	

Subtype A1

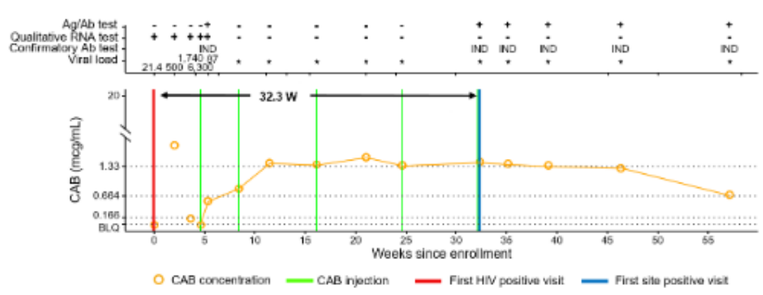

FIGURE 2. Cabotegravir: case A1, reclassified as prevalent HIV infection

Case A1 (Figure 2)

- The site first detected HIV infection 32.3 weeks post-enrolment.
- The participant received oral CAB and five CAB injections before the first site positive visit.
- CAB concentrations indicated inconsistent use during the oral run-in period; by the 3rd injection CAB was 1.33 µg/mL i.e., ≥8x PA-IC_{90} and remained above this threshold through to the first site positive visit. At that time, the CAB concentration was 2.58 µg/mL.
- Exposure to CAB was associated with diminished/delayed antibody expression and delayed HIV diagnosis.
- Retrospective testing of samples revealed that the participant was infected at enrolment with a viral load of 21.4 copies/mL.
- HIV RNA ranged from 500-6300 copies/mL during the oral lead in, but was not detectable using the qualitative RNA assay or the single-copy RNA assay for 27.7 weeks while receiving CAB injections and 24.9 weeks after the last CAB injection
- No major integrase strand transfer inhibitor (INSTI) mutations were detected. . The participant was successfully linked to antiretroviral therapy (ART) shortly after confirmation of infection.

FIGURE 3. Cabotegravir: case DX, incident HIV infection after delayed infections

Case DX, (Figure 3)

- The site first detected HIV infection 73 weeks post-enrolment.
- The participant received oral CAB and nine CAB injections; the ninth injection was administered at the first site positive visit, before the site received the reactive Ag/Ab test result.
- 5/9 injections were delayed (range: 2-57 days), the eighth injection occurred 16.1 weeks prior to the first HIV positive visit.
- CAB concentrations in the oral lead-in phase were all BLQ, indicating non-adherence to oral study drug. CAB concentrations were ≥8x PA-IC_{90} in plasma samples collected before the first HIV positive visit but were <4x PA-IC_{90} (0.416 mcg/mL) at the first HIV positive visit.
- HIV RNA was detectable at the first site positive visit.
- No major INSTI mutations were detected. The participant was successfully linked to ART.

TDF/FTC cases

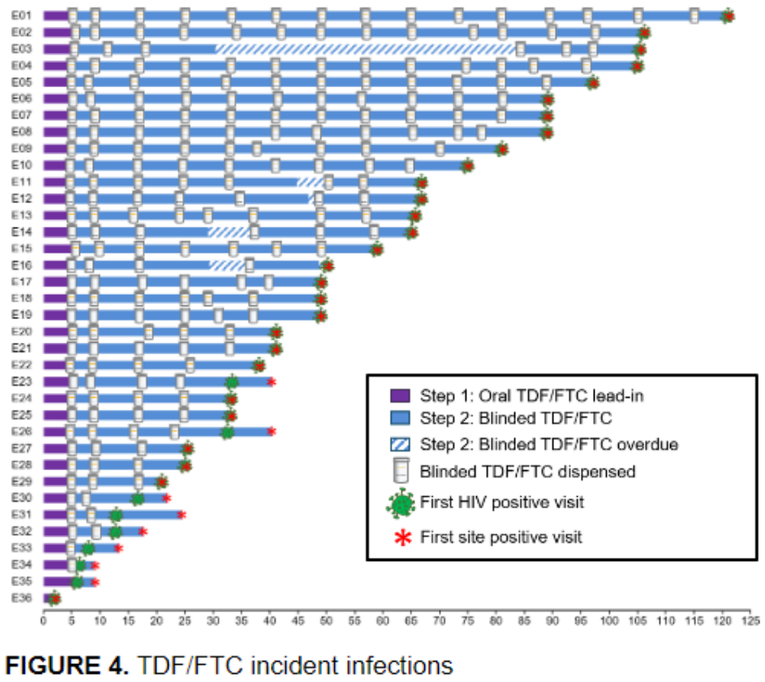

FIGURE 4. TDF/FTC incident infections

- 35/36 infections occurred in women with poor or inconsistent adherence (<4 pills/week based on TFV and TFV-DP concentrations)
- One case had partial adherence (>4 doses/week). This case was adjudicated as HIV positive by the endpoint adjudication committee based on site testing data, but all HIV tests were non-reactive at the HPTN LC.
- HIV detection was delayed in 8 incident TDF/FTC cases; all <40 weeks after enrolment when visits were frequent.(Figure 4).
- 7/8 cases with delayed detection had had HIV RNA detected at the first positive visit; a confirmatory antibody test was positive at the next visit (4 cases) or subsequent visits (4 cases).
- Genotyping results were obtained at the first viremic visit for 33/36 cases. Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations were detected in 9 (25%) cases. One (3%) case also had the M184V mutation (E32).

CONCLUSIONS

Most incident HIV infections in HPTN 084 occurred in the setting of unquantifiable or low drug concentrations. Detection of HIV infection may be delayed in this setting using routine diagnostic assays, particularly when long-acting products are used. Use of HIV RNA testing as primary screen for HIV infection will be assessed in the open-label extension. No major INSTI mutations were observed in the CAB arm. The prevalence of transmitted NNRTI drug resistance is a concern.

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