

Use of Long-Acting Cabotegravir for Pre-Exposure Prophylaxis in Cisgender Men and Transgender Women Who Have Sex with Men (HPTN 083)

Summary

- Through the most recent presentation of data (blinded and unblinded phases):¹⁻³
 - There have been a total of 97 infections overall – 25 in the long-acting cabotegravir (CAB LA) arm and 72 in the tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) arm.
 - CAB LA was statistically superior to TDF/FTC at preventing HIV acquisition among cisgender men and transgender women who have sex with men (HR = 0.34 [95% CI 0.22, 0.53]).
 - There were 66% fewer seroconversions in the CAB LA arm versus the TDF/FTC arm.
 - Among key subgroups, including Black men and transgender women who have sex with men (blinded phase only), there were numerically fewer new HIV infections in participants receiving CAB LA than those receiving TDF/FTC.
- Of the 25 infections (21 incident/4 baseline) among subjects with data available who were randomized to CAB LA, 10 were associated with the development of integrase strand-transfer inhibitor (INSTI) resistance which developed after a period of oral cabotegravir and/or CAB LA monotherapy due to a delay in the detection of HIV infection at the study sites.^{4,5}
- To date there have been no cases of INSTI resistance reported among the subjects who seroconverted during the pharmacokinetic tail of CAB LA.⁴⁻⁷
- Exposure to oral cabotegravir and CAB LA was associated with prolonged viral suppression and delayed antibody expression in 11 patients who became infected with HIV during the blinded phase of the trial.⁴⁻⁷
- The most common adverse events reported in the CAB LA arm were injection site reactions (ISRs).¹

HPTN 083 is a randomized, double-blind, double-dummy, phase 2b/3, non-inferiority study designed to assess the safety and efficacy of CAB LA compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP in HIV-uninfected cisgender men and transgender women who have sex with men.¹

Step 1:

Arm A – daily oral CAB 30 mg and oral TDF/FTC placebo for 5 weeks

Arm B – daily oral TDF/FTC 300 mg/200 mg and oral CAB placebo for 5 weeks

If subjects remain HIV-uninfected they will transition to Step 2.

Step 2:

Arm A – CAB LA 600 mg IM every 4 weeks x2 doses followed CAB LA 600 mg IM every 8 weeks and daily oral TDF/FTC placebo

Arm B – daily oral TDF/FTC 300 mg/200 mg and CAB LA placebo (Intralipid 20% fat emulsion) IM every 4 weeks x2 doses followed by every 8 weeks thereafter

On July 7, 2020, the HPTN announced that CAB LA demonstrated superiority to TDF/FTC for the prevention of HIV.² As a result, the blinded phase of HPTN 083 was stopped and the results shared via press release. HPTN 083 will continue through an open-label extension (OLE) where participants will be given the choice to stay on their current study product or switch to the other study product.³

During the OLE, the oral lead-in will be optional for subjects switching from TDF/FTC to CAB LA.³

Results

Baseline demographics and characteristics can be found in Table 1 below.¹

Table 1. Baseline Demographics and Characteristics of Subjects in HPTN 083¹

	CAB LA (N=2282)	TDF/FTC (N=2284)	Total (N=4566)
Cohort, n (%)			
MSM	2013 (88.2)	1979 (86.6)	3992 (87.4)
Transgender woman	266 (11.7)	304 (13.3)	570 (12.5)
No answer	3 (0.1)	1 (<0.1)	4 (0.1)
Age, median (IQR), years	26 (22-32)	26 (22-32)	26 (22-32)
Age, n (%)			
18-29	1572 (68.9)	1508 (66)	3080 (67.5)
30-39	498 (21.8)	550 (24.1)	1048 (23)
40-49	145 (6.4)	170 (7.4)	315 (6.9)
50-59	60 (2.6)	50 (2.2)	110 (2.4)
≥60	7 (0.3)	6 (0.3)	13 (0.3)
Region, n (%)			
United States	849 (37.2)	849 (37.2)	1698 (37.2)
Latin America	980 (42.9)	985 (43.1)	1964 (43)
Asia	375 (16.4)	377 (16.5)	752 (16.5)
Africa	78 (3.4)	74 (3.2)	152 (3.3)
Race/Ethnicity, n (%)			
United States			
Black	411 (48.4)	434 (51.1)	845 (49.8)
Non-Black	437 (51.5)	414 (48.8)	851 (50.1)
Data missing	1 (0.1)	1 (0.1)	2 (0.1)
LatinX or Hispanic	149 (17.6)	154 (18.1)	303 (17.8)
Latin America			
Black or mixed	198 (20.2)	194 (19.7)	392 (20.0)
Indigenous	435 (44.4)	427 (43.4)	862 (43.9)
Asian	6 (0.6)	2 (0.2)	8 (0.4)
White	319 (32.6)	340 (34.6)	659 (33.6)
Other	22 (2.2)	21 (2.1)	43 (2.2)
LatinX or Hispanic	894 (91.2)	912 (92.7)	1806 (92)
Asia			
Asian	374 (99.7)	375 (99.5)	749 (99.6)
Other	1 (0.3)	2 (0.5)	3 (0.4)
Africa			
Black	62 (79.5)	57 (77.0)	119 (78.3)
Other	2 (2.6)	3 (4.1)	5 (3.3)
Mixed	14 (17.9)	14 (18.9)	28 (18.4)

CAB LA = long-acting cabotegravir; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine

Primary Analysis and Re-Adjudication of Cases

There were a total of 52 incident HIV infections.¹ Among participants who were randomized to CAB LA there were 13 incident infections and among subjects who were randomized TDF/FTC there were 39 incident infections. Of the 13 HIV infections among participants randomized to CAB LA, 5 occurred despite adherence to on-time administration of the medicine.

CAB LA was statistically superior to TDF/FTC at preventing HIV acquisition (HR=0.34, 95% CI 0.18-0.62, $P<0.001$).¹

Among key subgroups, there were numerically fewer new HIV infections in subjects receiving CAB LA than those receiving TDF/FTC.¹ See Table 2 below.

Table 2. HIV Incidence in Populations Most at Risk in HPTN 083¹

	CAB LA Events/PY (IR%)	TDF/FTC Events/PY (IR%)	HR (95% CI)
Age			
≤30	11/2189 (0.50)	33/2116 (1.56)	0.33 (0.17-0.65)
>30	2/1016 (0.20)	6/1071 (0.56)	0.38 (0.08-1.77)
TGW	2/370 (0.54)	7/388 (1.80)	0.34 (0.08-1.56)
MSM	11/2831 (0.39)	32/2797 (1.14)	0.35 (0.18-0.68)
Race, United States			
Black	4/688 (0.58)	15/715 (2.10)	0.28 (0.10-0.84)
Non-Black	0/836	5/785 (0.64)	0.09 (0.00-2.05)
Region			
United States	4/1525 (0.26)	20/1502 (1.33)	0.21 (0.07-0.60)
Latin America	6/1018 (0.59)	11/1009 (1.09)	0.56 (0.21-1.51)
Asia	2/569 (0.35)	6/580 (1.03)	0.39 (0.08-1.82)
Africa	1/92 (1.08)	2/96 (2.08)	0.63 (0.06-6.50)

CAB LA = long-acting cabotegravir; TDF/FTC = tenofovir disoproxil fumarate/emtricitadine; PY = patient-years; HR = hazard ratio; CI = confidence interval;

Following the Primary Analysis reported above, a post-hoc re-adjudication of the results was completed.¹ In this analysis, 1 participant in the CAB LA arm was found to have been infected with HIV at baseline. As such, there were 12 incident infections in the CAB LA arm and 39 infections in the TDF/FTC arm (HR 0.32 [96% CI 0.16-0.58]).

See Table 3 for the updated breakdown of the relationship of baseline and incident HIV infection to CAB LA administration.

Table 3. Relationship of Incident HIV Infection to CAB LA Administration in HPTN 083⁴

	Number of Infections (n=16)
Group A: infection before enrollment	4
Group B: infection with no recent exposure to cabotegravir	5
Group C: infection prior to receipt of CAB LA	3
Group D: infection despite on-time CAB LA injections and expected plasma concentrations of cabotegravir	4
CAB LA = long-acting cabotegravir; OLI = oral lead in	

Following unblinding, data are available for an additional year of follow up.⁵ Through August 15, 2021, there have been a total of 25 incident infections among participants randomized to the CAB LA arm and 73 in the TDF/FTC arm (HR = 0.34; 95% CI 0.22-0.53). CAB LA remained superior (66% more effective) to TDF/FTC through this most recent analysis.

There were 2 new incident infections in the D Group (see subjects D5 and D6 in Table 4 below).⁵ Additionally, there were 3 new incident infections in participants who had been off CAB LA for <6 months (Dx Group) and 2 new incident infections in participants who had been off CAB LA for >6 months. The latter group had CAB LA restarted after a long hiatus (BR Group) and were subsequently found to have acquired HIV infection during the hiatus. Lastly, there were 7 new incident infections in the B Group.

More details about the D Group can be found in Table 4 below. See Table 5 below for an overall summary of HIV infections in patients randomized to CAB LA.

Table 4. Group D Laboratory Results⁴⁻⁷

Subject	Week of Positive Test (Site)	Week of Positive Test (Central Lab)	Genotype	INSTI Phenotype	Follow-up
NR due to low VL					
D1	~72	~56	<u>SGS Results</u> INSTI: N155H, Q148R, R263K	N/A	Suppressed on bPI-based regimen
NR due to low VL					
D2	41	27	<u>SGS Results</u> INSTI: N155H	N/A	-
D3	~37	~18	INSTI: R263K	CAB (2.32) DTG (2.29) BIC (2.89) EVG (4.14) RAL (1.38)	Suppressed on bPI-based regimen
D4	~25	~19	INSTI: G140A, Q148R	CAB (13) DTG (2.09) BIC (2.77) EVG (107) RAL (43)	Suppressed on EFV/TDF/FTC

Subject	Week of Positive Test (Site)	Week of Positive Test (Central Lab)	Genotype	INSTI Phenotype	Follow-up
D5	~41	~36	INSTI: R263K	N/A	Suppressed on bPU-based regimen
D6	~112	120	INSTI: Q148R	N/A	Suppressed on EFV/TDF/3TC

INSTI = integrase strand-transfer inhibitor; NR = not reported; VL = viral load; SGS = single genome sequencing; bPI = boosted-protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; CAB = cabotegravir; DTG = dolutegravir; BIC = bictegravir; EVG = elvitegravir; RAL = raltegravir; EFV/TDF/FTC = efavirenz/tenofovir disoproxil fumarate/emtricitabine

Table 5. Summary of HIV Infections by Group (unblinded and blinded phases)⁵

Group	Infections (n=34)	Infections with INSTI Resistance (n=10)	Mutations Detected
CAB LA Initiated or Re-Initiated with Occult HIV Infection			
A	4	1	E138E/K and Q148K/R
BR	2	1	Q148R
HIV Acquisition During the Oral Lead-In			
C	3	2	Q148R, E138E/K, and G140G/S; E138A and Q148R
HIV Breakthrough Infection with On-Time Injections			
D	6	6	N155H, Q148R, and R263K; N155H; R263K (n=2); G140A, Q148R; and Q148R
HIV Breakthrough Infections with At Least One 10+ Week Delay			
Dx	3	0	N/A
HIV Infections 6+ Months From Last Injection			
B	16	0	N/A

Group Definitions:

A = prevalent (baseline) cases

BR = incident cases >6 months after last CAB LA injection with CAB LA injections restarted after a hiatus (422 and 425 days after the prior injection)

C = incident infections that occurred during the oral-lead in phase prior to CAB LA injections

D = incident infections despite on-time CAB LA injections

Dx = incident infections <6 months after the last CAB LA injection

B = incident cases >6 months after last CAB LA injection

INSTI = integrase strand-transfer inhibitor; CAB LA = long-acting cabotegravir; N/A = not applicable

Delays in Diagnosis of HIV Infection

Of the participants randomized to CAB LA, 11 experienced a delay between diagnosis of incident HIV infection at the investigative site compared with the central laboratory.^{4,7} In all cases, antigen/antibody tests performed at the investigative site did not detect HIV infection. However, when qualitative HIV RNA

testing was performed post-hoc by the central laboratory HIV infection was detected at an earlier time point.

Among the 11 participants, INSTI resistance was reported in 7.

For more information about delays in HIV diagnosis in patients receiving oral cabotegravir or CAB LA please click [here](#).

Safety

Safety data is only available for the primary analysis at the end of the blinded phase of the trial.¹

Approximately 92% of subjects in each arm experienced a Grade 2 or higher adverse event.¹ The most common adverse events (Grade 2 or higher) in subjects receiving CAB LA or TDF/FTC, respectively, were creatinine clearance decreased (69.6% vs. 73.1%), creatine kinase increased (21.2% vs. 20.6%), nasopharyngitis (19.6% vs. 17.4%), and serum creatinine increased (16.8% vs. 18.8%).

Overall, 81.4% of subjects who received CAB LA experienced at least 1 ISR during the course of the study.¹ The most common ISR reported was pain (60.8%). The vast majority of events were categorized as either mild or moderate in severity. Of the 2117 subjects who received at least 1 CAB LA injection, 50 (2.4%) permanently discontinued the injections due to an ISR.

ISRs were mostly mild to moderate in severity and decreased in frequency over time.¹

In the US, ISRs were more common among non-Black versus Black MSM and TGW (65% versus 56%).⁸

Overall, 31.4% of subjects in the TDF/FTC arm who received placebo CAB LA (Intralipid 20% fat emulsion) experienced an ISR at some point during the course of the study.¹

More weight gain was seen in subjects treated with CAB LA than TDF/FTC.¹ See Table 8 below.

Table 8. Median Change from Baseline in Weight in HPTN 083¹

	CAB LA kg/year (95% CI)	TDF/FTC kg/year (95% CI)
Overall	1.23 (1.05, 1.42)	0.37 (0.18, 0.55)
Weeks 0 – 40	1.26 (0.98, 1.54)	-0.50 (-0.78, -0.22)
Weeks 40 – 105	1.11 (0.82, 1.41)	1.19 (0.90, 1.49)

CAB LA = long-acting cabotegravir; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; kg = kilograms; CI = confidence interval

Adherence to PrEP

Almost 92% of CAB LA and placebo injections were administered on time or with a delay of <2 weeks. Tenofovir diphosphate concentrations indicative of receipt of 4-7 doses/week (≥ 700 fmol/punch) were reported in approximately 72% of participants included in the adherence subset of HPTN 083.

When adherence was assessed among the subgroup of Black vs. non-Black MSM and TGW in the US, adherence was lower for Black participants for both TDF/FTC (65% versus 81%) and CAB LA (83% versus 90%).⁸

Incident Sexually Transmitted Infection

A secondary analysis from the blinded period of HPTN 083 was completed to characterize incident sexually transmitted infection (STI), including repeat events, to characterize STI incidence rates and CAB LA maintenance of efficacy.⁹ As part of the study, serologic testing for syphilis and nucleic acid amplification testing for rectal and urethral gonorrhea and chlamydia were conducted every six months or when participants reported STI symptoms or exposures.

Among 3859 participants included in the analysis, the overall STI incidence rate was 50.7 infections per 100 person years (PY). STIs were diagnosed in 1562 (40.5%) participants, with multiple STIs reported for 691 (17.9%), and 79% of STI diagnoses occurred in 25% of participants.⁹ There was a small numerical difference in STI incidence by PrEP arm (CAB LA 49.9 infections/100 PY, TDF/FTC 51.6 infections/100 PY).

HIV incidence was lower with CAB LA compared to TDF/FTC regardless of presence (HR 0.37, 95% CI 0.15 – 0.95) or absence (HR 0.31, 95% CI 0.13 – 0.71) of STIs.⁹ There was no statistically significant interaction between STI status and the CAB LA prevention efficacy ($p = 0.75$).

Incident Hypertension

A post-hoc analysis of HPTN 083 was completed to compare incidence rates of hypertension (HTN) in the absence of HIV infection.¹⁰ Incident HTN was defined as two consecutive BP readings with systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg, a new diagnosis of HTN, or initiation of new HTN medications with a HTN indication. Analyses adjusted for enrollment region and race, age, use of anti-HTN medications for other purposes, BMI at entry and percent change in weight as a time-updated covariate.

The primary analysis included 3,971 participants with a total of 10,293 person-years of follow-up. There were 237 incident cases of HTN with CAB compared to 213 with TDF/FTC (unadjusted HR = 1.11, 95% CI 0.92 - 1.33; adjusted HR = 1.00, 95% CI 0.83 - 1.21).¹⁰ No significant statistical difference in HTN incidence was found between CAB and TDF/FTC users, over 3 years of follow-up.

CASE SERIES OF INFECTIONS OVER THE LIFE-CYCLE OF HPTN 083

A post-hoc analysis was conducted to evaluate ART outcomes in participants who acquired HIV and were exposed to CAB LA during the study. The study evaluated HIV viral load and genotyping based on retrospective centralized testing.¹¹ The analysis included those diagnosed post ≥ 1 CAB-LA injection, with >30 days ART follow-up (first HIV+ visit prior to 12/1/23). Results are summarized in Table 9.

Table 9. ART Outcomes after HIV Acquisition After Exposure to CAB LA in HPTN 083¹¹

	INSTI-based ART			Other ART		
	Overall	<6 months ^a	≥ 6 months ^a	Overall	<6 months ^a	≥ 6 months ^a
Viral load <50 c/ml, n (%)	15/21 (71.4)	5/6 (83.3)	10/15 (66.7)	21/26 (80.8)	15/16 (93.8)	6/10 (60)
Days of follow-up, median (range)	236 (77-356)	341.5 (188-356)	162 (77-352)	316 (35-422)	334 (35-422)	161.5 (72-341)
ART regimen switch, N (%)	0/21	0/6	0/15	5/26 (19.2)	3/16 (18.8)	2/10 (20)
Maintained viral suppression	-	-	-	2/5 (40)	1/3 (33.3)	1/2 (50)
Became virally suppressed	-	-	-	2/5 (40)	1/3 (33.3)	1/2 (50)
No follow-up data	-	-	-	1/5 (20)	1/3 (33.3)	0/2
INSTI rams detected, N(%)	1/19 (5.3) ^b	1/6 (16.7)	0/13 ^b	8/25 (32.0) ^b	7/16 (43.8)	1/9 ^b (11.1)
viral load <50 c/ml, n(%)	1/1 (100)	1/1 (100)	-	8/8 (100)	7/7 (100)	1/1 (100)

ART= antiretroviral therapy ^aTime between last CAB injection and start of ART. ^b Pre-ART genotyping not available for 3 participants; two were not virally suppressed.

This information is scientific and non-promotional in nature and is not intended for further distribution. Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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