

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):
 - 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.
- To date there have been no cases of INSTI resistance reported among the subjects who seroconverted during the pharmacokinetic tail of CAB LA.
- 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.
- The most common adverse events reported in the CAB LA arm were injection site reactions (ISRs).
- Important Safety Information and Boxed Warning can be found in the [Prescribing Information](#) and can also be accessed from the [Our HIV Medicines](#) section of viivhealthcare.com/us.

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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			

	CAB LA (N=2282)	TDF/FTC (N=2284)	Total (N=4566)
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/emtricitabine; 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

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCES

1. Landovitz R DD, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *NEJM*. 2021;385(7):595-609. doi:<http://dx.doi.org/10.1056/NEJMoa2101016>.
2. HIV Prevention Trials Network. HPTN 083 Study Demonstrates Superiority of Cabotegravir for the Prevention of HIV. Available at: <https://www.hptn.org/news-and-events/press-releases/hptn-083-study-demonstrates-superiority-cabotegravir-prevention-hiv>. Accessed on December 21, 2021.
3. HIV Prevention Trials Network. HPTN 083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex with Men (protocol version 4.0; February 10, 2021. Available at: <https://www.hptn.org/research/studies/hptn083#views-field-field-public-files>. Accessed September 30, 2021.
4. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. *J Infect Dis*. 2021. doi:<http://dx.doi.org/10.1093/infdis/jiab152>.
5. Marzinke MA, et al. Laboratory analysis of HIV infections in the Year 1 unblinded period of HPTN 083: injectable cabotegravir for PrEP in MSM and TGW. Presented at HIV Glasgow 2022, October 23-26, 2022, Glasgow, UK and virtually. Oral Presentation.
6. Landovitz RJ. Laboratory analysis of HIV infection in HPTN 083: injectable CAB for PrEP. Presented at the 2021 Conference on Retroviruses and Opportunistic Infections (virtual), March 6-10, 2021. Abstract 00153.
7. Eshleman S, et al. CAB-LA PrEP: Early detection of HIV infection may reduce INSTI resistance risk. Presented at the 29th Conference on Retroviruses and Opportunistic Infections (CROI), February 12-16, 2022, Virtual Event. Oral Presentation.
8. Scott H, Hanscom B, Hutchinson C, et al. Cabotegravir for HIV PrEP in US Black men and transgender women who have sex with men. Presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI), February 19-22, 2023, Seattle, WA, USA.