

Transgender Women (TGW) in HPTN 083: An Evaluation of Safety, Efficacy, and Gender Affirming Hormonal Therapy (GAHT) Interactions with Long-acting Cabotegravir (CAB-LA)

Beatriz Grinsztejn¹, Brett Hanscom², Zhe Wang², Deborah Donnell², Paul Richardson³, Philip Sullivan³, Susan Eshleman³, Andrea Jennings⁴, Kailazarid Gomez-Feliciano⁴, Kritima Samitpol⁵, Emilia Jalil¹, Nadir Cardozo⁶, Bernardo Maia⁷, Taimur Khan⁸, Yashna Singh⁹, Julie Franks¹⁰, Javier Valencia¹¹, Christina Psaros¹², Steven Safren¹³, Naiymah Sanchez⁴, Jonathan Lucas⁴, Cheryl Blanchette⁴, James Rooney¹⁴, Alex Rinehart⁵, Susan Ford¹⁵, Adeola Adeyeye¹⁶, Myron Cohen¹⁷, Marybeth McCauley⁴, Raphael J Landovitz¹⁸, Mark A Marzinke³

¹Instituto Nacional de Infectologia Evandro Chagas-Fiocruz, RJ/Brazil, ²Fred Hutchinson Cancer Center, Seattle/US, ³Johns Hopkins University, Baltimore/US, ⁴FHI 360, Durham, North Carolina/US, ⁵Thai Red Cross AIDS Research Centre, Thailand, ⁶Fundación Huésped CRS, Argentina, ⁷Hospital Emilio Ribas, SP/Brazil, ⁸Fenway Health CRS, Boston, US, ⁹Groote Schuur HIV CRS, Cape Town/South Africa, ¹⁰Harlem Prevention Center CRS, New York/US, ¹¹Barranco CRS, Peru, ¹²Massachusetts General Hospital, Boston/US, ¹³Coral Gables, FL/US, ¹⁴Gilead Sciences, Foster City/US, ¹⁵ViiV Healthcare, Research Triangle, North Carolina/US, ¹⁶National Institutes of Health, Rockville, MD/US, ¹⁷University of North Carolina at Chapel Hill, Chapel Hill/US, ¹⁸Center for Clinical AIDS Research and Education, David Geffen School of Medicine, University of California, Los Angeles/US

Background

Despite major advances in treatment and prevention, the HIV pandemic continues to pose a major global public health challenge. HPTN 083 is a phase 2b/3 randomized, double-blind, double-dummy trial that showed that long-acting injectable cabotegravir (CAB-LA) was superior to oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in preventing HIV in cisgender men (MSM) and transgender women (TGW) who have sex with men. Pre-specified subpopulations historically underrepresented in PrEP registrational trials, including TGW, were successfully enrolled and retained in the study, thereby fostering inclusion and equity in scientific development. As transgender women (TGW) remain a priority group for HIV prevention, we report participant characteristics, safety, prevention efficacy, and pharmacokinetics (PK) of CAB-LA in TGW during the blinded phase of HPTN 083.

Methods

Participant characteristics, including gender affirming hormone therapy (GAHT) use, history of interpersonal violence, and HIV risk perception, were collected at baseline and throughout the study, and compared between TGW and cisgender MSM. Demographics were collected at screening by a healthcare professional.

The frequency of Grade 2+ adverse events (AEs) and incidence of curable STIs and HIV during the blinded phase of the trial were compared between TGW randomized to the TDF/FTC or CAB-LA.

In a subset of TGW who received all injections through study week 59 on time, CAB pharmacokinetics (PK) were compared between TGW in the presence or absence of GAHT.

Results

Of 4,566 participants enrolled in HPTN 083, 570 (12.5%) were TGW by self-identification. Age and geographic distributions are presented in **Table 1**. Among TGW, 330 (57.9%) reported GAHT use, with 249 at baseline and 81 initiating GAHT after enrollment. Among TGW enrolled in this trial, estradiol valerate was the most common medication accessed for gender affirmation (**Table 2**).

TABLE 1. Participant Demographics, HPTN 083.

	Overall (n=4566)		TGW (n=570)		MSM (n=3996)	
	n	%	n	%	n	%
Age (years)						
18-29	3080	67.5%	471	82.6%	2609	65.3%
30-39	1048	23.0%	71	12.5%	977	24.4%
>40	438	9.6%	28	4.9%	410	10.3%
Geographic Region						
United States	1698	37.2%	125	21.9%	1573	39.4%
Latin America	1964	43.0%	205	36.0%	1759	44.0%
Asia	752	16.5%	225	39.5%	527	13.2%
Africa	152	3.3%	15	2.6%	137	3.4%

TABLE 2. Most common gender affirming medications reported among TGW during the blinded phase of HPTN 083.

Self-Reported GAHT Medication	Overall (n=330)		Reported GAHT Use at Baseline (n=249)		Reported GAHT Initiation Post-Enrollment (n=81)	
	n	%	n	%	n	%
Cyproterone acetate; Ethinylestradiol	88	26.7%	74	29.7%	14	17.3%
Estradiol valerate	147	44.5%	110	44.2%	37	45.7%
Estradiol	94	28.5%	79	31.7%	15	18.5%
Spirolactone	107	32.4%	79	31.7%	28	34.6%

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E-poster Contact: gbeatriz@ini.fiocruz.br

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Regardless of study arm, at baseline, TGW enrolled in the study experienced an increased frequency of sexual (56.7% vs. 45.4%), physical (30.2% vs. 19.2%), and emotional (47.4% vs. 36.4%) interpersonal violence when compared to MSM (**Table 3**). Further, when study participants were queried regarding their perceptions about HIV acquisition risk, self-perceived risk was lower for TGW as compared to MSM (44.4% vs. 32.5%).

TABLE 3. History of interpersonal violence and HIV risk perception in HPTN 083 study participants at baseline.

	Overall (n=4566)		TGW (n=570)		MSM (n=3996)	
	n	%	n	%	n	%
Interpersonal Violence						
Emotional Abuse	1724	37.8%	270	47.4%	1454	36.4%
Physical Abuse	939	20.6%	172	30.2%	767	19.2%
Sexual Abuse	2137	46.8%	323	56.7%	1814	45.4%
Low HIV risk perception ¹	1551	34.0%	253	44.4%	1298	32.5%

¹Related to the phrase "I am worried about getting infected with HIV," the options "strongly disagree," "disagree," "neither agree nor disagree," and "don't know" were classified as "low HIV risk perception".

CAB-LA was well tolerated in TGW; the frequency of grade 2+ AEs did not meaningfully differ between TGW receiving CAB-LA or TDF/FTC (92.5% vs. 88.8%). HIV incidence among TGW during the blinded phase of the trial was 1.80% (TDF/FTC) and 0.54% (CAB-LA) (hazard ratio: 0.343, 95%, CI 0.08-1.56). Incidence of STIs among TGW were comparable between study arms (**Table 4**).

TABLE 4. AE frequency and HIV and curable STI incidence among TGW during the blinded phase of HPTN 083, stratified by study arm.

	Overall (n=570)		TDF/FTC (n=304)		CAB-LA (n=266)	
	n	%	n	%	n	%
HIV incidence rate	9	1.19%	7	1.80%	2	0.54%
Syphilis incidence rate		16.3%		18.6%		13.8%
Gonorrhea (rectal) incidence rate		11.7%		11.8%		11.5%
Chlamydia (rectal) incidence rate		20.6%		22.6%		18.6%
Participants who received at least one injection	516	90.5%	266	87.5%	250	94.0%
Participants who reported any injection site reaction (ISR)	294	57.0%	77	28.9%	217	86.8%
Participants with Grade 2+ AEs	516	90.5%	270	88.8%	246	92.5%
Participants with Grade 3+ AEs	142	24.9%	76	25.0%	66	24.8%

CAB PK was compared in a subset of TGW in the presence or absence of GAHT; in this analysis, 30 participants accessed GAHT, while 23 participants were not using GAHT. Study participants in this analysis received all CAB-LA injections on-time through week 53. CAB drug concentrations were comparable between the two groups, suggesting the lack of a GAHT effect on CAB PK (**Figure 1**).

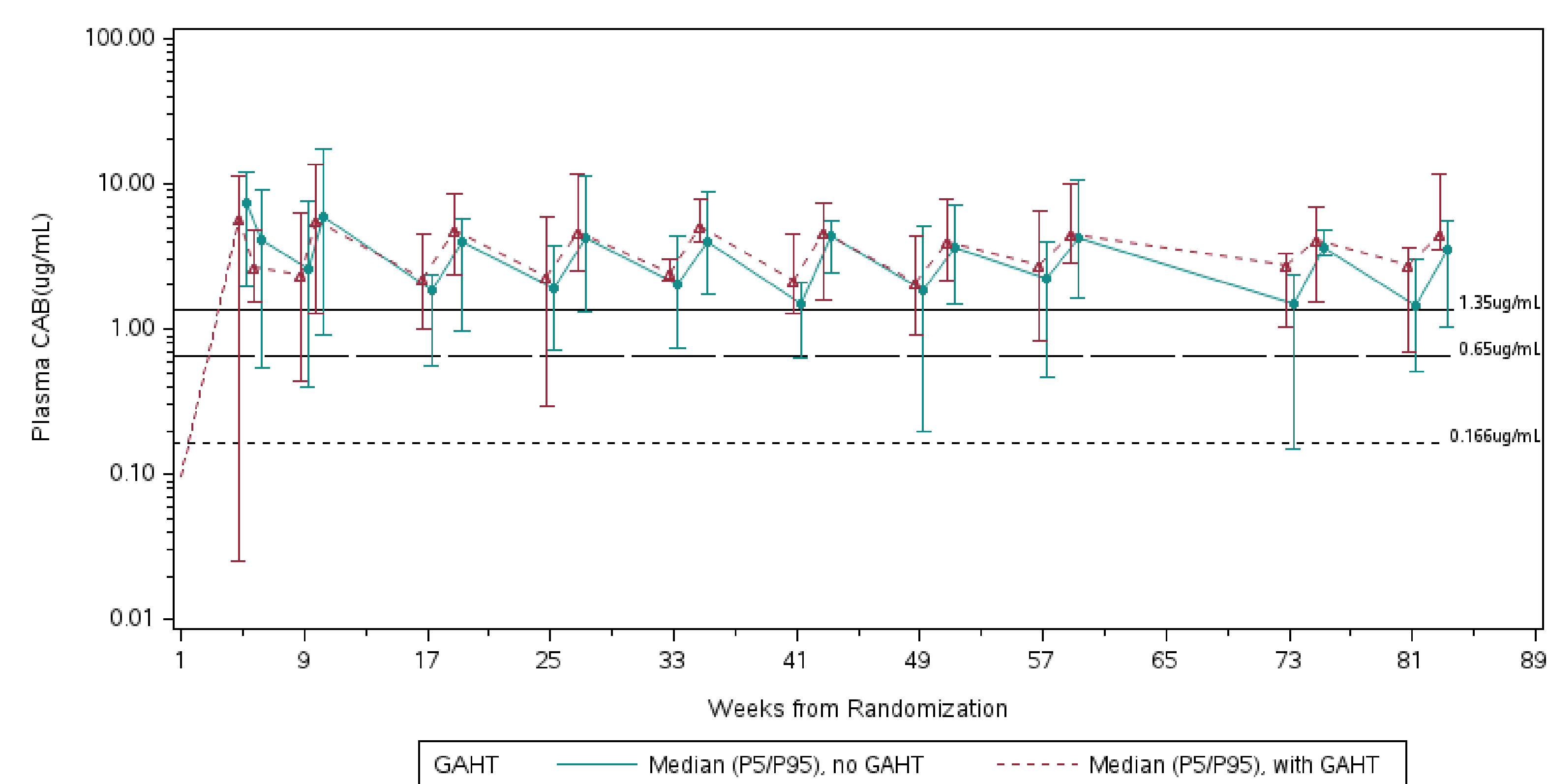


Figure 1. Concentration-time profiles of CAB in TGW in the absence (solid blue line) or presence (dotted red line) of GAHT. Dotted horizontal line: 1x PA-IC₉₀ (0.166 µg/mL); dashed horizontal line: 4x PA-IC₉₀ (0.664 µg/mL); solid horizontal line: 8x PA-IC₉₀ (1.33 µg/mL).

Conclusions

- CAB-LA is a safe and effective HIV prevention strategy for TGW.
- Efficacy: During a median follow-up of 1.4 years, TGW on CAB-LA had lower incidence of HIV infection as compared to TDF/FTC, which is consistent with observations in the overall population
- Safety: The occurrence of grade 2+ AEs were similar between study arms for TGW; incidence of ISRs was higher in TGW randomized to the CAB study arm.
- Initial findings suggest GAHT does not impact CAB concentrations.