Inclusion of Gender Diverse Populations in Clinical Trials: Laboratory Assessments Among Transgender Women Enrolled in HPTN 083

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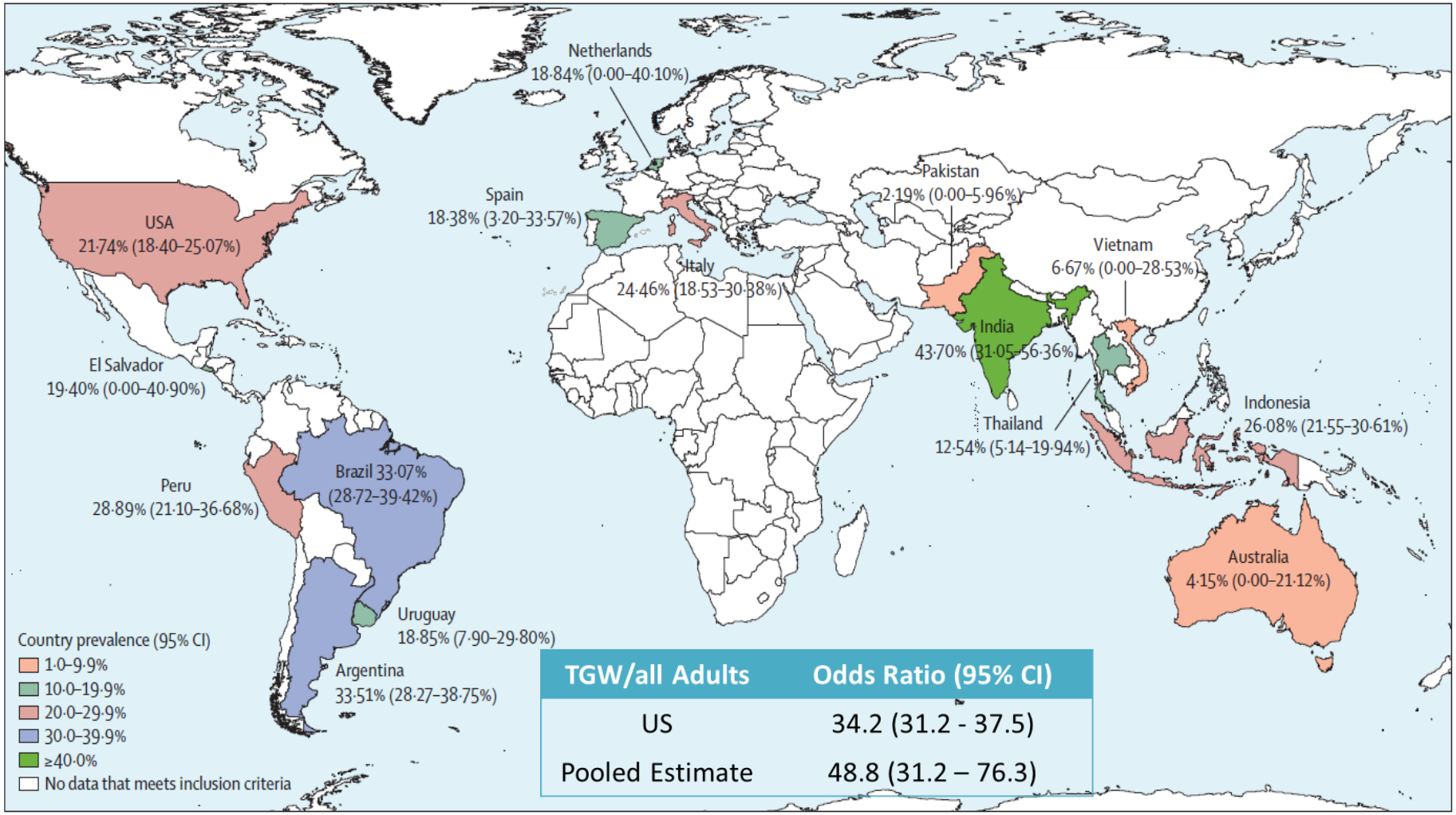
On Behalf of HPTN 083 Study Team

HPTN Annual Meeting

Take Home Message

Studies of PrEP should be designed and tailored to consider TGW, rather than extrapolated from studies in MSM; TGW, as well as transgender men and gender non-binary individuals, should be included and represented in PrEP research

Increased HIV Burden Among Transgender Women (TGW)



Baral et al., 2013

Barriers to PrEP Uptake Among Transgender and Gender Diverse (TGD) People, Including TGW

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- Marginalization within the public health system
- Medical and research mistrust
- Knowing one's HIV status
- Stigma
- Impact of PrEP on gender affirming hormone therapies (GAHT)

Rael, et al. 2018; Wilson et al; 2018

Considerations When Investigating Drug-Hormone Interactions

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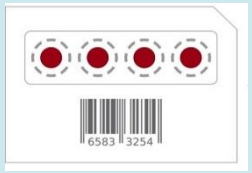
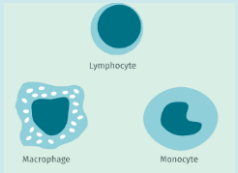
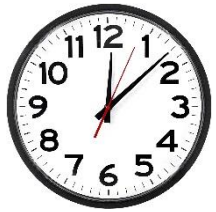
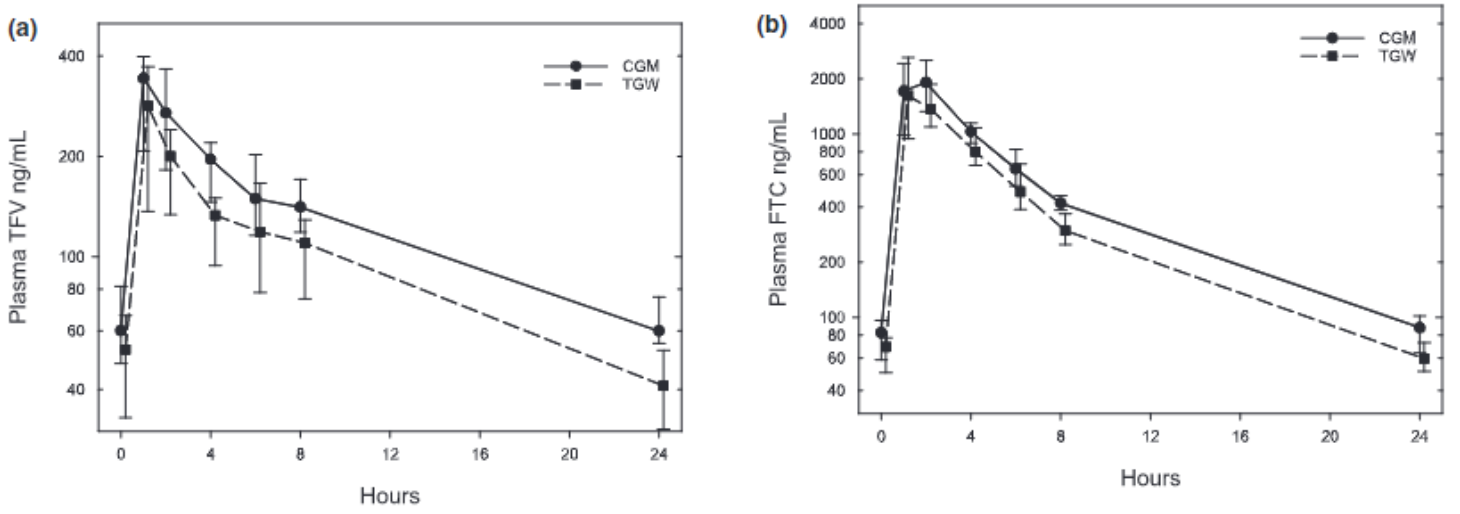
Study Product	  
Specimen Source	   
Sample collection points	
Directionality of Interaction	ARV ⟷ GAHT

Interrogation of Drug-Hormone Interactions Between TDF/FTC and GAHT

	TGW Median (IQR)	CGM Median (IQR)	TGW/ CGM %	p value
Age, years	29 (26, 41)	46 (28, 52)	63	0.195[a]
Weight, kg	98 (83, 123)	83 (71, 91)	118	0.130
BMI	31 (24, 36)	23 (21, 27)	133	0.061
Race, n (%)				
Asian ancestry	1 (12)	0 (0)		1.000[b]
African ancestry	6 (75)	6 (75)		
European ancestry	1 (12)	2 (25)		

IQR, interquartile range.
[a]Exact 2 sided *p* value, Wilcoxon rank sum test, comparing TGW and CGM; [b]Fisher's exact test.

Hormone	TGW Day 0[b]	TGW Day 7	CGM Day 7	Pre vs. Post TDF/FTC *p* value[a]	TGW versus CGM *p* value[a]
Oestradiol (pg/mL)	221 (60, 615)	380 (208, 437)	15 (12, 23)	0.669	<0.001
FSH (mIU/mL)	0.17 (0.10, 3.23)	0.10 (0.10, 3.87)	4.02 (2.23, 5.83)	0.806	0.047
LH (mIU/mL)	0.88 (0.13, 4.16)	0.46 (0.16, 5.63)	5.45 (2.98, 7.62)	0.626	0.048
Total Testosterone (ng/dL)	15 (10, 90)	17 (10, 297)	422 (346, 605)	0.151	0.028
Free Testosterone (ng/dL)	0.34 (0.19, 2.03)	0.35 (0.30, 3.48)	12.65 (8.10, 17.70)	0.375	0.011



Shieh, Marzinke, et al., 2019

Interrogation of Drug-Hormone Interactions Between TDF/FTC and GAHT

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Study	Population (n)	GAHT	Drug	Assessments	PK Impact on TGW
Nebraska	TGW (15)	Estradiol (oral, IM) MPA Progesterone Spironolactone	TDF/FTC	Plasma AUC_{0-24} PBMC C_{12}	**TFV, FTC AUC_{0-24}** ↓ by 24% and 14% TFV-DP and FTC-TP ↑
JHU-CFAR	CGM (8) TGW (8)	Estradiol (oral, IM) MPA Premarin Spironolactone	TDF/FTC	Plasma, PBMC AUC_{0-24}, C_{24} Tissue C_{24}	**Plasma TFV, FTC C_{24}** ↓ by 32% TFV, **FTC AUC_{0-24}** ↓ by 27% and 24%
iFACT	TGW (20)	Estradiol (IM) Cyproterone aceteate (IM)	TDF/FTC	Plasma AUC_{0-24}, C_{24}	**TFV AUC_{0-24}** and **C_{24}** 12% and 18% ↓ with GAHT No impact of F/TDF on E2
iFACT	TGW (20)	Estradiol (IM) Cyproterone aceteate (IM)	TDF/FTC/ EFV	Plasma AUC_{0-24}, C_{24}	**TFV AUC_{0-24h}** and **C_{24}** 14% and 17% ↓ with GAHT **E2 AUC_{0-24h}** and **C_{24}** 28% and 36% ↓ with ART
iBrEATHe	TGW (24)	Estradiol (oral, IM) MPA Progesterone Spironolactone	TDF/FTC	DBS TFV-DP (4 weeks)	TFV-DP trended 11% ↓ No impact of F/TDF on E2
PrEParadas	TGW (30)	Estradiol valerate Spironolactone	TDF/FTC	Plasma AUC_{0-24}	TFV, FTC AUC trended 12% ↑ **FTC C_{max}** ↑ No impact of F/TDF on E2

Strategies for Inclusion of TGD Participants in Clinical Trials

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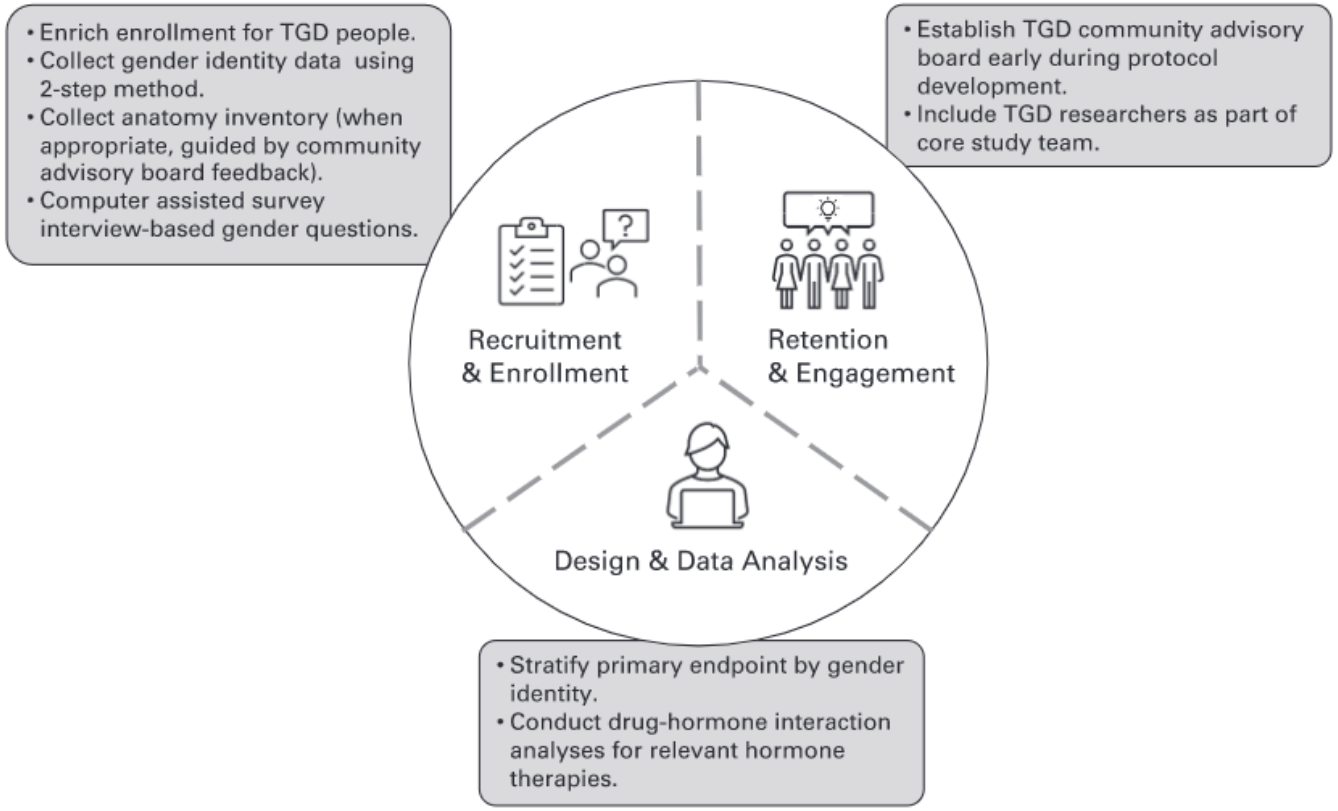
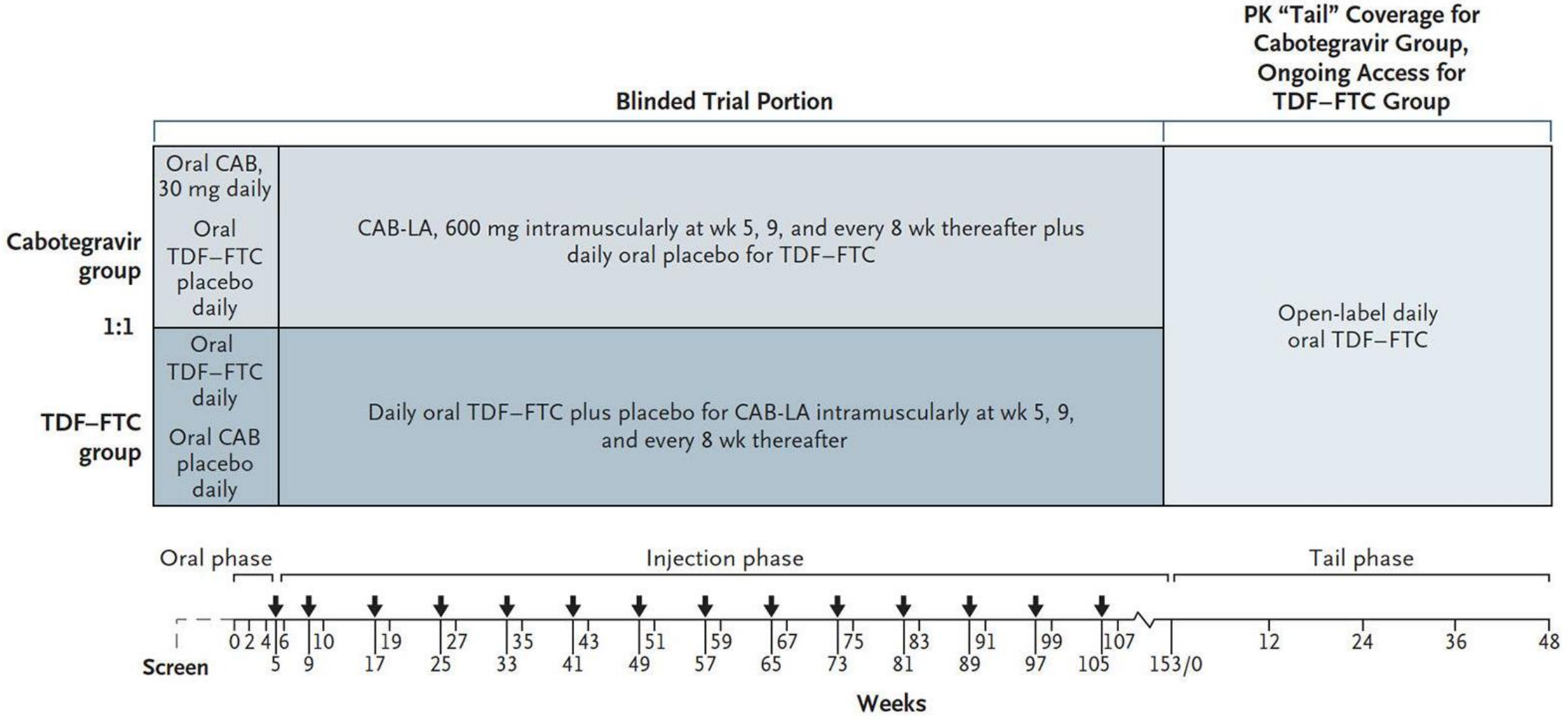
- Research should be conducted with community members
- Consider stratification of endpoints by gender identity
- Consider analyses for drug-hormone interactions
- Enrich enrollment for TGD populations



Cirrincione et al., 2023

HPTN 083 Study Design



Landovitz et al., 2021

HPTN 083: Geographic Distribution

Argentina (2)
Brazil (4)
Peru (5)
South Africa (1)
Thailand (3)
United States (27)
Vietnam (1)

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HPTN 083: Demographics

Participants Enrolled	TDF/FTC (n=304) n (%)	CAB-LA (n=266) n (%)
Self−identification		
Female	43 (14.1)	47 (17.7)
Transgender male	0 (0.0)	0 (0.0)
Transgender female	213 (70.1)	187 (70.3)
Gender queer	18 (5.9)	14 (5.3)
Gender variant or gender non-confirming	27 (8.9)	16 (6.0)
Other self-identification	3 (1.0)	2 (0.8)
Prefer not to answer	0 (0.0)	0 (0.0)
Age		
18-29	244 (80.3)	227 (85.3)
30-39	42 (13.8)	29 (10.9)
40+	18 (6.0)	10 (3.7)
Median (IQR)	23 (21, 28)	23 (21, 27)
Geographic Region		
US	71 (23.4)	54 (20.3)
Latin America	113 (37.2)	92 (34.6)
Asia	110 (36.2)	115 (43.2)
Africa	10 (3.3)	5 (1.9)

Marzinke et al., 2023 (in review)

HPTN 083: STI Prevalence and Incidence

Participants Enrolled	TDF/FTC (n=304) n (%)	CAB-LA (n=266) n (%)	p-value
Prevalence Rate			
Diagnosed with active Syphilis	22/303 (7.3)	17/266 (6.4)	0.69
Positive test for Gonorrhea (rectal)	24/304 (7.9)	17/266 (6.4)	0.48
Positive test for Chlamydia (rectal)	55/304 (18.1)	41/266 (15.4)	0.39
Incidence Rate - % (95%CI)			
Syphilis	18.6 (14.2-24.0)	13.8 (10.1-18.6)	0.19
Gonorrhea (rectal)	11.8 (8.30-16.2)	11.5 (8.09-16.0)	0.94
Chlamydia (rectal)	22.6 (17.7-28.5)	18.6 (14.1-24.0)	0.33

- STI prevalence rates among TGW ranged from 6.9% to 16.8%, and did not differ between study arms

- STI incidence was high for all rectal STIs

Marzinke et al., 2023 (in review)

HIV Incidence During Blinded Phase of HPTN 083 Among TGW

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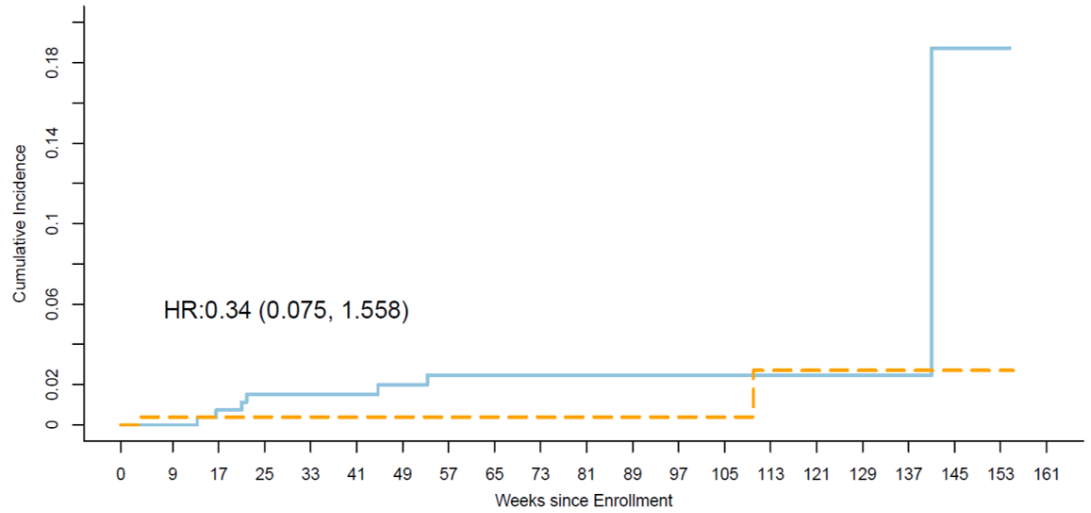
Blinded Phase, TGW Participants (n=9)



Number at Risk

TDF/FTC	304	282	267	254	236	217	204	189	168	138	105	90	71	49	39	31	20	10	5	2	0
Cabotegravir	266	254	244	238	223	211	197	178	157	138	115	90	71	52	36	32	20	10	6	3	0

Cumulative Number of Events

TDF/FTC	0	0	2	4	4	4	5	6	6	6	6	6	6	6	6	6	6	7	7	0
Cabotegravir	0	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	0

- Nine TGW acquired HIV during the blinded phase of HPTN 083 (7 TDF/FTC; 2 CAB-LA)

- CAB-LA Incident Cases
  - Acquisition during oral lead-in (n=1)
  - Acquisition 849 days after their last injection; CAB unquantifiable at first HIV positive visit (n=1)

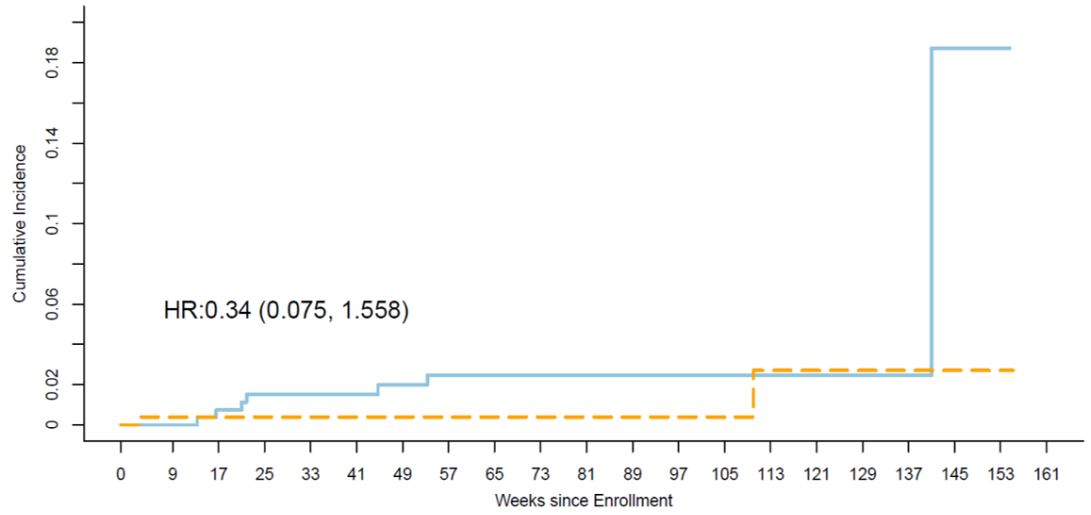
- TDF/FTC Incident Cases
  - 7/7 did not have TFV or TFV-DP concentrations associated with protection
  - 5/7 had unquantifiable drug concentrations at first HIV positive visit

Marzinke et al., 2023 (in review)

HIV Incidence During Blinded Phase of HPTN 083

HPTN HIV Prevention Trials Network

Blinded Phase, TGW Participants (n=9)



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Cumulative Number of Events																					
TDF/FTC	0	0	2	4	4	4	5	6	6	6	6	6	6	6	6	6	6	6	7	7	0
Cabotegravir	0	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	0

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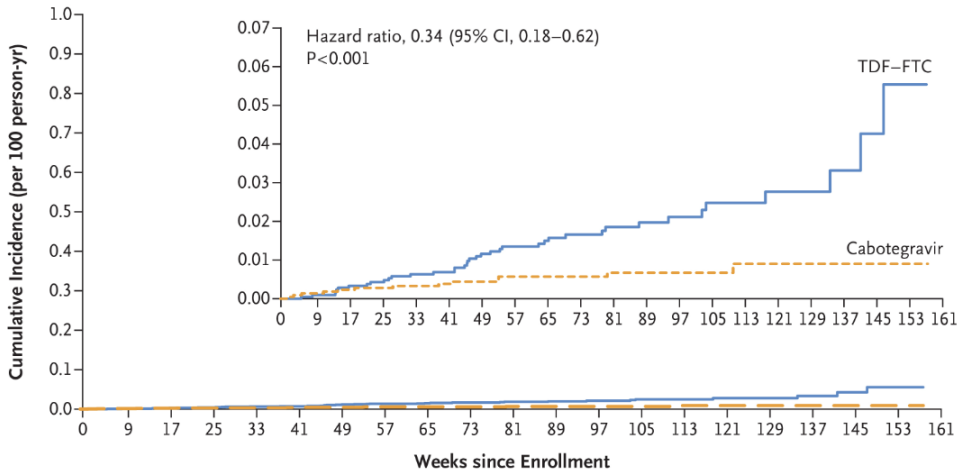
Blinded Phase, All Participants (n=9)

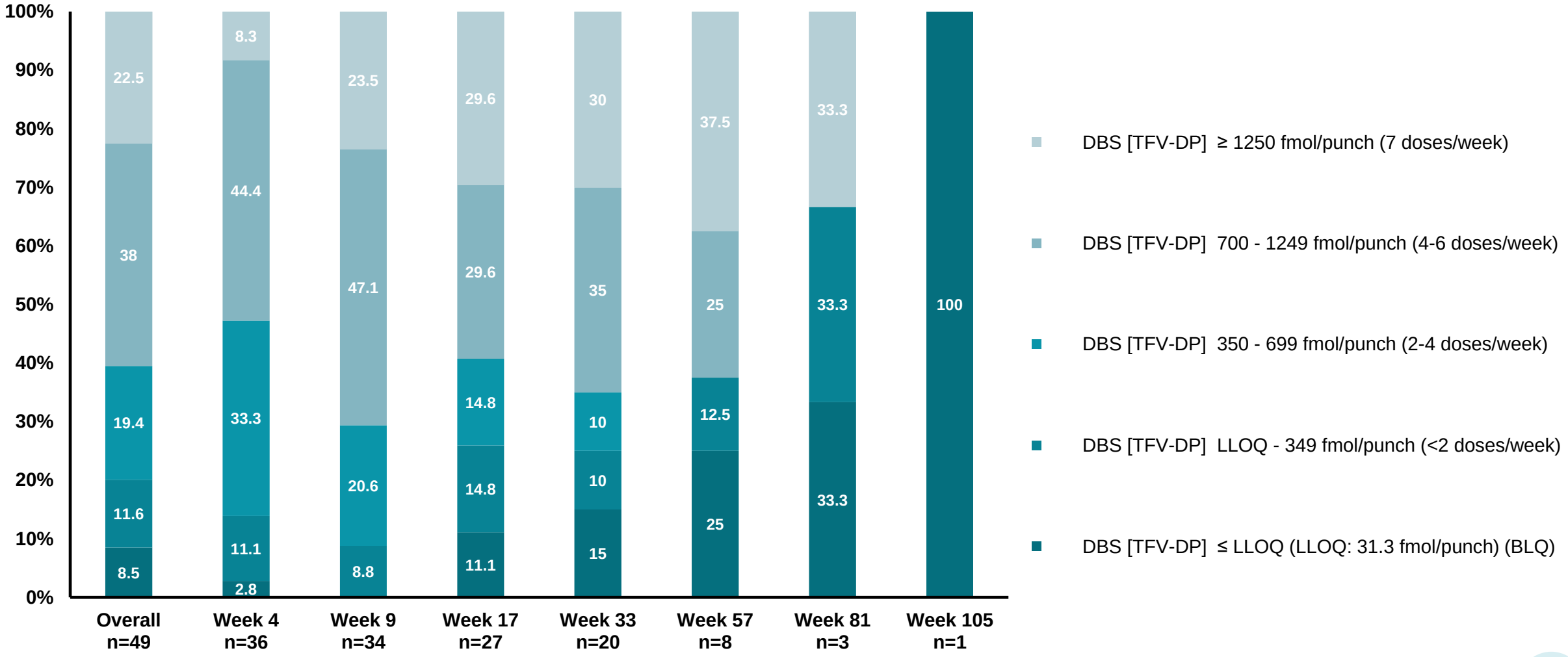


No. at Risk																					
TDF–FTC	2281	2132	2081	2019	1913	1765	1624	1494	1295	1132	965	817	644	517	401	311	231	150	85	33	0
Cabotegravir	2280	2138	2091	2031	1920	1776	1633	1489	1315	1124	957	798	644	503	401	318	243	173	111	42	0

Cumulative No. of Events																					
TDF–FTC	0	2	7	9	13	14	22	25	27	29	31	32	33	35	35	36	36	37	38	39	0
Cabotegravir	0	3	5	6	7	8	9	11	11	11	12	12	12	12	13	13	13	13	13	13	0

Landovitz et al., 2021

HPTN 083: TDF/FTC Adherence



Marzinke et al., 2023 (in review)

Gender Affirming Hormone Therapy Reported by Study Participants

	Reported GAHT Use (TGW)		
	GAHT Reported at Baseline n (%)	GAHT Initiated During Follow-up n (%)	Total GAHT Use Reported n (%)
Participants who self-reported GAHT	249/570 (43.7)	81/570 (14.2)	330/570 (57.9)
Hormone therapy type			
Anti-androgens	202/249 (81.1)	50/81 (61.7)	252/330 (76.4)
Estrogens	239/249 (96.0)	71/81 (87.7)	310/330 (93.9)
Progestogens	91/249 (36.5)	26/81 (32.1)	117/330 (35.5)

- GAHT use and therapies did not differ between study arms; 15% of TGW self-reported initiation of GAHT after study enrollment

- Most common therapies included estradiol valerate (44.5%), spironolactone (32.4%), estradiol (28.5%) and cyproterone acetate (27.9%)

Marzinke et al., 2023 (in review)

Gender Affirming Hormone Therapy Reported by Study Participants

	Reported GAHT Use (TGW)			Reported GAHT Use (MSM)		
	GAHT Reported at Baseline n (%)	GAHT Initiated During Follow-up n (%)	Total GAHT Use Reported n (%)	GAHT Reported at Baseline n (%)	GAHT Initiated During Follow-up n (%)	Total GAHT Use Reported n (%)
Participants who self-reported GAHT	249/570 (43.7)	81/570 (14.2)	330/570 (57.9)	7/3996 (0.2)	25/3996 (0.6)	32/3996 (0.8)
Hormone therapy type						
Anti-androgens	202/249 (81.1)	50/81 (61.7)	252/330 (76.4)	5/7 (71.4)	16/25 (64.0)	21/32 (65.6)
Estrogens	239/249 (96.0)	71/81 (87.7)	310/330 (93.9)	6/7 (85.7)	20/25 (80.0)	26/32 (81.3)
Progestogens	91/249 (36.5)	26/81 (32.1)	117/330 (35.5)	2/7 (28.6)	9/25 (36.0)	11/32 (34.4)

- GAHT use and therapies did not differ between study arms; 15% of TGW self-reported initiation of GAHT after study enrollment

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Marzinke et al., 2023 (in review)

Evaluation of CAB Concentrations in TGW ± GAHT

- CAB concentrations evaluated in a subset of participants who had high adherence to CAB-LA injections
  - All injections administered within ± 1 week of schedule injection
  - No missing injections through week 57
  - Participants self-reported use (n=30) or non-use (n=23) or GAHT

Marzinke et al., 2023 (in review)

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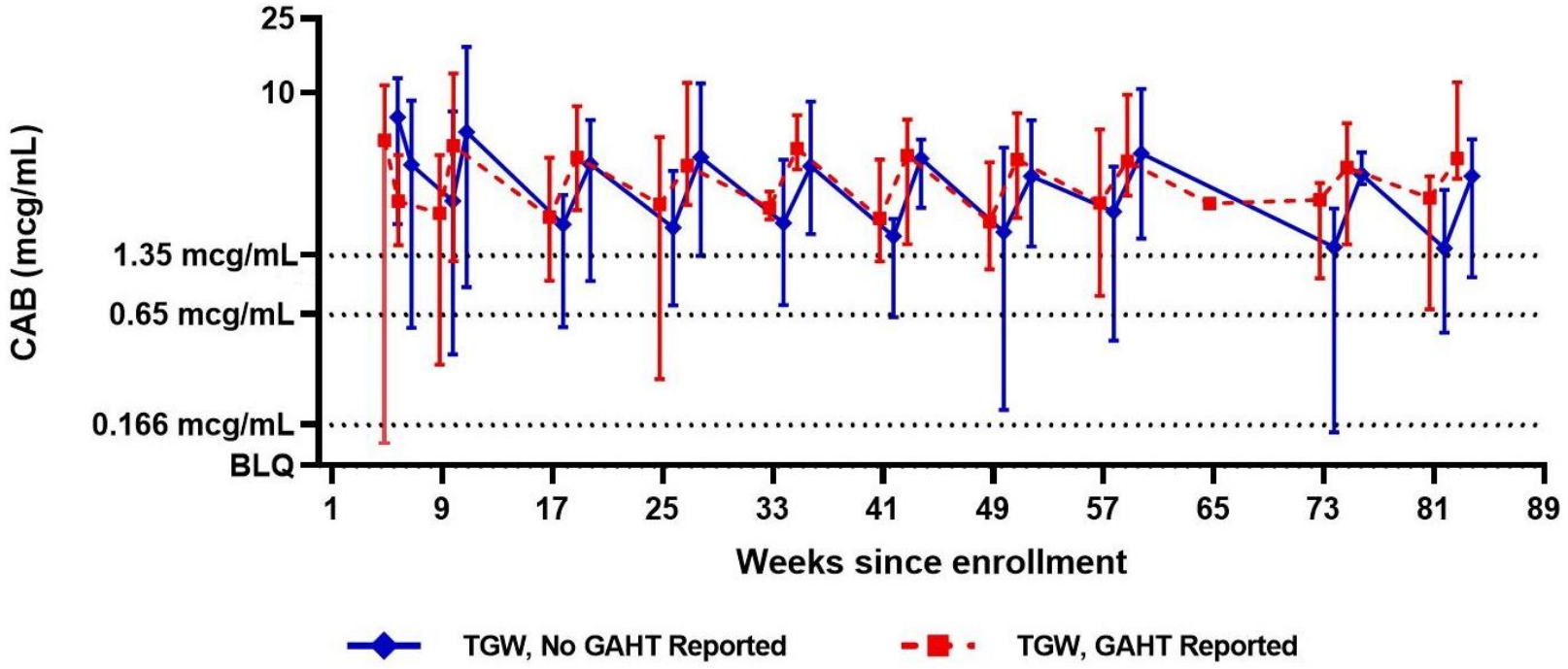
Visit	TGW Who Reported GAHT Use Mean [CAB]; n=30 (mcg/mL) (95% CI)	TGW Who Did Not Report GAHT Use Mean [CAB]; n=23 (mcg/mL) (95%CI)
Week 5	0.81 (0.02, 42.33)	6.69 (4.86, 9.21)
Week 6	2.60 (1.58, 4.29)	3.86 (2.44, 6.10)
Week 9	1.85 (1.2, 2.84)	2.29 (1.66, 3.14)
Week 10	4.74 (3.27, 6.88)	5.24 (3.73, 7.36)
Week 17	2.15 (1.79, 2.59)	1.57 (1.16, 2.13)
Week 19	4.60 (3.88, 5.44)	3.46 (2.42, 4.94)
Week 25	2.11 (1.36, 3.28)	1.84 (1.50, 2.26)
Week 27	4.87 (3.81, 6.23)	4.18 (3.07, 5.68)
Week 33	2.51 (2.04, 3.09)	1.82 (1.33, 2.50)
Week 35	5.21 (3.64, 7.44)	4.18 (2.94, 5.95)
Week 41	2.32 (1.87, 2.88)	1.32 (0.71, 2.43)
Week 43	4.13 (3.17, 5.38)	4.18 (3.08, 5.69)
Week 49	2.09 (1.69, 2.58)	1.31 (0.68, 2.53)
Week 51	4.01 (3.36, 4.80)	3.40 (2.30, 5.03)
Week 57	2.42 (1.85, 3.17)	1.83 (1.38, 2.43)
Week 59	4.62 (3.78, 5.65)	3.97 (2.93, 5.37)
Week 73	2.40 (1.97, 2.93)	1.06 (0.26, 4.27)
Week 75	3.90 (3.01, 5.04)	3.78 (2.81, 5.08)
Week 81	2.04 (0.99, 4.21)	1.24 (0.32, 4.91)
Week 83	5.20 (3.32, 8.13)	2.75 (0.74, 10.17)

Marzinke et al., 2023 (in review)

Evaluation of CAB Concentrations in TGW ± GAHT



- There were no statistically significant differences in CAB concentrations at evaluated time points (p=0.783)
- Hormone dosing data/measurements were not performed

Marzinke et al., 2023 (in review)

Summary

- HIV incidence among TGW during the blinded phase of HPTN 083 is consistent with overall study findings
- Adherence to TDF/FTC (≥ 4 doses/week) remained consistent through study week 57 (52.7%-70.6%)
- GAHT was self-reported by TGW and MSM at study enrollment and during study conduct
- CAB concentrations among TGW on GAHT were nominally higher than TGW who did not report GAHT use; however, there were no statistically significant differences in CAB concentrations at evaluated time points (p=0.783)

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