

# Evaluation of Potential Pharmacologic Interactions Between CAB-LA or F/TDF and hormonal contraceptive agents: a tertiary analysis of HPTN 084

**Marzinke MA**, Hanscom B, Haines D, Scarsi K, Agyei Y, Rose S, Mathew C, Panchia R, Spooner E, Kalonji D, Singh N, Bock P, Rinehart A, Ford S, Rooney J, Soto-Torres L, Cohen M, Hosseinipour M, Delany-Moretlwe S, HPTN 084 Study Team

- I have no relevant financial relationships with ineligible companies to disclose

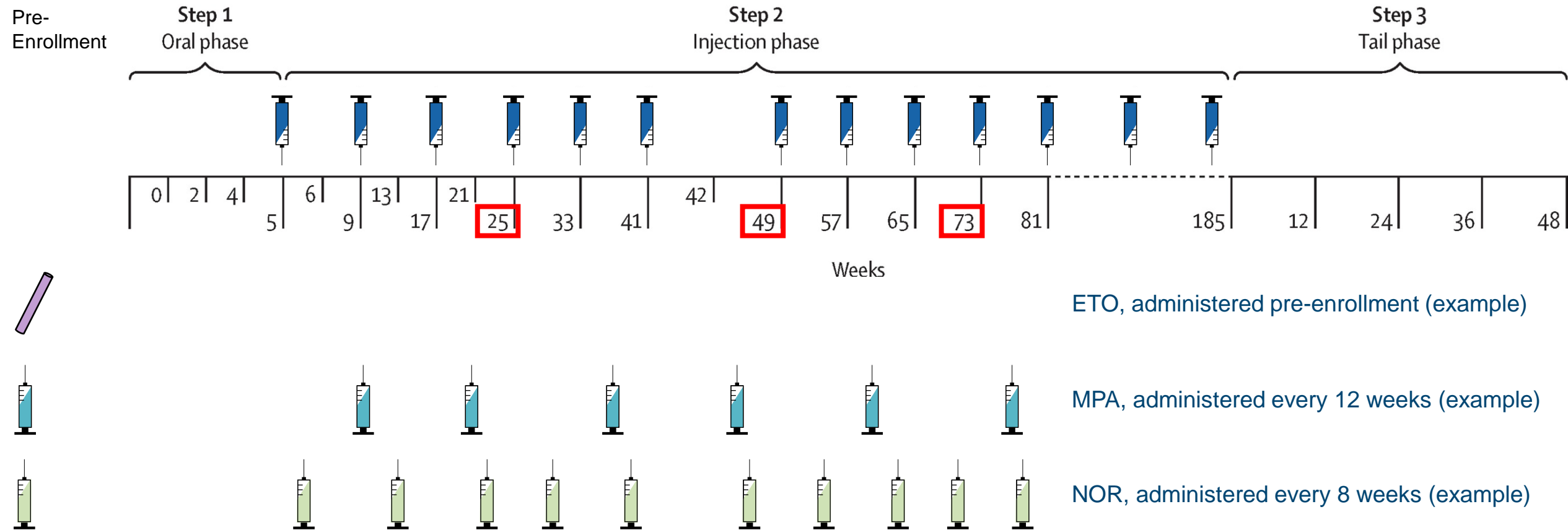
# Use of Long-Acting Reversible Contraceptive Agents in HPTN 084

- During the blinded phase of HPTN 084, use of a long-acting reversible contraceptive agent was required as an additional safety measure
  - Drug interactions between CAB-LA and contraceptive agents were considered unlikely, based on previous studies (*Trezza et al. 2017*)
  - Studies have not evaluated contraceptive agents used in Eastern and Southern Africa
- Long-acting reversible contraceptive agents commonly used in Eastern and Southern Africa include:
  - Etonogestrel (ETO)
  - Medroxyprogesterone acetate (MPA)
  - Norethindrone or Norethisterone ethanate (NOR)

# Hormonal Contraceptive Sub-Study

- A hormonal contraceptive sub-study assessed the potential pharmacologic interactions between PrEP agents (CAB-LA or F/TDF) and contraceptive agents (ETO, MPA, or NOR)
  - Evaluate the potential effects of CAB-LA on the concentrations and effectiveness of long-acting contraceptives, as compared to F/TDF
- Evaluate differences in CAB-LA concentration-time profiles between contraceptive groups

# HPTN 084 Study Schema



- Participants who consented to the hormonal contraceptive sub-study were asked to provide additional plasma samples at enrollment and weeks 25, 49, and 73

# Laboratory Assessments

Analyte	Reported Units	LLOQ	Concentrations Associated with Ovulation Suppression	Methodology
Cabotegravir (CAB)	µg/mL	0.025 µg/mL	N/A	LC-MS/MS
Tenofovir (TFV)	ng/mL	0.31 ng/mL	N/A	LC-MS/MS
Etonogestrel (ETO)	pg/mL	20 pg/mL	≥ 90 pg/mL	LC-MS/MS
Medroxyprogesterone acetate (MPA)	pg/mL	20 pg/mL	≥ 100 pg/mL	LC-MS/MS
Norethindrone (NOR)	pg/mL	20 pg/mL	≥ 1000 pg/mL	LC-MS/MS

- CAB-LA was evaluated from enrollment through week 73
- Plasma TFV was evaluated at enrollment, and study weeks 25, 49, and 73
- Plasma hormone concentrations (ETO, MPA, and NOR) were evaluated at enrollment and study weeks 25, 49, and 73

# Pharmacokinetic Assessments

- Measurement of plasma ETO, MPA, or NOR concentrations at enrollment, and study weeks 25, 49, and 73
  - Assess percentage of participants randomized to CAB-LA or F/TDF with concentrations consistent with ovulation suppression
- CAB-LA concentration-time profiles stratified by hormonal contraceptive agent
  - Comparison of CAB trough concentrations by hormonal contraceptive agent
- Describe TFV concentrations by contraceptive type and study visit

# HPTN 084 Hormonal Contraceptive Sub-Study

- 190 participants consented to the hormonal contraceptive sub-study
  - Participants were enrolled between 24 Feb 2020-26 Oct 2020
    - Enrollment stopped when the study was unblinded post-DSMB recommendation (05 Nov 2020)
  - 20 participants did not participate beyond the enrollment visit
  - **170 participants comprise the Contraceptive Sub-Study Cohort**
    - Switches in hormonal contraceptives were common amongst participants in the sub-study
    - Switches in hormonal contraceptive regimens were partially attributed to stockouts of MPA in the region at the time
    - Participants who switched were analyzed by the contraceptive agent reported at the visit in which additional samples were collected.

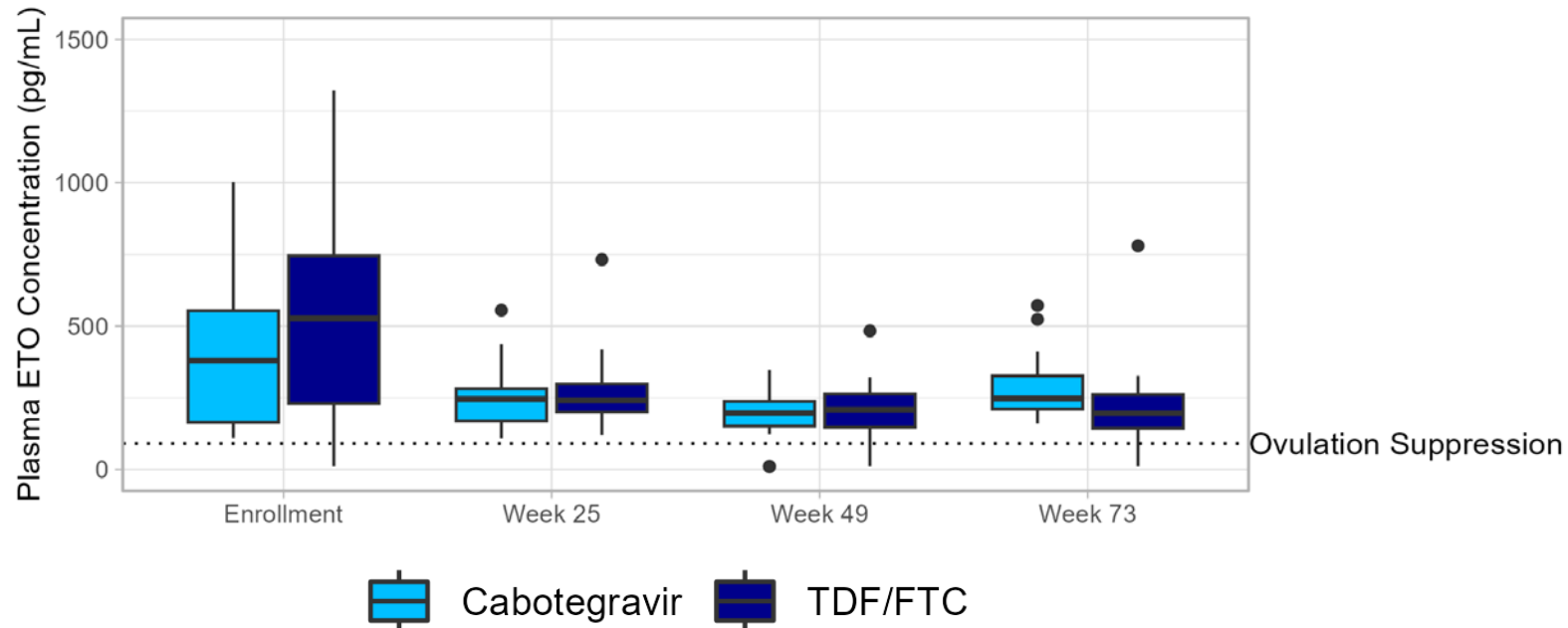


# HPTN 084 Hormonal Contraceptive Sub-Study: Participant Characteristics

	CAB-LA Arm	F/TDF Arm
Participants, n	80	90
Median Age, years (Q1, Q3)	23 (21, 26)	22 (20, 25)
Median BMI, kg/m <sup>2</sup> (Q1, Q3)	27.1 (22.8, 31.3)	28.8 (25.2, 32.7)
Hormonal Contraceptive Agent		
ETO, n (%)	28 (35%)	27 (30%)
MPA, n (%)	23 (29%)	29 (32%)
NOR, n (%)	29 (36%)	34 (38%)
Change in Hormonal Contraceptive Agent through Week 73, n (%)	19 (24%)	22 (24%)

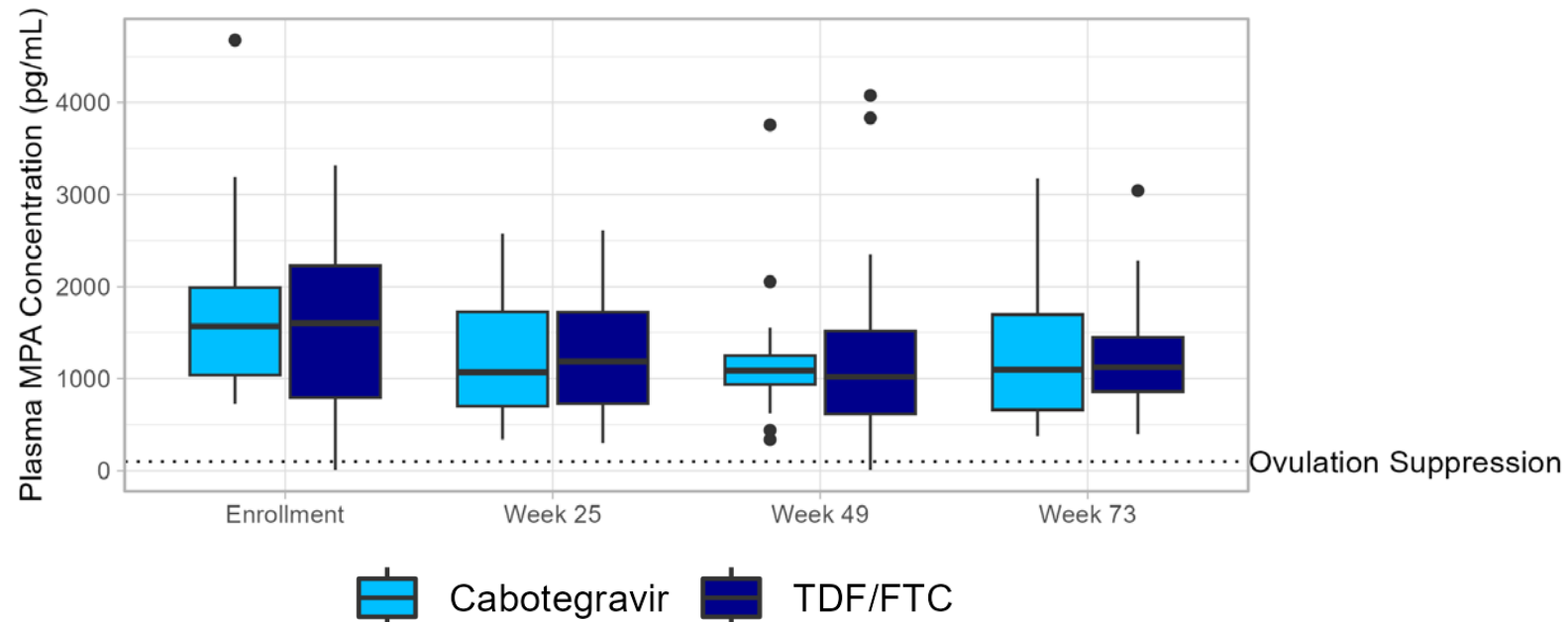
# Comparison of Geometric Mean ETO Concentrations by Study Treatment Arm

Visit	CAB-LA Arm		F/TDF Arm		p-value
	[ETO] pg/mL (95% CI)	Time from last ETO dose, days (95% CI)	[ETO] pg/mL (95% CI)	Time from last ETO dose, days (95% CI)	
Enrollment	335 (261, 430)	254 (134, 375)	390 (237, 642)	159 (38, 280)	0.577
Week 25	226 (193, 264)	421 (301, 541)	247 (210, 291)	273 (191, 356)	0.417
Week 49	158 (110, 227)	532 (415, 649)	185 (136, 253)	390 (324, 457)	0.501
Week 73	266 (218, 326)	509 (361, 656)	174 (101, 301)	473 (316, 411)	0.137



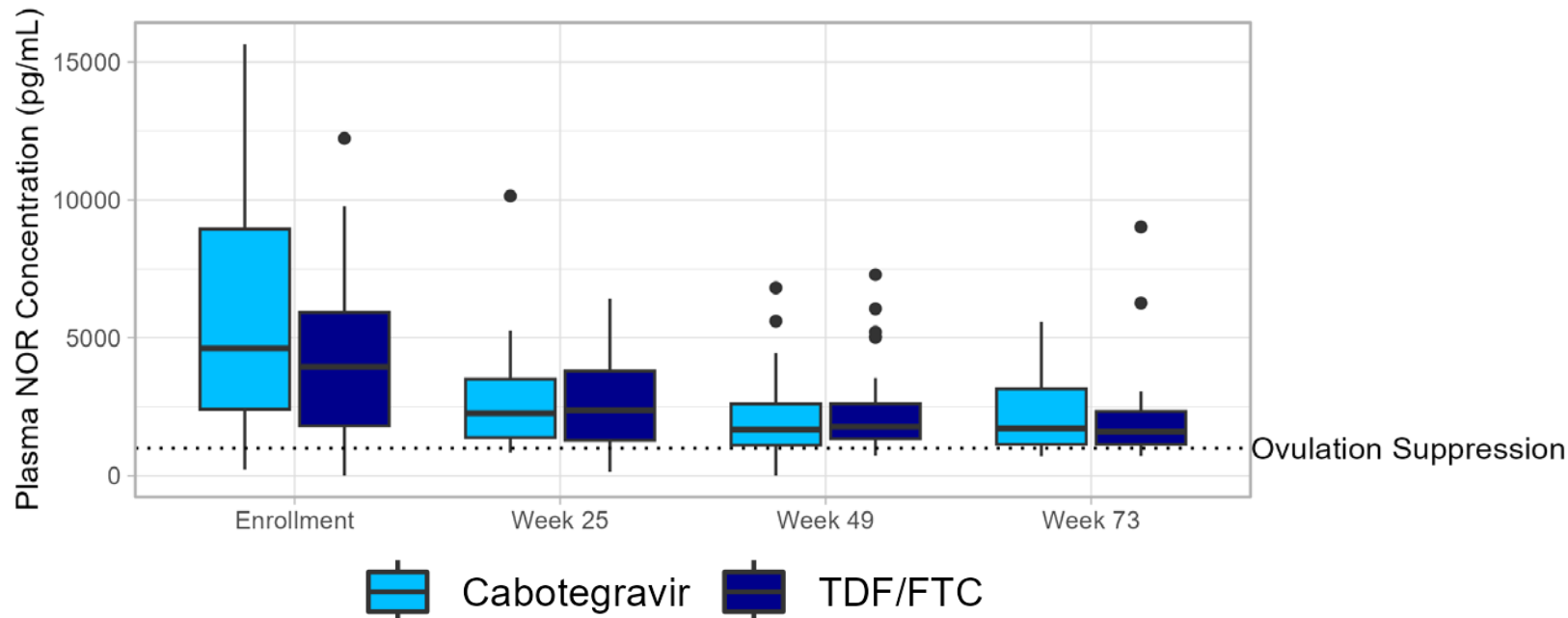
# Comparison of Geometric Mean MPA Concentrations by Study Treatment Arm

Visit	CAB-LA Arm		F/TDF Arm		p-value
	[MPA] pg/mL (95% CI)	Time from last MPA dose, days (95% CI)	[MPA] pg/mL (95% CI)	Time from last MPA dose, days (95% CI)	
Enrollment	1520 (1234, 1873)	33 (24, 42)	1210 (808, 1813)	25 (18, 32)	0.309
Week 25	1072 (859, 1340)	53 (43, 63)	1135 (935, 1377)	57 (48, 67)	0.607
Week 49	1057 (850, 1316)	54 (43, 65)	884 (603, 1296)	62 (46, 79)	0.410
Week 73	1075 (820, 1408)	64 (49, 79)	1087 (892, 1325)	65 (54, 76)	0.945



# Comparison of Geometric Mean NOR Concentrations by Study Treatment Arm

Visit	CAB-LA Arm		F/TDF Arm		p-value
	[NOR] pg/mL (95% CI)	Time from last NOR dose, days (95% CI)	[NOR] pg/mL (95% CI)	Time from last NOR dose, days (95% CI)	
Enrollment	3715 (2455, 5620)	13 (10, 16)	2810 (1819, 4343)	15 (12, 19)	0.347
Week 25	2299 (1802, 2934)	36 (30, 42)	1883 (1301, 2724)	37 (30, 43)	0.358
Week 49	1473 (901, 2407)	51 (41, 61)	1970 (1536, 2527)	56 (46, 67)	0.284
Week 73	1857 (1457, 2453)	50 (45, 56)	1442 (970, 2143)	52 (43, 61)	0.247



# Frequency of Contraceptive Measurements Below Cutoffs Associated with Ovulation Suppression

[ETO] < 90 pg/mL

	CAB-LA Arm	F/TDF Arm
Enrollment	0/28 (0%)	2/27 (7.4%)
Week 25	0/25 (0%)	0/24 (0%)
Week 49	2/25 (8%)	1/23 (4.3%)
Week 73	0/16 (0%)	1/14 (7.1%)

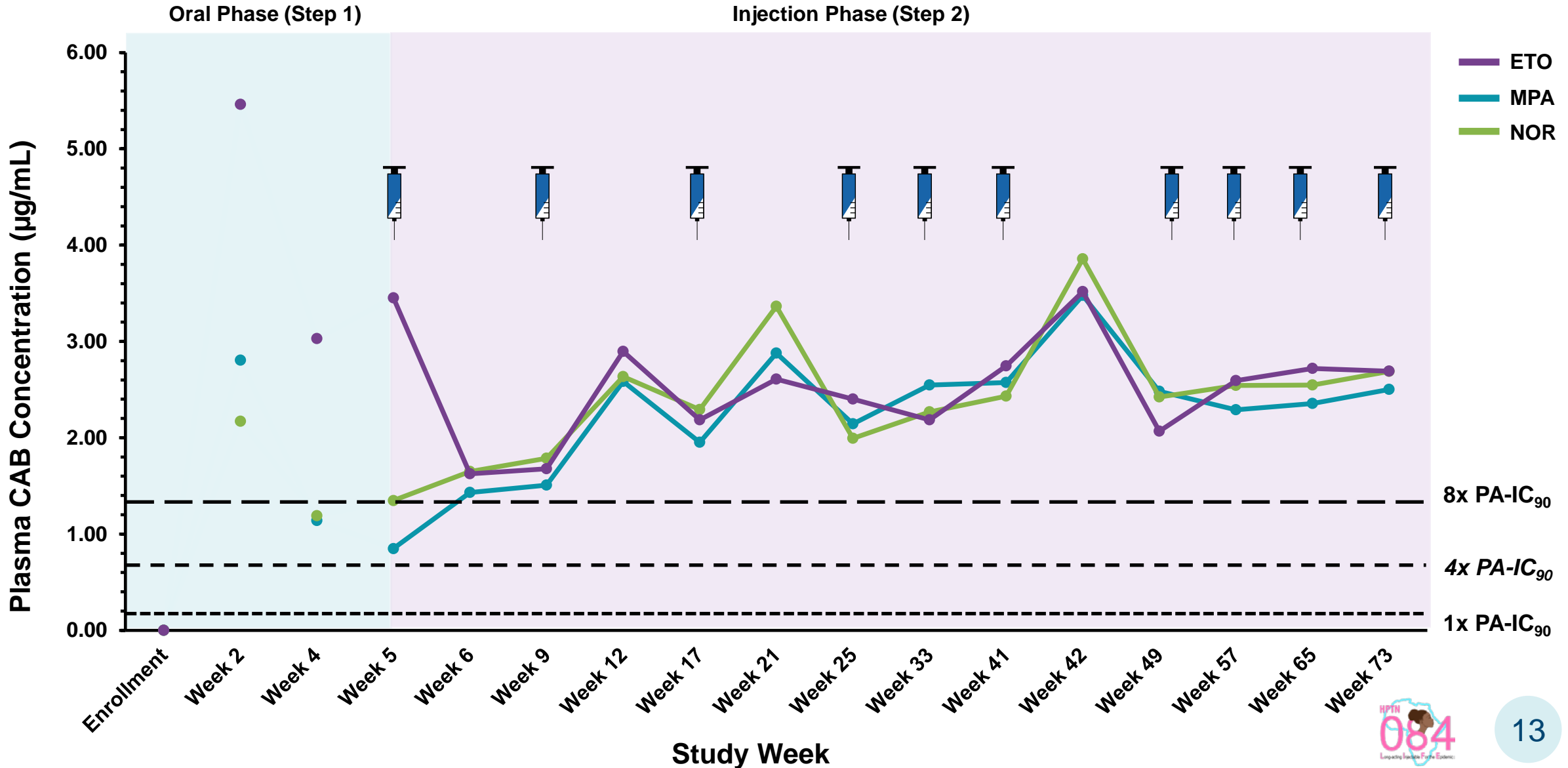
[MPA] < 100 pg/mL

	CAB-LA Arm	F/TDF Arm
Enrollment	0/23 (0%)	1/29 (3.4%)
Week 25	0/27 (0%)	0/33 (0%)
Week 49	2/22 (8%)	1/32 (3.1%)
Week 73	0/22 (0%)	0/25 (0%)

[NOR] < 1000 pg/mL

	CAB-LA Arm	F/TDF Arm
Enrollment	4/29 (13.8%)	3/34 (8.8%)
Week 25	2/26 (7.7%)	6/28 (21.4%)
Week 49	5/26 (19.2%)	3/27 (11.1%)
Week 73	4/25 (16.0%)	7/31 (22.6%)

# Comparison of Geometric Mean CAB Concentrations by Hormonal Contraceptive Type



# Plasma TFV Concentrations at Selected Study Weeks, Stratified by Hormonal Contraceptive Type

Study Visit	ETO Use	MPA Use	NOR Use
Enrollment TFV, ng/mL (95% CI)	0.16 (0.16, 0.16)	0.16 (0.16, 0.16)	0.16 (0.16, 0.16)
Week 25 TFV, ng/mL (95% CI)	0.90 (0.27, 2.98)	2.28 (0.78, 6.63)	0.62 (0.23, 1.63)
Week 49 TFV, ng/mL (95% CI)	0.51 (0.19, 1.36)	0.72 (0.27, 1.94)	1.15 (0.39, 3.38)
Week 73 TFV, ng/mL (95% CI)	1.73 (0.32, 9.45)	1.02 (0.31, 3.32)	0.87 (0.29, 2.61)

- Plasma TFV concentrations were unquantifiable at all visits for 36% (32/90) of participants in the cohort, irrespective of contraceptive agent used
- Comparisons of plasma TFV concentrations with the context of contraceptive agent used were uninformative as adherence to oral F/TDF was poor among participants evaluated in the sub-study

# Summary

- Interactions between CAB-LA and ETO, MPA, and NOR were not observed
  - CAB-LA concentration-time profiles were comparable for participants accessing ETO, MPA, or NOR
    - Geometric mean CAB-LA trough concentrations remained above the protocol-specified threshold ( $4 \times \text{PA-IC}_{90}$ ) during the injection phase of the study
  - ETO, MPA, and NOR concentrations did not differ between CAB-LA and F/TDF study arms
- Associations between F/TDF and contraceptive concentrations could not be effectively evaluated due to low adherence to F/TDF



# Acknowledgments

## Sponsor

- U.S. National Institute of Allergy and Infectious Diseases (NIAID), all components of the U.S. National Institutes of Health (NIH)

## Additional funding support

- ViiV Healthcare
- Bill & Melinda Gates Foundation
- National Institutes of Mental Health

## Pharmaceutical support

- Gilead Sciences

## HIV Prevention Trials Network

- Leadership and Operations Centre, FHI360
- Laboratory Centre (Johns Hopkins)
- Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center
- HPTN Leadership

## HPTN 084 Study team

- 20 sites in 7 countries in sub-Saharan Africa
- Community advisory boards and partners

... and our study participants!