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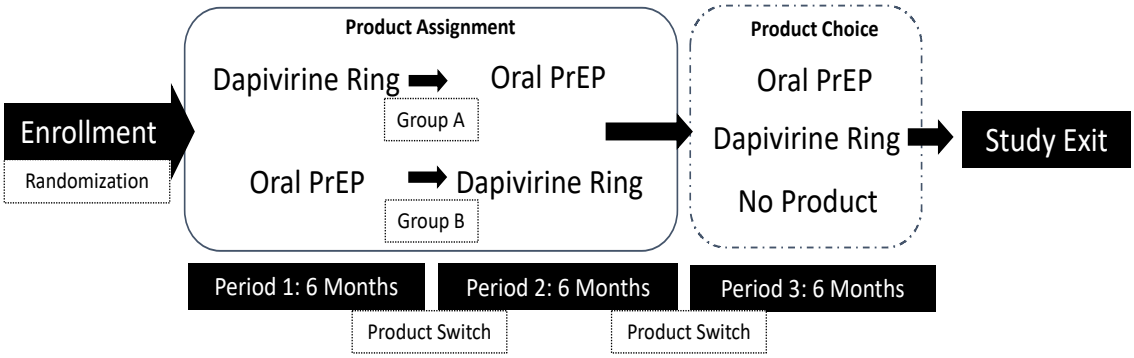
Supplement Figure 1: MTN-034 crossover design of six months of oral PrEP and six months of monthly dapivirine ring (ring)



Legend for Supplement, Figure 1: Participants in the REACH study (MTN-034) were randomized 1:1 to Sequence A (monthly ring for six months followed by oral PrEP for six months) or Sequence B (oral PrEP for six months followed by monthly ring for six months). Participants attended monthly visits for product dispensation, adherence, and safety assessments. In the final product choice period, participants were offered the ring, oral PrEP, or no product and could switch between products or discontinue products.

Supplement Figure 2: Adherence counseling in MTN 034/REACH based on semi-quantitative measures of product use

Dapivirine ring residual drug level cut-offs*	Adherence Category	Oral PrEP Cut-Offs based on intracellular TFV-DP levels**
DPV release rate ≥ 0.1071 mg/day	 **High Use**	>700 fmol/punch (4 or more doses per week)
DPV release rate 0.0321 - 0.1071 mg/day	 **Some Use**	16.6 to 699 fmol/punch (~1-3 doses per week)
DPV release <= 0.0321 mg/day	 **No use**	< 16.6 fmol/punch (no TDF-FTC detected)

Legend for Supplement, Figure 2

* The dapivirine release rate was calculated by subtracting the amount of residual dapivirine (DPV) in a returned ring from the amount of DPV in control rings from the same lot divided by the duration of time during which the participant had the ring.

**The intracellular concentrations of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) provide a cumulative measure of dosing and average adherence to oral PrEP in the prior four to six weeks. [21,22] Because steady-state levels for FTC/TDF are not reached until approximately six weeks, a lower threshold was used for counseling about FTC/TDF based on the month one DBS result: >500 fmol/punch for high and 16.6-499 fmol/punch for medium adherence.

Supplement Table 1: Baseline characteristics of REACH participants by site

Number of Participants n/%	Cape Town, South Africa N=60	Johannesburg South Africa N=67	Kampala Uganda N=60	Harare Zimbabwe N=60
Demographic characteristics				
Age				
16-17	18 (30%)	19 (28%)	20 (33%)	28 (47%)
18-19	29 (48%)	33 (49%)	28 (47%)	24 (40%)
20-21	13 (22%)	15 (22%)	12 (20%)	8 (13%)
Marital Status				
Single	60 (100%)	65 (97%)	53 (88%)	36 (60%)
Married	0 (0%)	0 (0%)	0 (0%)	10 (17%)
Cohabitating	0 (0%)	2 (3%)	7 (12%)	11 (18%)
Separated or divorced	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Highest level of education				
Primary	1 (2%)	0 (0%)	28 (47%)	4 (7%)
Secondary	55 (92%)	57 (85%)	22 (37%)	55 (93%)
College or university	4 (7%)	10 (15%)	9 (15%)	0 (0%)
Currently in school	33 (55%)	36 (54%)	9 (15%)	14 (23%)
Earns income	2 (3%)	6 (9%)	31 (52%)	14 (23%)
Partner as a source of income	0 (0%)	24 (36%)	38 (63%)	19 (32%)
Behavioral characteristics				
Ever pregnant	5 (8%)	21 (31%)	32 (53%)	41 (68%)
Alcohol consumption prior month				
Never	13 (22%)	13 (19%)	36 (60%)	41 (68%)
Monthly or less	24 (40%)	34 (51%)	6 (10%)	6 (10%)
2-4 times a month	16 (27%)	17 (25%)	13 (22%)	8 (13%)
2-3 times a week	6 (10%)	3 (4%)	3 (5%)	2 (3%)
4 or more times a week	1 (2%)	0 (0%)	2 (3%)	3 (5%)
CES-D-10				
< 10	41 (68%)	38 (58%)	30 (50%)	34 (72%)
≥ 10	19 (32%)	28 (42%)	30 (50%)	13 (28%)
Primary sexual partner				
Has a primary sex partner	52 (87%)	61 (91%)	54 (90%)	52 (87%)
Age, mean (SD)	21.3 (3.1)	22.6 (4.1)	23.6 (3.7)	24.5 (3.7)
In partnership >1 year	25 (48%)	44 (72%)	32 (59%)	32 (63%)
HIV status				
HIV positive	1 (2%)	1 (2%)	0 (0%)	1 (2%)
HIV negative	33 (63%)	47 (77%)	43 (80%)	38 (73%)
Don't know	18 (35%)	13 (21%)	11 (20%)	13 (25%)
Has other partners				
Yes, I know or think so	10 (19%)	14 (23%)	14 (26%)	13 (25%)
No	16 (31%)	24 (39%)	6 (11%)	6 (12%)
Don't know	26 (50%)	23 (38%)	34 (63%)	33 (63%)
Sexual Behavior, past 3 months				
Vaginal sex	50 (83%)	64 (96%)	49 (82%)	40 (69%)
Condom use with last sex act	29 (60%)	35 (59%)	23 (48%)	21 (55%)
Anal sex	7 (12%)	4 (6%)	6 (10%)	3 (5%)
No sex partners, median (IQR)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.5 (1.0 – 3.0)	1.0 (1.0 – 2.0)
Received goods or money for sex	7 (12%)	10 (15%)	33 (55%)	16 (27%)
Intimate partner violence, past 6 months	3 (5%)	3 (4%)	11 (18%)	19 (32%)
Perceived HIV risk in next year				
Very worried	22 (37%)	19 (28%)	6 (10%)	24 (40%)
Somewhat worried	7 (12%)	8 (12%)	0 (0%)	14 (23%)
A little worried	23 (38%)	23 (34%)	10 (17%)	12 (20%)
Not at all worried	8 (13%)	17 (25%)	44 (73%)	10 (17%)
Laboratory STI diagnosis at enrollment				
Gonorrehea	11 (18%)	5 (7%)	3 (5%)	2 (3%)
Chlamydia	26 (43%)	19 (28%)	16 (27%)	10 (17%)
Trichomonas	5 (8%)	1 (1%)	1 (2%)	6 (10%)
Syphilis seropositive	2 (3%)	0 (0%)	1 (2%)	3 (5%)
Contraceptive use at enrollment				
IUD	1 (2%)	8 (12%)	9 (15%)	9 (15%)

Implant	11 (18%)	30 (45%)	37 (62%)	33 (55%)
Oral	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injectable	48 (80%)	29 (43%)	14 (23%)	18 (30%)

Supplement Table 2: Adverse events during product use period and one month post product use periods

	Monthly dapivirine ring						**Oral PrEP**					
	During product use period			One month post product use period*			During product use period			One month post product use period*		
AEs	1st period	2nd period	Overall	1st period	2nd period	Overall	1st period	2nd period	Overall	1st period	2nd period	Overall
Total AEs	318	305	623	179	84	263	436	391	827	118	82	200
Grade 2 and higher AEs	202	240	442	81	61	142	223	233	456	98	66	164
Product holds due to AEs	0	0	0	0	0	0	0	0	0	0	0	0
grade 2 AE	34	41	75	34	13	47	27	57	84	27	19	46
grade 3AE	0	0	0	0	0	0	0	1	1	0	0	0
grade 4 AE	0	0	0	0	0	0	0	0	0	0	0	0
Total SAEs	0	0	0	0	0	0	2	1	3	0	0	0
SAEs resulting in hospitalization or death	0	0	0	0	0	0	2	1	3	0	0	0

Legend for Supplement, Table 2:

*Given the lack of a washout period between the randomized periods, the AEs reported in the first month post-product use for that period are separated out given the potential for misclassification or misattribution of AEs in the first month when participants switched from the ring to oral PrEP or oral PrEP to the ring.

Supplement Table 3: Chronology of HIV seroconversions and drug levels prior to HIV seroconversion

Seroconverter 1: Seroconversion at month 6 of oral PrEP with moderate adherence

Visit/week on study	TFV (fmol/punch)	DPV (mg) [release rate]	Adherence Category	HIV RNA
2/Enroll				HIV RNA not detected
4/Week 4	702		High	
5/Week 8	597		Some	
6/Week 12	677		Some	HIV RNA not detected
7/Week 16	608		Some	
8/Week 20	378		Some	
9/Week 24	145		Some	HIV seroconversion 21,382 c/mL HIV RNA
11/Week 28		22.6 [4.1 mg/month]	High	742,114 c/mL

Seroconverter 2: Seroconversion during choice period in which participant chose oral PrEP with low adherence

Visit/week on study	TFV-DP (fmol/punch)	DPV (mg) [release rate]	Adherence Category	HIV
2/Enroll				HIV RNA not detected
4/Week 4	850		High	
5/Week 8	358		Some	
6/Week 12	253		Some	
7/Week 16	271		Some	
8/Week 20	543		Some	
9/Week 24	288		Some	
11/Week 28		3.2	Some	
12/Week 32		4.6	High	
13/Week 36		4.7/0	High/None	HIV RNA not detected
14/Week 40		2.9	Some	
15/Week 44		4.0	High	
16/Week 48		5.4	High	HIV RNA not detected
18/Week 52	22.4		Some	
19/Week 56	65.5		Some	HIV seroconversion; 3,073,349 c/mL

Seroconverter 3: Seroconversion during first month of dapivirine ring use in choice period

Visit/week on study	TFV-DP (fmol/punch)	DPV (mg) [release rate]	Adherence Category	HIV
2/Enroll				HIV RNA not detected
4/Week 4	122		Some	
5/Week 8	30.1		Some	
6/Week 12	161		Some	
7/Week 16	96.6		Some	
8/Week 20	217		Some	
9/Week 24	275		Some	HIV RNA not detected
11/Week 28		3.4	Some	
12/Week 32		4.2	High	
13/Week 36		6.3	High	HIV RNA not detected
14/Week 40				
15/Week 44				
16/Week 48				
18/Week 52				
19/Week 56				
20/Week 60				
21/Week 64				
22/Week 68		3.2	Some	HIV seroconversion; 47,305 c/mL

Seroconverter 4: Seroconversion in month five of randomized dapivirine ring period with no use

Visit/week on study	TFV-DP (fmol/punch)	DPV mg [release rate]	Adherence Category	HIV
2/Enroll				HIV RNA not detected
4/Week 4	1607		High	
5/Week 8	1911		High	
6/Week 12	1856		High	
7/Week 16	1520		High	
8/Week 20	1702		High	
9/Week 24	1642		High	

11/Week 28		1.9	Some	
12/Week 32		0.2	None	
13/Week 36				HIV RNA not detected
14/Week 40				
15/Week 44		0.5/0	None/None	
16/Week 48		0.3	None	HIV seroconversion; 1433873 c/mL

APPENDIX

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