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ORIGINAL PAPER

Correlates of Adherence to Oral and Vaginal Pre-exposure Prophylaxis (PrEP) Among Adolescent Girls and Young Women (AGYW) Participating in the MTN-034/REACH Trial

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Abstract

We evaluated correlates of adherence to PrEP, including daily oral tenofovir disoproxil fumarate in combination emtricitabine (oral FTC/TDF) and the monthly dapivirine ring (ring)among adolescent girls and young women (AGYW) in the MTN-034/REACH study. We enrolled 247 AGYW aged 16–21 years in South Africa, Uganda and Zimbabwe (ClinicalTrials.gov: NCT03074786). Participants were randomized to the order of oral FTC/TDF or ring use for 6 months each in a crossover period, followed by a 6-month choice period. We assessed potential adherence correlates—individual, interpersonal, community, study, and product-related factors—quarterly via self-report. We measured biomarkers of adherence monthly; high adherence was defined as > 4 mg dapivirine released from returned rings or intracellular tenofovir diphosphate levels ≥ 700 fmol/punch from dried blood spots (DBS). We tested associations between correlates and objective measures of high adherence using generalized estimating equations. High adherence to oral FTC/TDF was significantly associated with having an older primary partner (p = 0.04), not having exchanged sex in the past 3 months (p = 0.02), and rating oral FTC/TDF as highly acceptable (p = 0.003). High ring adherence was significantly associated with unstable housing (p = 0.01), disclosing ring use to a male family member (p = 0.01), and noting a social benefit from study participation (p = 0.03). All associations were moderate, corresponding to about 6%–10% difference in the proportion with high adherence. In our multinational study, correlates of adherence among African AGYW differed for oral FTC/TDF and the ring, highlighting the benefit of offering multiple PrEP options.

Keywords Adherence · Heterosexual women · Pre-exposure prophylaxis (PrEP) · Africa

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Introduction

Women accounted for 63% of all new HIV infections in sub-Saharan Africa in 2021, with adolescent girls and young women (AGYW) aged 15–24 being twice as likely to be living with HIV compared to their male counterparts [1]. Several biological and social factors, including physical susceptibility, intimate partner violence and challenges in negotiating safer sex put AGYW at increased risk of HIV acquisition [2, 3]. Methods that are female-initiated have the potential to address some of these challenges.

Multinational clinical trials and implementation studies have demonstrated that daily oral tenofovir disoproxil fumarate in combination emtricitabine (FTC/TDF) and the monthly dapivirine vaginal ring (ring) are safe and efficacious HIV prevention strategies for women [4–11]. However, these biomedical prevention products require consistent and correct use to be effective. In a systematic review, HIV acquisition risk was reduced by 70% in trials and demonstration products with high oral FTC/TDF adherence, but there was no risk reduction in trials with low adherence [12]. Adherence and persistence with oral FTC/TDFhas been low among AGYW in multiple studies and demonstration projects across sub-Saharan Africa [5, 13–17], and most adherence support measures evaluated to date have not had a significant impact on adherence [13, 18]. Similarly, the ring reduced HIV risk by ~30% in two phase III trials, with open-label extensions suggesting efficacy of 50% [8, 11, 19, 20], and subgroup analyses indicating efficacy of 75% in those with high adherence [21]. However, in subgroup analysis women aged < 21 years had significantly lower adherence, and there was no HIV risk reduction observed in this younger age group in ASPIRE [19].

In recent studies among African AGYW, correlates of oral FTC/TDF sadherence have included factors at the individual level (e.g. age, education, depression, perception of HIV risk, duration of use), interpersonal level (e.g. number of sex partners, knowledge of partner HIV status, relationship power, intimate partner violence (IPV), disclosure to partners or family members), community level (e.g. oral FTC/TDF s use stigma), and structural level (e.g.travel time/distance to the clinic), though results have often been inconsistent across studies [22–25]. Among women ages 18–45 in the ASPIRE efficacy trial of the ring, correlates of adherence to the ring included age, duration of ring use, calendar time, condom use, disclosure of study participation to primary partner, worries about the ring, frequency of menstrual bleeding, having a new vs. ongoing partnership, vaginal washing, and use of long-acting contraceptive methods [26]. However, to our knowledge no published studies have reported on correlates of adherence to the ring among younger women, or compared them directly to correlates of adherence to oral FTC/TDF.

The MTN 034/REACH study recently reported high adherence for both oral FTC/TDF and the ring among AGYW aged 16–21 years [27]. This analysis sought to identify and compare correlates of objectively measured adherence to the two products. Understanding whether correlates of adherence to these two products are the same or different could inform demand generation and adherence support efforts, providing useful insights to implementation of these two biomedical products for African AGYW.

Methods

Study Design and Participants

Reversing the Epidemic in Africa with Choices in HIV Prevention (MTN-034/REACH) was a Phase IIa open-label randomized crossover trial with young women ages 16–21 enrolled at four sites in Johannesburg and Cape Town, South Africa; Kampala, Uganda; and Harare, Zimbabwe between February 2019 and September 2021 (ClinicalTrials.gov: NCT03074786) [28]. Participants were randomized (1:1) to one of two sequences: use of a vaginal ring containing 25 mg of dapivirine (ring) inserted monthly for six months followed by six months of 200 mg FTC/300 mg TDF oral tablets taken daily (oral FTC/TDF), or vice versa. After completing the one-year randomized crossover sequence (crossover period), participants were able to choose either or neither of the two products to use in the final six months of the trial (choice period). At any time during the choice period participants could elect to stop or switch products.

Measures

Adherence

Adherence was assessed monthly throughout the study by objective drug level evaluation. Oral FTC/TDF adherence was measured using intracellular concentrations of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) TFV-DP in red blood cells provides a cumulative measure of dosing and average adherence to oral FTC/TDF in the prior four to six weeks [29]. TFV-DP levels were analyzed by a liquid chromatography-tandem mass spectrometry assay at the University of Cape Town, South Africa, with levels ≥ 700 fmol/punch (consistent with at least 4 doses per week) considered "high adherence" for oral FTC/TDF. Assessment of ring adherence in the past month was based on residual dapivirine drug levels in returned rings, determined by acetone extraction and high-pressure liquid chromatography

(Farmovs, South Africa). The dapivirine release rate was calculated by subtracting the amount of residual dapivirine in returned rings from the amount of dapivirine in control rings from the same lot, divided by the length of time during which the participant had the ring. A release rate > 4.0 mg/month (consistent with 28 continuous days of use) was considered "high adherence" for the ring [8].

Potential Correlates

Data on sociodemographic characteristics (e.g., age, education, income, food security, parity, and housing stability ["have a regular place where [they] stay and store [their] things]) and HIV risk perception were collected via surveys administered by trained study staff at the study screening visit. Updates to these measures and additional measures of participant characteristics across levels of the socioecological framework were collected through audio computer-assisted self-interviews (ACASI) at baseline and quarterly throughout the study. These included measures of mental well-being and psychological development, sexual behavior, relationship characteristics, peer social support, community engagement, product use disclosure and support or opposition, product-related stigma, product acceptability, and experiences of social harms and benefits during the study. Community engagement was defined by any participation in clubs, sports teams, or other social group activities outside of home or school. The following validated scales were used: (1) the 10-item Center for Epidemiological Studies—Depression scale (CES-D-10) [30], (2) the Alcohol Use Disorders Identification Test (AUDIT-C) [31], (3) an abbreviated version Brief Self-Control Scale (BSCS) [19] and (4) the peer subscale of the Multidimensional Scale of Perceived Social Support (MSPSS) [32–35]. The interpretation of these scores in our study is reported elsewhere [36]. Data on factors unrelated to the study or products were generally collected at the start and end of each product period (i.e., months 0, 6, 12, 18) while data related to specific dimensions of product acceptability (e.g. ease of use, product characteristics) were collected in the middle of the study period only (months 3, 9, 15), and certain variables hypothesized to be most strongly related to product use were collected at all time points (e.g. sexual behavior, partnership status, disclosure, overall acceptability) (Table 1).

Statistical Analysis

In total, there were 3980 adherence observations collected from all enrolled participants (n = 247). At times participants were given two rings at a visit (when it was anticipated they

Table 1 Data collection schedule

	Screening	Enrollment	Months 3, 9, 15 (middle of each study period)	Months 6, 12 (in between study periods)	Month 18 (study exit)
Individual					
Demographics	X				
Risk perception	X		X		X
Brief self-control scale (BSCS)		X		X	
Sexual behavior		X	X	X	X
Alcohol use (AUDIT-C)		X		X	
Depression (CESD-10)		X		X	
Housing and Food Security		X		X	
Schooling and income	X			X	
Interpersonal					
Peer Social Support Scale (MSPSS)		X		X	
Partnership characteristics		X	X	X	X
Partner & non-partner violence		X		X	X
Product Use Disclosure		X	X	X	X
Community					
Community engagement		X			
Stigma & Product Awareness			X		
Study design & Product-related					
Overall acceptability		X	X	X	X
Experience of social harms or benefits			X	X	X
Crossover vs. choice period		X	X	X	X

could not return for a new ring within the 30 days or during COVID-19 clinic closure). Observations from visits where multiple rings were returned were excluded from the analysis, given the uncertainty of which ring was used for how many days and hence uncertainty in a calculated dapivirine release rate. This analysis included 3816 observations (96%) from 247 participants.

Descriptive statistics were calculated for all measures of potential adherence correlates. We used generalized estimating equations (GEE) to estimate the proportion of the sample with high adherence over time and to test the association between each correlate and high adherence. Poisson models were estimated with a log link function, unstructured working correlation structure, and robust standard errors. The model to estimate the proportion with high adherence included an interaction term between product and month of product use. Models to assess correlates of adherence each included an interaction term between the correlate measure and product, as well as an interaction term between product and study period (crossover versus choice), to estimate the effect of the correlate on adherence to each product separately while accounting for time and study design effects specifically product sequence phase. Correlate values were carried forward from each measurement point until the next measurement was taken. The only exception was for the overall acceptability measure, which was collected after use, and was therefore carried back to prior visits where no measure was available. Models also controlled randomization arm and site. Associations are presented as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). All analyses were performed using Stata 16.1.

Ethics Statement

The study was approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to implementation. Written informed consent was obtained from adult participants, and from minors who were legally able to consent as per local regulations. Written informed assent and parental/guardian consent was obtained from all other minors and their respective parents/guardians. Minors who turned 18 during the study subsequently signed the adult informed consent form.

Results

Of the 247 AGYW enrolled, 207 (84%) had adherence data from at least 10 of 12 monthly visits during the crossover periods, and 194 participants (79%) had at least five of six adherence measure during the choice period; Table 2 describes the participants at enrollment. The average age was 18 years (standard deviation 1.4), most (86%) had completed secondary education and 37% were currently in school. Nearly all had a primary partner (89%), and about a third had had more than one sex partner in the past 3 months (36%). Characteristics of the sample were generally consistent during the study (Supplemental Table 1). All participants were assumed to be assigned female at birth though we did not ask their gender identity [37].

Figure 1 depicts the estimated probability of high adherence over time for each of the two products during each period. Overall, there was no statistically significant difference in the probability of high adherence by product ($p = 0.18$). On average, the probability of high monthly adherence was 0.60 for the ring and 0.57 for oral FTC/TDF during the crossover periods, $p = 0.30$. The probability of high monthly adherence dropped for both products during the choice period; the average probability of high adherence was 0.54 for those who chose the ring (RR 0.90, 95% CI 0.82, 0.99; $p = 0.03$) and 0.46 for those who chose oral FTC/TDF (RR 0.82, 95% CI 0.70, 0.95; $p < 0.01$).

Different factors were associated with high adherence for each product (Table 3). For oral FTC/TDF the probability of high adherence during the month was associated with having an older primary partner (RR 1.18, 95% CI 1.01, 1.37; $p = 0.04$) and inversely associated with having exchanged goods or money for sex in the past 6 months (RR 0.87, 95% CI: 0.77, 0.98; $p = 0.02$). Those who rated oral TDF/FTC as highly acceptable were more likely to have high adherence (RR 1.21, 95% CI 1.08, 1.35; $p = 0.003$). There were non statistically significant trends between those who perceived stigma in the community about using oral FTC/TDF (RR 0.88, 95% CI: 0.76, 1.00; $p = 0.07$) and those who had any engagement in the community (RR 0.87, 95% CI: 0.74, 1.02; $p = 0.09$) and high monthly adherence.

In contrast, participants were more likely to have high monthly adherence with the dapivirine ring if they were unstably housed; RR 1.17; 95% CI: 1.04, 1.31; $p = 0.008$), had disclosed ring use to a male family member (RR 1.11, 95% CI: 1.03, 1.24; $p = 0.01$), and had noted a social benefit from participating in the study (RR 1.19, 95% CI 1.01, 1.39; $p = 0.03$). Risk ratios correspond to differences in high adherence of about 6–10%.

In a subgroup analysis among younger participants (aged 16–17), different measures were found to be associated with oral FTC/TDF adherence (Table 4). Younger participants who had been with their partner for less than 6 months (RR 1.45, 95% CI: 1.05, 2.00; $p = 0.03$), who were living with their partner (RR 1.29, 95% CI: 1.07, 1.56; $p = 0.01$), or who were unstably housed (RR 1.36, 95% CI 1.10, 1.68; $p < 0.01$) were more likely to have high adherence using oral FTC/TDF, and these associations were significantly different than those for ring adherence (p-values ≤ 0.01). In addition, those who were worried about HIV were somewhat more likely to have high adherence with oral FTC/TDF (RR 1.25,

Table 2 Description of participants at enrollment in MTN-034/REACH Crossover Study

	N (%)
Total	247 (100)
Age < 18 years	85 (34)
Secondary education completed	212 (86)
Currently in school	92 (37)
Lives with parent(s)	156 (63)
Earns own income	53 (22)
Food insecure	62 (25)
Unstably housed	45 (18)
Self-control scale score—*mean, median (range)*	26, 27 (13–35)
Parous at enrollment	99 (40)
Hazardous drinking (AUDIT-C)	97 (39)
Depression indicated (CESD-10)	91 (37)
Risk perception, somewhat/very worried about HIV	100 (41)
Sexual behavior	
Sexually active in past 3 months	203 (83)
Condom use at last sex	112 (55)
Vaginal sex at least weekly in past 3 months	107 (43)
More than 1 sex partner in past 3 months	90 (36)
Transactional sex in past 6 months	66 (27)
Interpersonal	
Peer social support scale score—*mean, median (range)*	14, 15 (4–20)
Has a primary partner	219 (89)
Primary partner > 4 years older	106 (43)
Newer partnership (< 6 months)	58 (24)
Primary partner has/may have other partners[a]	167 (68)
Primary partner provides financial support	136 (55)
Lives with partner	22 (10)
Any physical partner violence past 6 months	36 (15)
Any verbal partner violence past 6 months	75 (30)
Any sexual partner violence past 6 months	27 (11)
Any non-partner sexual violence past 6 months	17 (7)
Community	
Any community engagement[b]	131 (53)
Study design & product-related	
Arm	
A: Ring → oral FTC/TDF	124 (50)
B: oral FTC/TDF → Ring	123 (50)
Location	
Cape Town, South Africa	60 (24)
Johannesburg, South Africa	67 (27)
Kampala, Uganda	60 (24)
Harare, Zimbabwe	60 (24)

[a]Includes don't know if partner has other partners

[b]participation in clubs, sports teams, or other social group activities outside of home/school

95% CI 0.98, 1.58; p = 0.07) and less likely with the ring (RR 0.84, 95% CI 0.63, 1.13; p = 0.25; p-value for interaction = 0.02). Although not statistically significant, younger women who disclosed oral FTC/TDF use to their partner were more likely to have high adherence (RR 1.31, 95% CI 1.00, 1.41; p = 0.05), and those with higher peer social support scores (RR 0.66, 95% CI 0.39, 1.11; p = 0.12) and higher self-control scores (RR 0.52, 95% CI: 0.26, 1.05; p = 0.07) were less likely to have high adherence using oral FTC/TDF. Only disclosure to a male family member was

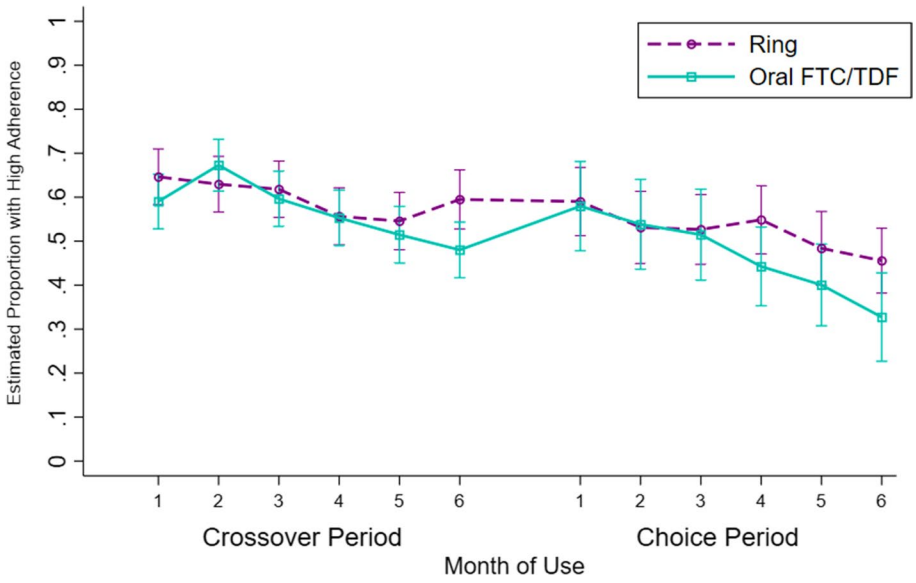

Fig. 1 The estimated proportion of participants with high adherence per month, by product and study period

significantly associated with high ring adherence among younger participants (RR 1.34, 95% CI 1.16, 1.55; $p < 0.01$).

Discussion

In a crossover study where participants used oral FTC/TDF and the ring for six months each before choosing a product to use for another six months, roughly half of participants were able to use the products consistently in any given month. Different factors were associated with adherence for each product, suggesting that offering a range of options may help AGYW to choose the product that best suits their circumstances. However, there were no strong associations between characteristics or experiences of AGYW and high monthly adherence; all effect sizes were modest. Notably, for both products, the proportion with high adherence decreased modestly in the choice period, but still remained higher than previous studies of AGYW in sub-Saharan Africa [13–17]. Therefore, adherence may remain a challenge regardless of the product chosen or the fact that participants were able to try products before making a choice.

Among participants in this study, there were inconsistent associations between oral FTC/TDF adherence and factors associated with higher risk of HIV acquisition. Epidemiological studies have demonstrated that age-disparate relationships increase the risk of HIV acquisition especially for AGYW [38, 39], and we found that having an older primary partner was associated with high adherence to oral FTC/TDF. However, participants who had exchanged sex in the past 6 months were less likely to have high oral FTC/TDF adherence, and there was no association between having more than one sex partner and high oral FTC/TDF adherence. Further, none of these factors were associated with ring adherence. The robust adherence support program may have helped participants recognize HIV risk within their primary or only partnerships in addition to risk from additional partners [22]. However, women who exchange sex often face stressful life circumstances such as poverty, discrimination, and sexual violence, all of which may impede oral FTC/TDF use [40, 41] despite recognition of its protective benefits.

PrEP-related stigma has been a key barrier to optimal PrEP adherence for AGYW in SSA, where several studies have reported that participants who anticipated/experienced stigma were reluctant to disclose oral FTC/TDF use and reported adherence challenges [25, 42, 43]. Similarly in the REACH study, those who perceived stigma in the community about using oral FTC/TDF were less likely to have high monthly adherence. Though this finding was not statistically significant, it still points to the need to deliver oral FTC/TDF in AGYW friendly spaces. In addition, we have previously reported that very few participants disclosed ring use to male family members [44] (other than male partners), both because they found it unnecessary and because they feared stigmatizing reactions. Yet in the current analysis, those who had disclosed ring use to male family members were more likely to adhere. Those who chose to disclose may have anticipated less stigma, which may in turn have facilitated ring use.

Participants rating oral FTC/TDF as highly acceptable was a strong correlate of high adherence. This further points to the need to consider AGYW preferences and choices when providing HIV prevention services. A recent study among women aged 18–24 years who had been on oral FTC/TDF for two years demonstrated that only a third of women would prefer oral FTC/TDF if other methods of HIV prevention such as injectables, rings or implants were available [45]. This supports the need for

Table 3 Correlates of high adherence, for oral FTC/TDF and the Dapivirine vaginal ring (N = 247; obs = 3816)

Measures	Oral FTC/TDF			Dapivirine ring			
	RR[a]	95% CI	p-value	RR[a]	95% CI	p-value	p-value interaction
Individual							
Age < 18 years	0.93	(0.79, 1.10)	0.38	0.99	(0.86, 1.14)	0.93	0.48
Secondary education completed	1.10	(0.82, 1.50)	0.52	0.91	(0.73, 1.14)	0.40	0.14
In school	1.14	(1.00, 1.30)	0.05	1.06	(0.93, 1.20)	0.37	0.38
Earns own income	1.11	(0.98, 1.26)	0.10	1.02	(0.90, 1.15)	0.80	0.28
Lives with parent(s)	1.02	(0.90, 1.16)	0.78	0.94	(0.84, 1.06)	0.31	0.36
Food insecure	0.96	(0.85, 1.10)	0.57	1.01	(0.91, 1.13)	0.85	0.56
Unstably housed	0.96	(0.81, 1.13)	0.61	**1.17**	**(1.04, 1.31)**	**0.01**	**0.06***
Self-control scale score (range 13–35)	0.79	(0.50, 1.25)	0.31	0.99	(0.98, 1.00)	0.42	0.42
Parous at enrollment	0.96	(0.80, 1.15)	0.65	1.06	(0.91, 1.24)	0.43	0.29
Hazardous drinking (AUDIT-C)	1.00	(0.88, 1.13)	0.99	1.00	(0.88, 1.13)	0.96	0.96
Depression indicated (CESD-10)	0.96	(0.85, 1.08)	0.46	1.06	(0.97, 1.17)	0.21	0.14
Risk perception—worried about HIV	1.08	(0.91, 1.28)	0.36	0.97	(0.84, 1.12)	0.64	0.24
Sexual behavior							
Vaginal sex at least weekly in past 3 months	1.04	(0.95, 1.14)	0.39	0.96	(0.87, 1.04)	0.32	0.16
More than 1 sex partner in past 3 months	0.95	(0.85, 1.06)	0.37	1.01	(0.92, 1.10)	0.81	0.36
Condom use at last sex	0.98	(0.88, 1.09)	0.73	0.95	(0.86, 1.05)	0.31	0.66
Exchanged sex in past 6 months	**0.87**	**(0.77, 0.98)**	**0.02**	1.10	(0.98, 1.23)	0.12	**0.01***
Interpersonal							
Peer social support scale score (range 4–20)	0.95	(0.73, 1.23)	0.70	1.00	(0.99, 1.02)	0.70	0.97
Has a primary partner	1.06	(0.94, 1.21)	0.35	0.95	(0.84, 1.08)	0.45	0.21
Primary partner > 4 years older	**1.18**	**(1.01, 1.37)**	**0.04**	0.99	(0.87, 1.13)	0.87	**0.07***
Newer partnership (< 6 months)	1.03	(0.91, 1.18)	0.63	1.03	(0.90, 1.17)	0.69	0.96
Primary partner has/may have other Partners[b]	0.99	(0.88, 1.10)	0.80	0.97	(0.86, 1.10)	0.68	0.90
Primary partner provides financial Support	1.04	(0.89, 1.22)	0.62	1.01	(0.89, 1.15)	0.85	0.76
Lives with partner	0.91	(0.75, 1.10)	0.32	1.09	(0.93, 1.28)	0.30	0.15
Any physical partner violence past 6 mos	0.96	(0.85, 1.08)	0.48	1.10	(0.98, 1.22)	0.09	**0.09***
Any verbal partner violence past 6 mos	1.00	(0.89, 1.12)	0.94	1.02	(0.90, 1.15)	0.81	0.81
Any sexual partner violence past 6 mos	0.93	(0.78, 1.11)	0.45	0.93	(0.79, 1.11)	0.43	0.99
Any non-partner sexual violence past 6 mos	0.86	(0.69, 1.08)	0.21	0.91	(0.76, 1.10)	0.34	0.72
Disclosure of product use, to							
Primary partner	1.02	(0.89, 1.17)	0.78	0.96	(0.83, 1.11)	0.57	0.14
Female family member	1.10	(0.89, 1.35)	0.37	0.92	(0.81, 1.05)	0.22	0.14
Male family member	1.08	(0.96, 1.22)	0.21	**1.11**	**(1.01, 1.22)**	**0.03**	0.73
Friends	0.94	(0.83, 1.07)	0.34	1.02	(0.91, 1.15)	0.72	0.34
Community							
Community engagement, at all vs never	0.87	(0.74, 1.02)	0.09	0.94	(0.82, 1.07)	0.33	0.42
Believe community not aware of product	1.11	(0.91, 1.35)	0.29	1.07	(0.92, 1.24)	0.39	0.77
Perceive stigma in community about product	0.88	(0.76, 1.00)	0.07	1.00	(0.89, 1.12)	0.99	0.16
Study design & product related							
Rated product highly acceptable	**1.21**	**(1.08, 1.35)**	**< 0.01**	1.01	(0.91, 1.12)	0.89	**0.02***
Experienced social harm	0.93	(0.65, 1.33)	0.70	0.87	(0.58, 1.30)	0.49	0.79
Experienced social benefit	1.11	(0.93, 1.33)	0.25	**1.19**	**(1.01, 1.39)**	**0.03**	0.51
Crossover period (vs choice period)	**1.23**	**(1.06, 1.42)**	**0.01**	**1.11**	**(1.01, 1.22)**	**0.03**	0.26

*Interaction p-value < 0.10 are indicates in bold

[a]All models controlled for randomization arm and study site and included an interaction term between product and study period

[b]Response of yes or don't know compared to no

Table 4 Correlates of adherence for AGYW ages 16–17 years (N = 85; observations = 1249)

Measures	Oral FTC/TDF			Dapivirine ring			
	RR[a]	95% CI	p-value	RR[a]	95% CI	p-value	p-value inter-action
Individual							
Secondary education completed	0.95	(0.72, 1.25)	0.72	0.92	(0.68, 1.23)	0.56	0.79
Currently in school	1.03	(0.79, 1.34)	0.81	1.05	(0.83, 1.33)	0.70	0.93
Earns own income	1.18	(0.93, 1.50)	0.16	1.25	(0.92, 1.70)	0.15	0.76
Lives with parent(s)	0.92	(0.74, 1.15)	0.48	0.92	(0.71, 1.18)	0.50	0.97
Food insecure	1.07	(0.85, 1.34)	0.55	0.83	(0.66, 1.04)	0.10	0.11
Unstably housed	**1.36**	**(1.10, 1.68)**	**< 0.01**	0.99	(0.83, 1.19)	0.95	**< 0.01***
Self-control scale score (range 13–35)	0.52	(0.26, 1.05)	0.07	0.98	(0.96, 1.00)	0.05	0.12
Parous at enrollment	0.86	(0.61, 1.22)	0.40	1.00	(0.71, 1.43)	0.97	0.41
Hazardous drinking (AUDIT-C)	0.86	(0.68, 1.08)	0.20	0.98	(0.79, 1.21)	0.84	0.43
Depression indicated (CESD-10)	0.85	(0.67, 1.08)	0.18	1.07	(0.87, 1.31)	0.54	0.08
Risk perception—worried about HIV	1.25	(0.98, 1.58)	0.07	0.84	(0.63, 1.13)	0.25	**0.02***
Sexual behavior							
Vaginal sex at least weekly in past 3 months	0.91	(0.66, 1.23)	0.54	0.97	(0.76, 1.23)	0.79	0.70
More than 1 sex partner in past 3 months	0.97	(0.66, 1.43)	0.88	1.11	(0.86, 1.42)	0.26	0.50
Condom use at last sex	0.92	(0.71, 1.19)	0.54	0.86	(0.67, 1.11)	0.24	0.68
Exchanged sex in past 6 months	0.83	(0.66, 1.05)	0.12	1.02	(0.83, 1.26)	0.77	0.22
Interpersonal							
Peer social support scale score (range 4–20)	0.66	(0.39, 1.11)	0.12	0.99	(0.97, 1.02)	0.63	0.19
Has a primary partner	0.99	(0.79, 1.23)	0.90	1.04	(0.79, 1.37)	0.78	0.74
Primary partner > 4 years older	1.06	(0.82, 1.38)	0.64	0.92	(0.70, 1.20)	0.54	0.35
Newer partnership (< 6 months)	**1.45**	**(1.05, 2.00)**	**0.03**	0.87	(0.71, 1.07)	0.19	**0.01***
Primary partner has/may have other Partners[b]	1.05	(0.81, 1.37)	0.71	1.08	(0.90, 1.29)	0.41	0.89
Primary partner provides financial support	1.16	(0.76, 1.77)	0.49	1.01	(0.83, 1.24)	0.88	0.57
Lives with partner	**1.29**	**(1.07, 1.56)**	**0.01**	0.86	(0.64, 1.16)	0.32	**0.01***
Any physical partner violence past 6 mos	0.87	(0.70, 1.09)	0.23	0.96	(0.77, 1.21)	0.75	0.55
Any verbal partner violence past 6 mos	0.91	(0.72, 1.14)	0.39	0.89	(0.71, 1.12)	0.33	0.93
Any sexual partner violence past 6 mos	0.95	(0.70, 1.29)	0.75	0.84	(0.60, 1.17)	0.58	0.59
Any non-partner sexual violence past 6 mos	0.95	(0.71, 1.28)	0.73	0.79	(0.57, 1.10)	0.16	0.42
Disclosure of product use, to							
Primary partner	1.31	(1.00, 1.71)	0.05	1.13	(0.89, 1.43)	0.33	0.62
Female family member	1.32	(0.95, 1.82)	0.10	1.15	(0.94, 1.41)	0.17	0.44
Male family member	1.13	(0.92, 1.38)	0.24	**1.34**	**(1.16, 1.55)**	**< 0.01**	0.12
Friends	0.96	(0.76, 1.21)	0.71	1.02	(0.83, 1.25)	0.85	0.68
Community							
Community engagement, at all vs never	1.00	(0.79, 1.27)	0.98	1.07	(0.83, 1.37)	0.60	0.68
Believe community not aware of product	1.17	(0.90, 1.53)	0.23	1.14	(0.90, 1.44)	0.29	0.83
Perceive stigma in community about product	0.91	(0.72, 1.16)	0.45	0.95	(0.75, 1.20)	0.68	0.80
Study design & product related							
Rated product highly acceptable	1.11	(0.94, 1.32)	0.22	1.12	(0.93, 1.35)	0.23	0.96
Experienced social harm	0.75	(0.49, 1.16)	0.20	0.79	(0.42, 1.46)	0.45	0.93
Experienced social benefit	1.13	(0.85, 1.51)	0.39	0.94	(0.69, 1.26)	0.67	0.25
Crossover period (vs choice period)	1.37	(1.01, 1.88)	0.05	1.14	(0.93, 1.40)	0.22	0.40

*Interaction p-value < 0.10 are indicated in bold

[a]All GEE models controlled for randomization arm and study site and included an interaction term between product and study period

[b]Response of yes or don't know compared to no

providing multiple options of HIV prevention to cater for individual preferences that could translate to higher uptake and adherence.

Longer acting products that have recently been approved or are in development that could be inserted or given in the clinic such as the ring, long-acting cabotegravir (CAB-LA) and semi-annual lenacapivir could appeal to populations of AGYW who have product storage concerns, which may explain why unstable housing was a significant predictor of ring adherence in our study. For women who do not have a safe space or access to running water, etc. may be less likely to take it out during the month for lack of a way to store or clean it [46]. However, other structural factors such as distance to the clinic have been reported to influence oral FTC/TDF adherence and may be more important for products that are not stored at home [47]. A differentiated model of oral FTC/TDF delivery that provides products closer to where AGYW live and work such as through retail pharmacies could overcome this barrier [48].

In sub-Saharan Africa studies have shown partners have a strong influence on adult women's oral FTC/TDF and ring adherence [49, 50], and in a recent South African study among AYGW, disclosure to parents was strongly associated with oral FTC/TDF adherence [51]. Surprisingly, these findings were not replicated in our study. However, in sub-group analysis we found that younger participants (aged 16–17) who disclosed oral FTC/TDF use to their male partner or female family members were marginally more likely to have high oral FTC/TDF adherence. The adherence support provided through the study may have helped participants use both products without disclosure and have provided an alternative source of social support. Disclosure to partners and parents could lead to negative consequences such as violence and discrimination, and therefore AGYW should be counseled and supported through the process of disclosure should they choose to disclose. The recent additions of CAB-LA to the HIV prevention toolbox, and other products in the pipeline such as monthly pills, 6-monthly injections and implants may enhance discreet use and could be preferable for those who may not be ready to disclose.

Although younger participants (ages 16–17 years) had similar adherence as older participants (ages 18–21), correlates of adherence differed somewhat for younger participants. In particular, product-related factors such as oral FTC/TDF acceptability and social benefits of ring use were not correlated with adherence among younger participants, but newer primary partnership and cohabitation with their male partner were associated with higher adherence. Young women may retain more independence in newer relationships and may be more likely to have disclosed product use to partners whom they live with, both of which could facilitate adherence. It is surprising that unstable housing was correlated with higher oral FTC/TDF adherence in this subgroup and was not correlated with higher ring adherence as in the overall sample.

Our study had several strengths. First, we used an innovative study design that allowed the participants to use both the oral FTC/TDF and the ring in a crossover fashion before making a choice. Additionally, the study population was from four sites in three African countries, with a third of participants being aged 16 and 17 years old which provides important adherence insights from the younger population. Data were collected at several time points longitudinally over an 18-month period and adherence was measured objectively for both oral FTC/TDF and the ring in the same setting. There are also two key limitations to note. First, the high adherence in our study could be explained by the comprehensive adherence support interventions during the implementation of the trial, which could have diluted the effect of some correlates [52]. Moreover, the adherence support provided in this study was intended to encourage high adherence to achieve the study objective of measuring safety. In addition, this being a purposively selected sample that agreed to monthly visits and extensive procedures (and so may have been highly motivated) coupled with a narrow age group of 16–21 years may limit the generalizability of our findings.

In conclusion, adherence to oral FTC/TDF and the ring was high during the crossover periods and declined slightly during the choice period, despite participants being able to choose what they preferred after 12 months. Therefore, maintaining a high level of use over an extended period of time may remain a challenge regardless of the product chosen. Notably, the factors associated with high oral FTC/TDF (e.g. having an older partner, rating oral FTC/TDF as highly acceptable) differed from correlates with ring adherence (e.g. unstably housed, disclosure to male partners and social benefits), exemplifying the need to have different HIV prevention product options.

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Data Availability The data that support the findings of this study are available for researchers who provide a methodologically sound proposal in accordance with policies of the Microbicide Trials Network (MTN).

Declarations

Conflict of interests The authors have no competing interests to declare that are relevant to the content of this article.

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