Adherence, safety, and choice of the monthly dapivirine vaginal ring or oral emtricitabine plus tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis among African adolescent girls and young women: a randomised, open-label, crossover trial

Gonasagrie Nair, Connie Celum*, Daniel Szydlo, Elizabeth R Brown, Carolyne A Akello, Rita Nakalega, Pippa Macdonald, Gakiema Milan, Thesla Palanee-Phillips, Krishnaveni Reddy, Eunice Tahuringana, Felix Muhlanga, Clemensia Nakabiito, Linda-Gail Bekker, Bekezela Siziba, Sharon L Hillier, Jared M Baeten, Morgan Garcia, Sherri Johnson, Tara McClure, Lisa Levy, Edward Livant, Cindy Jacobson, Lydia Soto-Torres, Ariane van der Straten, Sybil Hosek, James F Rooney, John Steytler, Katherine Bunge, Urvi Parikh, Craig Hendrix, Peter Anderson, Kenneth Ngure, on behalf of the REACH Protocol Team*

Summary

Background Half of new HIV acquisitions in Africa occur in adolescent girls and young women. Pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate plus emtricitabine or the monthly dapivirine vaginal ring is efficacious but has lower adherence and effectiveness among adolescent girls and young women. We aimed to assess product adherence, safety, and choice of oral PrEP compared with the dapivirine ring among African adolescent girls and young women.

Methods MTN-034/REACH was a randomised, open-label, phase 2a crossover trial among HIV-seronegative, non-pregnant adolescent girls and young women aged 16–21 years at four clinical research sites in South Africa, Uganda, and Zimbabwe. Participants were randomly assigned (1:1) to either the dapivirine ring or daily oral PrEP (200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) for 6 months, then switched to the other product option for 6 months, followed by a third 6-month period in which participants were given a choice of oral PrEP, the dapivirine ring, or neither. Fixed block randomisation was used, stratified by site. The primary adherence endpoint was use of each product during the randomised periods, with high use defined as tenofovir-diphosphate concentrations greater than or equal to 700 fmol/punch (associated with taking an average of four or more tablets per week in the previous month) and greater than or equal to 4 mg dapivirine released from the returned ring (continuous use for 28 days in the previous month) based on residual drug concentrations. The primary safety endpoint was grade 2 or higher adverse events during each randomised period of 24 weeks of ring and oral PrEP. This trial is registered at ClinicalTrials.gov, NCT03593655.

Findings From Feb 6, 2019 to Sept 9, 2021, 396 adolescent girls and young women were screened, 247 of whom were enrolled and randomly assigned (6 months of the ring followed by 6 months of oral PrEP n=124; 6 months of oral PrEP followed by 6 months of the ring n=123). Median age was 18 years (IQR 17–19). 54 grade 2 or higher product-related adverse events were reported during oral PrEP and five during dapivirine ring use, with no product-related serious adverse events. High adherence was observed in 753 (57%) of the 1316 oral PrEP visits and 806 (57%) of the 1407 dapivirine ring visits. Four women acquired HIV during follow-up.

Interpretation Adherence was moderately high and similar between oral PrEP and the dapivirine ring with favourable safety and tolerability. Oral PrEP and the dapivirine ring are effective, safe, and well tolerated HIV prevention options for adolescent girls and young women who would benefit from a choice of PrEP formulations to meet their needs and preferences.

Funding National Institutes of Health.

Lancet HIV 2023; 10: e779–89

Published Online October 25, 2023 https://doi.org/10.1016/S2352-3018(23)00227-8

See Comment e757

*Joint primary authors

Stellenbosch University, Centre for Medical Ethics and Law, Stellenbosch, South Africa (G Nair MBChB); **Department of Global Health, Department of Medicine, and Department of Epidemiology, University of Washington, Seattle, WA, USA** (Prof C Celum MD, Prof J M Baeten MD); **Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (D Szydlo MS, Prof E R Brown PhD); **Makerere University—Johns Hopkins University Research Collaboration, Kampala, Uganda** (C A Akello MBChB, R Nakalega MBChB, C Nakabiito MBChB); **Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa** (P MacDonald MBChB, G Milan BA, Prof L-G Bekker MBChB); **Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (T Palanee-Phillips PhD, K Reddy MS); **Department of Epidemiology, University of Washington, Seattle, WA, USA** (T Palanee-Phillips); **University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe** (E Tahuringana MBChB,

Introduction

Adolescent girls and young women in sub-Saharan Africa remain disproportionately impacted by HIV in the context of declining population HIV incidence.[1] HIV incidence among African adolescent girls and young women in recent HIV prevention efficacy trials has remained at 4% per year, despite the provision of frequent counselling and other prevention services.[2–5]

Multiple placebo-controlled phase 3 trials of oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate alone or coformulated with emtricitabine have shown very high efficacy among men and women.[6–10]

F Muhlanga MBChB, B Siziba MBChB); **Magee Womens Research Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA** (Prof S L Hillier PhD, E Livant MPH, C Jacobson PharmD, K Bunge MD, U Parikh PhD); **Gilead Sciences, Foster City, CA, USA** (Prof J M Baeten, J F Rooney MD); **FHI 360, Durham, NC, USA** (M Garcia MPH, S Johnson MPH, T McClure MPH, L Levy MPH); **National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA** (L Soto-Torres MD); **ASTRA Consulting, Kensington, CA, USA** (A van der Straten PhD); **Center for AIDS Prevention Studies, University of California San Francisco, San Francisco, CA, USA** (A van der Straten); **Department of Medicine, University of Illinois, Chicago, IL, USA** (Prof S Hosek PhD); **International Partnership for Microbicides, Johannesburg, South Africa** (J Steytler MBChB); **Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA** (U Parikh); **Department of Medicine, Johns Hopkins University, Baltimore, MD, USA** (Prof C Hendrix MD); **Department of Pharmacology, University of Colorado, Denver, CO, USA** (Prof P Anderson PharmD); **Jomo Kenyatta University of Agriculture and Technology, School of Public Health, Nairobi, Kenya** (Prof K Ngure PhD)

Correspondence to: Prof Connie Celum, Department of Global Health, Department of Medicine, and Department of Epidemiology, University of Washington, Seattle, WA 98104, USA
ccelum@uw.edu

Research in context

Evidence before this study

Daily oral tenofovir disoproxil fumarate plus emtricitabine tablets and the monthly dapivirine vaginal ring are safe and effective as HIV pre-exposure prophylaxis (PrEP) among women and recommended by WHO as part of combination HIV prevention. We searched PubMed and Embase for studies published in English on the safety, adherence, and preferences related to oral tenofovir disoproxil fumarate plus emtricitabine and the dapivirine vaginal ring between Jan 1, 2018, and Sept 31, 2022 with the terms "HIV" and "Africa South of the Sahara" and ("safety" OR "adherence" OR "preferences" OR "choice"). Findings from randomised clinical trials and demonstration projects have shown that African adolescent girls and young women younger than 21 years have lower product use, adherence, and persistence through to 6 months with oral tenofovir disoproxil fumarate plus emtricitabine than women aged 21 years and older. Randomised placebo-controlled trials and open-label extension studies of the dapivirine ring in Africa have shown that women younger than 21 years had lower use of the ring, which was associated with a lack of effectiveness.

Added value of this study

Given the need for more consistent and higher effective use of HIV prevention products by young African women who continue to have high rates of HIV acquisition, this randomised, open-label crossover study of oral PrEP and the dapivirine ring followed by a product choice period provides a direct comparison of adherence and safety of both products. Study participants had monthly visits and were provided flexible adherence support and drug concentration feedback in adherence counselling. African adolescent girls and young women had higher adherence to oral PrEP and the dapivirine ring than has been previously reported. Experience with these PrEP products informed the choice of products. A majority of African adolescent girls and young women chose the dapivirine ring, which is a PrEP option that is less burdensome to the user than oral PrEP. Sexual activity and high adherence to oral PrEP during the randomised periods were associated with choice of product in the product choice period. The study provides evidence that the majority of African adolescent girls and young women were able to use both oral tenofovir disoproxil fumarate plus emtricitabine and the dapivirine ring with high adherence, that both products were safe and well tolerated, and that two-thirds of participants chose the dapivirine ring in the final product choice period.

Implications of all the available evidence

This study shows higher adherence to daily oral PrEP and the monthly vaginal dapivirine ring among African adolescent girls and young women than previous studies, which is important given the ongoing high HIV incidence in this population. The crossover design provided adolescent girls and young women with experience in both daily pill-taking and a monthly vaginal ring for HIV prevention, which informed their choice of product. HIV prevention coverage is likely to be higher if a choice of PrEP options is offered to meet the needs and preferences of users.

However, two PrEP placebo-controlled efficacy trials that enrolled African adolescent girls and young women showed no protection, in large part due to low adherence to products.[6,7,11–14] Demonstration projects among African adolescent girls and young women have shown high initiation rates of oral PrEP with low adherence and persistence to oral PrEP, indicating a high motivation for HIV prevention but that stigma and the burden of daily pill-taking is challenging in this population,[14–16] possibly reflecting stage of neurocognitive development, dynamic partnerships, and uncertainty regarding HIV exposure.

The monthly dapivirine vaginal ring might provide a more discrete and less challenging option for some young women, because no active effort is needed to remain adherent for a month after inserting the ring. Two placebo-controlled, phase 3 trials of the dapivirine ring showed reductions in HIV acquisition of 27% and 31%, respectively; post-hoc analyses suggested lower adherence and either no or lower protection, respectively, in women aged 18–21 years compared with women older than 21 years.[3,4] Effectiveness of the dapivirine ring was approximately 50% in the open-label extension studies in which participants were aware of the efficacy data and HIV incidence was compared with a counterfactual estimate.[17–19] Based on these findings, WHO has recommended the dapivirine ring as an additional choice for HIV prevention for women at substantial risk of HIV infection.[20]

To guide implementation of oral PrEP and the dapivirine ring among African adolescent girls and young women, given previously observed lower adherence in this younger population, we aimed to assess product adherence, safety, and choice of oral PrEP compared with the dapivirine ring among African adolescent girls and young women.

Methods

Study design and population

MTN-034/Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH) was a randomised, open-label, phase 2a crossover trial done at four Microbicide Trials Network (MTN)-affiliated clinical research sites: Cape Town and Johannesburg, South Africa; Kampala, Uganda; and Harare, Zimbabwe. The primary objectives were to evaluate safety and adherence to oral PrEP and the dapivirine ring during the crossover periods, and the secondary objective was choice of product after the randomised periods with use of each product. The crossover design allowed for intraindividual comparisons of safety, adherence, and acceptability. The study enrolled

healthy, sexually active, HIV-seronegative, non-pregnant and non-breastfeeding female participants aged 16–21 years on a hormonal contraceptive method or intrauterine device for more than 2 months, with no post-exposure prophylaxis or PrEP use in the previous 3 months, and no chronic medical conditions. By design, one-third of participants were aged 16–17 years to increase data on safety and adherence in adolescent girls. At screening, participants were assumed to have been assigned female sex at birth and were not asked to report their gender identity. However, required safety pelvic examinations that occurred during the screening process confirmed sex at birth. Sites used youth-focused recruitment strategies, adolescent-friendly clinics, staff training on non-judgemental counselling, and education of parents or guardians about the study.

The study protocol was approved by the ethics review committees at each study site: University of Cape Town Faculty of Health Sciences Human Research Ethics Committee, University of Witwatersrand Human Research Ethics Committee, University of Zimbabwe Joint Research Ethics Committee, and Makerere University. All participants provided written informed consent in English or their local language (ie, Xhosa, i-Zulu, Setswana, and Luganda). Following local regulations, participants below the legal age for consent provided assent and parent or guardian permission was obtained.

Randomisation and masking

Participants were randomly assigned (1:1) to one of two sequences of either the dapivirine ring or oral PrEP for 6 months, then switched to the other product option for 6 months, followed by a third 6-month period in which participants were given a choice of oral PrEP, the dapivirine ring, or neither product, for a total of 18 months study participation (appendix p 2). A window of 70 days from screening to enrolment allowed participants to initiate and become familiar with the highly effective contraceptive method of their choice and reduced potential confounding of side-effects during initiation of a contraceptive method with oral PrEP or the dapivirine ring. Fixed block randomisation was used, stratified by site, generated by the MTN statistical and data management centre. Participants and clinical research staff were not masked to randomisation allocation.

Procedures

Participants received 6 months of daily oral tenofovir disoproxil fumarate plus emtricitabine (fixed dose of 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) or used the dapivirine ring for 6 months before crossing over to the other PrEP formulation. Participants were counselled on methods for easy swallowing of tablets and ring insertion. Ingestion of the first tablet and first ring insertion were observed in the study clinics. Participants were counselled to keep the ring in place for the entire month until their next visit and to return with the used ring still inserted for removal in clinic. A new ring or bottle with 30 PrEP tablets was dispensed at each monthly visit. There was no washout between crossover periods based on the ethical obligation to not withhold efficacious HIV prevention products in a population at high risk of acquiring HIV.

Study products were permanently discontinued for confirmed HIV acquisition, an allergic reaction to either product, reported use of oral PrEP for HIV prevention outside of the study, and injection drug use. At the onset of the study, there was less experience with oral PrEP and ring use during pregnancy, so product holds were initiated for pregnancy, breastfeeding, reported use of post-exposure prophylaxis, suspected HIV acquisition, or grade 3 or higher product-related adverse events. Oral PrEP was withheld when creatinine clearance levels were less than 60 mL/min. Pelvic examinations were done at enrolment, at 6, 9, 13, 16, and 20 months, and when clinically indicated. Ring use was temporarily withheld in instances of deep epithelial disruption, generalised erythema, severe oedema, or cervicitis. Study product was resumed 8 weeks after end of pregnancy based on a negative pregnancy test, unless the participant was breastfeeding.

For the **study protocol** see https://www.mtnstopshiv.org/research/studies/mtn-034/mtn-034-protocols

Participants received contraceptive counselling and access to effective contraceptive methods, with Ω to use long-acting reversible methods to minimise time off product during holds for unplanned pregnancy. Participants also received female or male condoms, or both, testing and treatment for sexually transmitted infections, partner referral for sexually transmitted infection treatment, and risk reduction counselling. Sexually transmitted infection testing included nucleic acid amplification for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (GeneXpert, Cepheid, Sunnyvale, CA, USA), a rapid test for *Trichomonas vaginalis* (Osom Rapid Trichomonas test, Sekisui Diagnostics, San Deigo, CA USA), and syphilis serology (rapid plasma reagin screening and *Treponema pallidum* specific confirmatory assay) at screening, if indicated at enrolment, every 3 months as per protocol, and when participants reported symptoms. Sexually transmitted infections were treated per national guidelines. HIV testing was done with two parallel rapid tests, at least one of which was US Food and Drug Administration approved. If the rapid results were positive or discordant, a confirmatory assay (Geenius HIV 1/2 Supplemental Assay, Bio-RAD, Marnes-la-Coquette, France) was done.

See **Online** for appendix

Participants with confirmed HIV acquisition were counselled about living with HIV, and access to HIV care was facilitated. Participants had the option to continue in the study without product use.

Adherence assessments included participant self-report by computer-assisted self-interview, interviewer-administered questionnaires, and objective drug concentration evaluation using intracellular concentrations of tenofovir-diphosphate in dried blood spots

and residual dapivirine concentrations in returned rings. Tenofovir-diphosphate in red blood cells provides a cumulative measure of dosing and average adherence to oral PrEP in the previous 4–6 weeks.[21] Tenofovir-diphosphate concentrations were analysed by a liquid chromatography-tandem mass spectrometry assay (University of Cape Town Pharmacology Lab, Cape Town, South Africa). Assessment of ring adherence was based on residual drug concentrations in returned rings, determined by acetone extraction and high pressure liquid chromatography (Farmovs, Bloemfontein, South Africa). Adherence measurements were obtained monthly during the randomised and product choice periods. 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 duration of time that the participant had the ring.[17] Drug concentration feedback counselling was required at the second and fifth month of each product use period, reflecting the first and third months of use, respectively. Study counsellors were permitted to share drug concentration feedback at other visits, if available, per their discretion or if results were requested by the participant.

For counselling and adherence outcome measures, categorical adherence thresholds were defined. Counselling was provided when the drug concentration result was available in order to initiate conversations with participants about what adherence support might be needed to achieve optimal adherence. Client-facing adherence counselling used images to show the semiquantitative thresholds (appendix p 3). A green zone for oral PrEP use depicted the threshold for high adherence of intracellular tenofovir-diphosphate greater than or equal to 700 fmol/dried blood spot punch (correlating with an average of four to six doses per week in the previous month) in directly observed dosing studies and was associated with 100% efficacy in an open-label extension study among men who have sex with men (efficacy for cisgender women with fewer than 6–7 doses per week is not known and currently being studied).[8,22] The yellow zone depicted any to moderate oral PrEP adherence, defined as 17–700 fmol/punch, and the red zone depicted no use (<17 fmol/punch, the lower limit of detection). Because steady-state levels for tenofovir disoproxil fumarate plus emtricitabine are not reached until approximately 6 weeks, lower thresholds were used for counselling about tenofovir disoproxil fumarate plus emtricitabine based on the month 1 dried blood spot result: more than 500 fmol/punch for high adherence and 17–499 fmol/punch for medium adherence.

The semiquantitative images and counselling messages for ring adherence were categorised as a green zone for high use (>4·0 mg dapivirine released per month, associated with 28 days of use), yellow zone as some to moderate use (0·9–4·0 mg dapivirine released per month, associated with 1–27 days of use), and red zone as no use (<0·9 mg dapivirine released), based on the rate of dapivirine release over 28 days and the correlation of more than 4 mg released per month with reduced risk of HIV acquisition in the MTN 025/HOPE trial.[17,19]

Participants were offered a menu of adherence support options, including digital support (text messages daily or weekly), group support (in-person or WhatsApp group meetings), and individual support (extra counselling sessions or peer buddies).[23]

Safety assessments were done at each visit based on laboratory parameters, symptoms, and physical and pelvic examinations by trained study clinicians. Adverse events were reported per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[24] Adverse events were classified into period 1 if the reported onset date was between randomisation and 30 days after the month 6 visit, and period 2 if the onset date was between months 6 and 7. The number and proportion of participants with at least one grade 2 or higher adverse event were ascertained by product and period. Each participant-period contributed once with the highest severity adverse event for that period. The five most common product-related grade 2 and higher adverse events were tabulated for each product across the two randomised periods.

Outcomes

The primary adherence endpoint was use of each product during the randomised periods, with high use defined as tenofovir-diphosphate concentrations greater than or equal to 700 fmol/punch (associated with taking an average of four or more tablets per week in the previous month) and greater than or equal to 4 mg dapivirine released from the returned ring (continuous use for 28 days) in the previous month based on residual drug concentrations.

A secondary adherence measurement for oral PrEP was greater than or equal to 1200 fmol/punch tenofovir-diphosphate, which is associated with seven doses per week and aligns with the threshold of more than 4 mg dapivirine release indicating continuous use of the dapivirine ring.

The primary safety endpoint was grade 2 or higher adverse events during each randomised period of 24 weeks of dapivirine ring and oral PrEP. Given the open-label design, the analysis focused on adverse events considered related to the study product.

The secondary outcome of study product choice was assessed 12 months after the two 6-month crossover periods (appendix p 2). Participants were asked to select the ring, oral PrEP, or neither product for the final 6-month period. Participants could switch or restart a product during the final 6-month product choice period.

Statistical analysis

The initial enrolment goal was 300 participants; the sample size was reduced to 247 in June, 2020, due to

the impact of COVID-19 on active recruitment efforts. The sample size and power calculations were based on the primary comparisons of safety and adherence between the first and second periods of the study (ie, the randomised periods). For the primary safety outcome, the study had 80% power to detect a minimum difference of 5·8–9·2% depending on the rate of adverse events in the treatment regimen with the lower adverse event rate, if there was no intraparticipant correlation for safety outcomes. If the intraparticipant correlation was moderately high (ie, 0·5), the minimum detectable difference range was 4·1–6·5%. For the primary adherence outcome, the study had more than 80% power to detect a difference of 8·4% (with an intraparticipant correlation of 0·5) to 11·9% (with an intraparticipant correlation of 0·0), assuming that 60% of participant visits with lower adherence would have low concentrations of tenofovir-diphosphate or high residual dapivirine concentrations in returned rings.

Data from all randomly assigned participants were included in the intention-to-treat analysis of the first two randomised periods. For the primary safety endpoint, paired analyses conducted using generalised estimating equation models with a Poisson (log) link, an offset of the number of visits per study product use period, an exchangeable correlation structure, and robust errors (controlling for study product use periods) were used to compare the two treatment regimens for the safety endpoints during the first two randomised study product use periods. Because there was no washout period between the two randomised study product periods, it was not possible to assign adverse events that occurred in the first month of the second and third period to one product or the other, so adverse events reported in the first month in period 2 (month 6) and period 3 (month 7), reflecting potential ongoing adverse events from the previous period, are reported in appendix p 6.

The primary adherence endpoints were analysed descriptively by calculating the medians of continuous measures and the proportions of measures falling into pre-determined adherence categories. Adherence measures were taken from dried blood spots and residual dapivirine concentrations in returned rings, and the analysis was limited to visits with available concentrations.

For the secondary outcome of product choice, the initial product choice at the beginning of the third period was calculated. To select and model correlates of product choice, we used an adaptive Least Absolute Shrinkage and Selection Operator with ten-fold cross validation to select the tuning parameter. Candidates for inclusion in the final multivariable model were age and perceived risk of acquiring HIV at enrolment, randomisation sequence, any product-related grade 2 or higher adverse event (disaggregated for the ring and oral PrEP), drug concentration results during ring and oral PrEP randomised periods (always green *vs* at least one non-green report), sexually transmitted infection at baseline, and self-reported behavioural and demographic variables at baseline and month 12 at the beginning of the choice period (ie, having a primary partner, vaginal and anal sex in the past 3 months, and currently in school).

Statistical analyses were conducted in SAS version 9.4 and R version 4.0.4. This trial is registered at ClinicalTrials.gov, NCT03593655.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The funder of the study reviewed the report.

Results

Between Feb 6, 2019, and Sept 9, 2021, the MTN-034/REACH study screened 396 potential participants, 247 of whom were enrolled and randomly assigned (figure 1). The median age of participants was 18 years (IQR 17–19). The majority (214 [87%]) were single and 219 (89%) reported a primary sex partner, most of whom were reported to be HIV negative, although one-quarter

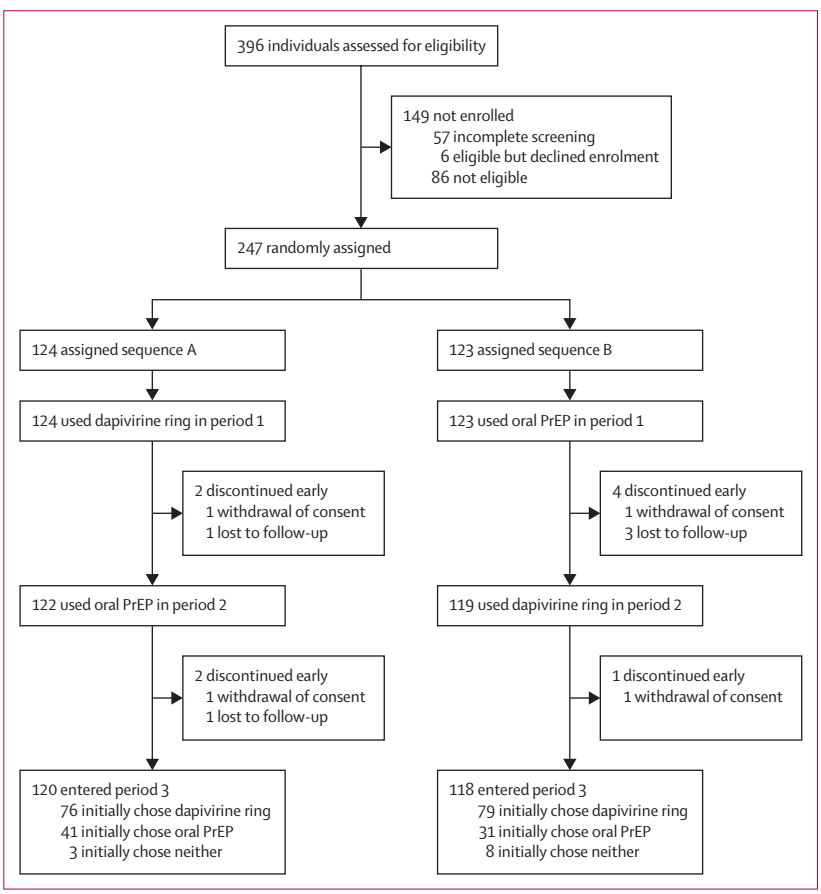

Figure 1: **Trial profile**
Participants were first randomly assigned (1:1) to one of two sequences of either the dapivirine ring or oral PrEP for 6 months, then switched to the other product option for 6 months (periods 1 and 2 and sequences A and B). At month 12, participants were given a choice of oral PrEP, the dapivirine ring, or neither product for 6 months (period 3). PrEP=pre-exposure prophylaxis.

	Sequence A (n=124)	Sequence B (n=123)	Total (n=247)
Demographic characteristics			
Age, years			
Median	18 (17–19)	18 (17–19)	18 (17–19)
16–17	41 (33%)	44 (36%)	85 (34%)
18–19	57 (46%)	57 (46%)	114 (46%)
20–21	26 (21%)	22 (18%)	48 (19%)
Marital status			
Single	106 (85%)	108 (88%)	214 (87%)
Married	7 (6%)	3 (2%)	10 (4%)
Cohabitating	9 (7%)	11 (9%)	20 (8%)
Separated or divorced	2 (2%)	1 (1%)	3 (1%)
Highest level of education			
Primary	15 (12%)	18 (15%)	33 (13%)
Secondary	92 (74%)	97 (79%)	189 (77%)
College or university	15 (12%)	8 (7%)	23 (9%)
Currently in school	51 (41%)	41 (33%)	92 (37%)
Earns income	22 (18%)	31 (25%)	53 (21%)
Partner as a source of income	34 (27%)	47 (38%)	81 (33%)
Behavioural characteristics			
Ever pregnant	52 (42%)	47 (38%)	99 (40%)
Alcohol consumption, previous month			
Never	52 (42%)	51 (41%)	103 (42%)
Monthly or less	38 (31%)	33 (27%)	70 (28%)
2–4 times a month	24 (19%)	29 (24%)	54 (22%)
2–3 times a week	9 (7%)	5 (4%)	14 (6%)
4 or more times a week	1 (1%)	5 (4%)	6 (2%)
CES depression scale			
<10	78/117 (67%)	65/116 (56%)	143/233 (61%)
≥10	39/117 (33%)	51/116 (44%)	90/233 (39%)
Primary sexual partner			
Has primary sex partner	111 (90%)	108 (88%)	219 (89%)
Mean age of primary sex partner, years	22·8 (3·3)	23·2 (4·4)	23·0 (3·9)
In partnership >1 year	70/111 (63%)	63/107 (59%)	133/218 (61%)
HIV status of partner			
HIV positive	2/111 (2%)	1/108 (1%)	3/218 (1%)
HIV negative	82/111 (74%)	79/108 (73%)	161/218 (74%)
Do not know	27/111 (24%)	28/108 (26%)	55/218 (25%)
Has other partners			
Yes or probably	25/111 (23%)	26/108 (24%)	51/218 (23%)
No	30/111 (27%)	22/108 (20%)	52/218 (24%)
Do not know	56/111 (50%)	60/108 (56%)	116/218 (53%)

(Table 1 continues on next page)

of participants with a primary sex partner were unsure of their partner's HIV status (table 1). At enrolment, almost half reported they were very or somewhat worried about their HIV risk in the next year. Around a third were diagnosed with gonorrhoea or chlamydia. Perceived risk of HIV in the next year, sexually transmitted infection prevalence at baseline, and specific type of contraception used at baseline differed by site (appendix p 4).

Retention at the end of the product choice period (week 72) was 118 (95%) in sequence A and 114 (93%) in sequence B). The proportion of visits not completed ranged from two (1%) participants not completing the visit to 19 (8%) participants not completing the visit, with sites completing remote and off-site visits during COVID-19 lockdown periods.

The proportions of participants with high, some, and no use of the dapivirine ring and oral tenofovir disoproxil fumarate plus emtricitabine did not differ by sequence A or B and thus are combined in figure 2. 1316 dried blood spots were tested for intracellular tenofovir-diphosphate to assess oral tenofovir disoproxil fumarate plus emtricitabine use in the previous month, representing 89% of expected dried blood spots. The median tenofovir-diphosphate concentration was 789 fmol/punch; 295 (22%) dried blood spots indicated very high use (>1200 fmol/punch associated with seven tablets per week), 458 (35%) indicated high use (700–1200 fmol/punch associated with an average of four–six tablets per week), 542 (41%) indicated moderate use (17–700 fmol/punch), and 21 (2%) indicated no use (<17 fmol/punch; figure 2A). The median time from dried blood spot collection to counselling about tenofovir-diphosphate concentrations was 42 days (IQR 29–70).

1407 used rings were returned from participants to measure residual dapivirine concentrations, representing 95% of expected used rings collected and analysed. The median dapivirine release rate was 4·3 mg/month (IQR 3·3–5·2). Based on residual drug concentrations, 806 (57%) indicated continuous use (dapivirine ring release rate >4·0 mg/month), 541 (39% had moderate use, and 60 (4%) suggested that the rings were not used (<0·9 mg/month released; figure 2C). The median time between return of used dapivirine rings and adherence counselling about dapivirine was 56 days (IQR 29–76).

1450 adverse events were reported during the randomised crossover periods: 827 during the oral PrEP period, of which 456 were grade 2 or higher; and 623 during the dapivirine ring period, of which 442 were grade 2 or higher; table 2). 347 adverse events during the randomised period were determined by clinicians as related to oral PrEP and 30 as related to the dapivirine ring, with 54 grade 2 and higher adverse events related to oral PrEP and five to the dapivirine ring. The most common product-related grade 2 and higher adverse events attributed to oral PrEP were decreased creatinine clearance, headache, nausea, diarrhoea, and vomiting; the product-related grade 2 and higher adverse events reported during use of the dapivirine ring were intermenstrual bleeding, vaginal discharge, vaginal odour, and vulvovaginal discomfort (table 2). Because there was no washout period between the randomised crossover periods and to minimise potential misclassification of adverse events, the adverse events reported in the first

month of the first and second crossover periods are separated in the appendix (p 6). Median baseline creatinine clearance was 101·7 mL/min (IQR 91·2–114·0). All but one adverse events related to creatinine clearance were grade 2, which included a 10% change from the baseline creatinine clearance. The median creatinine clearance was 99·6 mL/min (IQR 90·3–110·7) at the end of 6 months of oral PrEP use and 101·8 mL/min (90·0–114·1) at the end of 6 months of dapivirine ring use. No participants discontinued oral PrEP during the randomised period and one participant discontinued oral PrEP in the product choice period due to tolerability. No participants discontinued the ring due to tolerability issues. There were no product-related serious adverse events with either product.

In period 3, 155 (65%) of 238 participants initially chose the ring, 72 (30%) initially chose oral PrEP, and 11 (5%) chose neither product. During the subsequent 6 months, those choices were quite stable; 137 (58%) participants continued with the ring, 62 (26%) continued with oral PrEP, 30 (13%) switched products during the product choice period, and nine (4%) did not use either product. Adherence to chosen products in the third period was similar to adherence in the randomised 6-month periods (figure 2B, D).

Three predictors were selected for the final multivariable product choice model (table 3), with two significant factors being reporting vaginal sex in the 3 months before enrolment in favour of choosing the ring and always receiving feedback of high adherence in favour of choosing oral PrEP.

Four participants seroconverted to HIV during follow-up: one seroconverted at month 6 of the randomised oral PrEP period, one at month 5 of the randomised dapivirine ring period, one during the choice period in which she had chosen oral PrEP, and one during the choice period in which she had chosen the dapivirine ring. The four seroconversions were associated with low or no product use based on tenofovir-diphosphate concentrations and dapivirine release rates before seroconversion (appendix p 7).

	Sequence A (n=124)	Sequence B (n=123)	Total (n=247)
(Continued from previous page)			
Sexual behaviour			
Vaginal sex, past 3 months	100/123 (81%)	103/122 (84%)	203/245 (83%)
Condom use with last vaginal sex in past months	55/100 (55%)	57/103 (55%)	112/203 (55%)
Anal sex, past 3 months	6 (5%)	13 (11%)	20 (8%)
Median number of sex partners, past 3 months	1 (1–2)	1 (1–2)	1 (1–2)
Received goods or money for sex, past 6 months	33 (27%)	33 (27%)	66 (27%)
Intimate partner violence, past 6 months	15 (12%)	21 (17%)	36 (15%)
Perceived HIV risk in next year			
Very worried	38 (31%)	33 (27%)	71 (29%)
Somewhat worried	18 (15%)	11 (9%)	29 (12%)
A little worried	30 (24%)	38 (31%)	68 (28%)
Not at all worried	38 (31%)	41 (33%)	79 (32%)
Laboratory sexually transmitted infection diagnosis			
Gonorrhoea	13 (10%)	8 (7%)	21 (9%)
Chlamydia	30 (24%)	41 (33%)	71 (29%)
Trichomonas	8 (6%)	5 (4%)	13 (5%)
Syphilis seropositive	3 (2%)	3 (2%)	6 (2%)
Any sexually transmitted infection	40 (32%)	47 (38%)	87 (35%)
Current contraceptive use			
Intrauterine device	13 (10%)	14 (11%)	27 (11%)
Implant	60 (48%)	51 (41%)	111 (45%)
Oral	0	0	0
Injectable	51 (41%)	58 (47%)	109 (44%)
Median baseline creatinine clearance, mL/min	102·1 (94·2–118·1)	100·6 (89·9–111·0)	101·6 (91·2–114·0)

Data are median (IQR), n (%), mean (SD), or n/N (%). Sequence A: period 1 dapivirine ring; period 2 oral PrEP with tenofovir disoproxil fumarate plus emtricitabine. Sequence B: period 1 oral PrEP with tenofovir disoproxil fumarate plus emtricitabine; period 2 dapivirine ring. CES=Center for Epidemiologic Studies. PrEP=pre-exposure prophylaxis.

Table 1: **Participant baseline characteristics by randomised crossover sequence**

Discussion

This randomised, open-label crossover study of the monthly dapivirine ring and daily oral PrEP among sexually active adolescent girls and young women from South Africa, Uganda, and Zimbabwe showed high safety, adherence, and persistence with oral PrEP and the dapivirine ring. Notably, 57% of participants had objective evidence of high adherence to the dapivirine ring and oral PrEP during the randomised periods, around 40% showed some use, and less than 5% showed no product use. Participants' motivation for HIV prevention was evident in the final product choice period; only 5% chose to use neither product, 65% of participants chose the dapivirine ring, and 30% chose oral PrEP. Encouragingly, young women's adherence to their preferred HIV prevention product and persistence remained high during the choice period, supporting the concept of providing women with a choice of PrEP formulation, which in this study was informed by their previous use of both oral PrEP and the dapivirine ring.

The randomised crossover design enabled a direct comparison of the adherence and safety for oral PrEP and the dapivirine ring. Although more adverse events were reported in the randomised oral PrEP period than in the dapivirine ring period, the safety and tolerability of both oral PrEP and the dapivirine ring were high. Consistent with safety and tolerability findings from the placebo-controlled efficacy trials of these products, safety profiles were favourable and no new safety concerns were identified for either product; only one participant discontinued the product (oral PrEP) due to poor tolerability. Study participants reported more systemic adverse events during oral PrEP use and more vaginal complaints during use of the dapivirine ring, which is consistent with safety findings from the placebo-controlled efficacy trials of these products.[3,4,6,7] No clinically significant nephrotoxicity was observed during

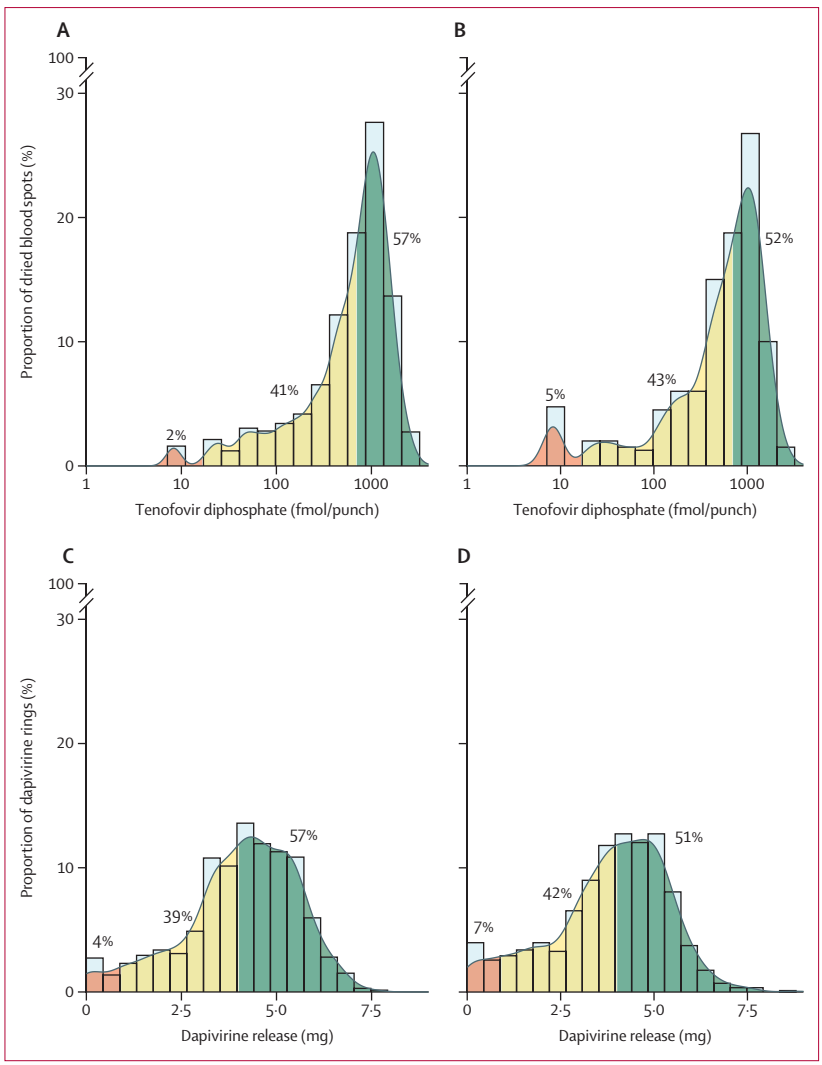

Figure 2: **Adherence to monthly dapivirine vaginal ring and daily oral tenofovir disoproxyl fumarate plus emtricitabine PrEP during the randomised periods**

(A) The proportion of dried blood spots with semiquantitative thresholds for adherence in the randomised oral PrEP period. (B) The proportion of dried blood spots with semiquantitative thresholds for adherence among those who chose oral PrEP in the choice period. For both A and B, the green zone for oral PrEP use depicts the threshold for high adherence with intracellular tenofovir-diphosphate concentration ≥700 fmol/punch. The yellow zone depicts any to moderate oral PrEP adherence, defined as 16·6–700 fmol/punch, and the red zone depicts no use (<16·6 fmol/punch, the lower limit of detection). (C) Dapivirine ring use based on calculated release of dapivirine in returned rings in the randomised dapivirine ring user period. (D) Dapivirine ring use based on calculated release of dapivirine in returned rings among those who chose the dapivirine ring in the choice period. For both C and D, the green zone depicts high use (>4·0 mg dapivirine released per month with 28 days of use), the yellow zone depicts some to moderate use (0·9–4·0 mg dapivirine released per month associated with 1–27 days of use), and the red zone depicts no use (<0·9 mg dapivirine released). To provide a comparable monthly use of the dapivirine ring with the highest level of adherence to oral PrEP, seven doses of oral PrEP per week is correlated with tenofovir-diphosphate >1200 fmol/punch, which was observed in 374 (22%) dried blood spot samples. PrEP=pre-exposure prophylaxis.

oral PrEP use in this young population; changes in creatinine clearance were minor and observed with both products. The median creatinine clearance was 99·6 mL/min after 6 months of oral PrEP use, which was very similar to the baseline median creatinine clearance (102·1 mL/min) and after 6 months of the dapivirine ring (101·8 mL/min), highlighting the lack of nephrotoxicity of oral PrEP with tenofovir disoproxil fumarate–emtricitabine in this young population.

Adherence to the dapivirine ring and oral PrEP were higher than in the placebo-controlled efficacy trials and in other projects with open-label use.[16–18,25] Previous studies of oral PrEP and the dapivirine ring have not included monthly visits or offered adolescent girls and young women a choice of products and supportive adherence counselling based on objective markers of product use. Although it is not possible to identify the precise influence of these factors on the high adherence, persistence, and retention during the trial, the higher adherence to the dapivirine ring and oral PrEP in this cohort of adolescent girls and young women compared with previous efficacy trials, open-label extensions, and demonstration projects is encouraging in terms of a multipronged effort to provide a welcoming environment, more frequent visits, and supportive and flexible adherence strategies. Although receiving drug concentration feedback could have contributed to the adherence observed in this study (ie, the Hawthorne effect), the provision of drug concentration feedback for both oral PrEP based on dried blood spots and residual dapivirine in used rings should have been similar between the randomised product use periods.

Almost all (95%) participants chose to use either the dapivirine ring or oral PrEP after 6 months of use of each product in the randomised periods. Two-thirds of participants chose the dapivirine ring and the strongest predictor for choosing the ring was vaginal sex in the 3 months before enrolment, perhaps due to a preference for a longer acting discrete or topical PrEP formulation. However, a third of participants chose oral PrEP, indicating that an important subset preferred the oral option. The association of choosing oral PrEP with having consistently received drug concentration feedback indicative of high adherence during the randomised periods could reflect that participants who found strategies for high adherence to oral PrEP were motivated to continue to use it. Similar to the effect of contraceptive method mix on meeting women's preferences and needs and increasing contraceptive coverage,[26,27] a growing number of HIV prevention options, including with longer acting, lower user burden, and less user-adherence dependent formulations, are anticipated to meet the needs of a larger proportion of young women.[28]

Limitations of the study include a modest reduction in the sample size due to the impact of COVID-19 during national lockdowns in each country, which restricted recruitment efforts. In spite of these lockdowns, retention through to 18 months was 94%. During these lockdown periods, participants could be dispensed more than one dapivirine ring or bottle of tablets to reduce clinic visits; there was potential misclassification of dapivirine rings to a specified use period and a greater likelihood of rings not being returned, and fewer dried blood spot samples were obtained due to increased spacing of visits. The lack

	Dapivirine ring			Oral PrEP		
	First period	Second period	Overall	First period	Second period	Overall
Total adverse events	318	305	623	436	391	827
Grade 2 and higher adverse events	202	240	442	223	233	456
Grade 2 and higher adverse events related to study product	3	2	5	12	42	54
Product holds due to adverse events	0	0	0	0	0	0
Most common grade 2 and higher adverse events related to study product						
Decreased creatinine clearance*	0	0	0	6	18	24
Headache	0	0	0	3	5	8
Nausea	0	0	0	0	8	8
Diarrhoea	0	0	0	2	3	5
Vomiting	0	0	0	0	3	3
Intermenstrual bleeding	2	0	2	0	0	0
Bacterial vaginosis	1	0	1	0	0	0
Vaginal odour	0	1	1	0	0	0
Vulvovaginal discomfort	0	1	1	0	0	0
Decreased creatinine clearance regardless of association with study product†						
Grade 2 adverse event	34	41	75	27	57	84
Grade 3 adverse event	0	0	0	0	1	1
Grade 4 adverse event	0	0	0	0	0	0
Total serious adverse events	0	0	0	2	1	3
Study product-related serious adverse events	0	0	0	0	0	0
Serious adverse events resulting in hospitalisation or death	0	0	0	2	1	3

PrEP=pre-exposure prophylaxis. *Includes all decreased creatinine clearance values from baseline, following Division of AIDS grading criteria that clinician attributed to that study product. †Includes all decreased creatinine clearance values from baseline, following Division of AIDS grading criteria during that product use period, regardless of clinician attribution to study product. Grade 2 adverse events for creatinine clearance includes a change in baseline of 10%.

Table 2: **Adverse events and serious adverse events during dapivirine ring and oral PrEP use, by period of use**

of a washout period due to ethical concerns about withholding effective HIV prevention products from adolescent girls and young women at risk of HIV confounds attribution of adverse events in the first months of the second crossover period when side-effects could be residual from the previous product or the new randomly assigned product. A cumulative measure of adverse events over each product use period was analysed and, to address the potential of carryover effect, adverse events in the first month of the second crossover period were analysed separately from the remaining 5 months in that period. In the context of a randomised crossover trial with careful implementation and monitoring, a strategy of sequential product use was useful. However, this study has limitations in generalisability given potential selection bias in enrolling adolescent girls and young women who were willing to have monthly visits for 18 months and the study was not designed to inform programmatic implementation of HIV prevention product choice with briefer product use periods, which would require a different study design.

HIV prevention remains a priority for African adolescent girls and young women who have persistently high HIV incidence and previously had lower adherence to oral PrEP and the dapivirine ring. The study population was at high risk of sexually transmitted HIV and other infections,

	Proportion choosing dapivirine ring	Odds ratio (95% CI)	p value
Vaginal sex, 3 months before enrolment			
No	19/36 (53%)	..	..
Yes	136/189 (72%)	2·91 (1·29–6·69)	0·011
Oral PrEP adherence feedback always high during crossover period			
No	106/126 (84%)	..	..
Yes	49/99 (49%)	0·16 (0·08–0·31)	<0·0001
One or more grade 2 or higher adverse events related to dapivirine ring during crossover period			
No	153/220 (70%)	..	..
Yes	2/5 (40%)	0·29 (0·03–1·96)	0·20

PrEP=pre-exposure prophylaxis.

Table 3: **Predictors of initial choice of oral PrEP or dapivirine ring among the 227 participants in product choice period**

which is similar to other PrEP demonstration projects among young African women.[16,25,29] This observation highlights the need for aetiological sexually transmitted infection testing, ideally point-of-care testing, and sexually transmitted infection treatment as part of integrated sexual and reproductive health care with PrEP delivery.

The findings from the MTN-034/REACH study are encouraging in that they highlight that adolescent

women and girls can have high adherence and persistence with oral PrEP and the dapivirine ring for up to 18 months, with client-centred, non-judgemental, flexible adherence support strategies and monthly visits. More than half of participants had high adherence to oral PrEP and the dapivirine ring and only 5% did not use their assigned product during the randomised periods. Safety and tolerability of both products was high and no new safety signals were identified. Participants in this study made informed choices about HIV prevention after 6 months of use of oral PrEP and the dapivirine ring, with two-thirds choosing the dapivirine ring. Longer-acting formulations of PrEP might be more acceptable to African adolescent women and girls even if the efficacy is lower, and higher adherence and persistence with a chosen product might increase coverage and partly offset lower efficacy of the dapivirine ring in this population. Implementation science studies are needed to establish whether a sequential form of product choice in which adolescent girls and young women can use different PrEP methods for a brief period provides women with a greater opportunity to choose a product that meets their needs.

Contributors

CC, GN, and KN conceptualised the study, led the investigation, and drafted and edited the manuscript. SLH and JMB conceptualised the study, acquired funding, and reviewed and edited the manuscript. DS and ERB curated and verified the data, conducted formal analysis, and provided figures for visualisation of the data. DS and ERB had access to the full dataset, led the statistical methodology, and conducted formal analysis. CAA, RN, PM, GM, TP-P, KR, ET, FM, CN, L-GB, BS, LS-T, AvdS, SH, JFR, JS, KB, UP, CH, and PA conducted investigations and reviewed and edited the manuscript. MG, SJ, TM, LL, EL, and CJ supervised the project, and reviewed and edited the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CC has received consulting fees from Gilead Sciences and Merck, and has been an expert witness for Gilead. SLH has received consulting fees and funds to her institution from Merck. KN has received research funds from Merck (Merck Sharpe & Dohme). JMB and JFR are employees of Gilead Sciences. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this Article, after de-identification, are available, beginning after publication, as well as the study protocol, data dictionary, statistical analysis plan, and informed consent forms. Data are available for researchers who provide a methodologically sound proposal in accordance with policies of the Microbicide Trials Network (MTN). For data access requests contact sc.mtn-data-access@scharp.org.

Acknowledgments

The study was designed and implemented by the MTN. The MTN was fully funded by the National Institutes of Health, including the National Institute of Allergy and Infectious Diseases through individual grants (UM1AI068633, UM1AI068615, and UM1AI106707), with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the US National Institutes of Health. The National Institutes of Health was the regulatory sponsor. LS-T is an employee of the National Institute of Allergy and Infectious Diseases. PA, JMB, L-GB, CC, ERB, CH, SLH, SH, KN, TP-P, and AvdS have received grants from the National Institutes of Health. The International Partnership for Microbicides (Silver Spring, MD, USA) developed the dapivirine ring and supplied rings for this trial and participated in the design of this trial, the interpretation of the results, and manuscript preparation. Tenofovir disoproxil fumarate–emtricitabine tablets were supplied by Gilead Sciences (Foster City, CA, USA), which participated in the design of the trial, interpretation of the results, and manuscript preparation. We thank the women who participated in this study for their motivation and dedication, the communities that supported this work, and the leadership and staff at the clinical research sites that conducted the study. The National Institutes of Health funded the trial and was the regulatory sponsor. The authors vouch for the accuracy and completeness of the data and analyses.

References

1 Joshi K, Lessler J, Olawore O, et al. Declining HIV incidence in sub-Saharan Africa: a systematic review and meta-analysis of empiric data. *J Int AIDS Soc* 2021; **24:** e25818.

2 Ahmed K, Baeten JM, Beksinska M, et al. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet* 2019; **394:** 303–13.

3 Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med* 2016; **375:** 2121–32.

4 Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med* 2016; **375:** 2133–43.

5 Gray GE, Bekker LG, Laher F, et al. Vaccine efficacy of ALVAC-HIV and bivalent subtype C gp120-MF59 in adults. *N Engl J Med* 2021; **384:** 1089–100.

6 Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 2016; **30:** 1973–83.

7 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.

8 Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; **14:** 820–29.

9 Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; **367:** 423–34.

10 Martin M, Vanichseni S, Suntharasamai P, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. *AIDS* 2015; **29:** 819–24.

11 Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372:** 509–18.

12 Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367:** 411–22.

13 Hanscom B, Janes HE, Guarino PD, et al. Brief Report: preventing HIV-1 infection in women using oral preexposure prophylaxis: a meta-analysis of current evidence. *J Acquir Immune Defic Syndr* 2016; **73:** 606–08.

14 van der Straten A, Montgomery ET, Hartmann M, Minnis A. Methodological lessons from clinical trials and the future of microbicide research. *Curr HIV/AIDS Rep* 2013; **10:** 89–102.

15 Stoner MCD, Rucinski KB, Giovenco D, et al. Trajectories of PrEP adherence among young women aged 16 to 25 in Cape Town, South Africa. *AIDS Behav* 2021; **25:** 2046–53.

16 Celum C, Hosek S, Tsholwana M, et al. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: results from HPTN 082, a randomized controlled trial. *PLoS Med* 2021; **18:** e1003670.

17 Baeten JM, Palanee-Phillips T, Mgodi NM, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. *Lancet HIV* 2021; **8:** e87–95.

18 Nel A, van Niekerk N, Van Baelen B, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. *Lancet HIV* 2021; **8:** e77–86.

19 Brown ER, Hendrix CW, van der Straten A, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. *J Int AIDS Soc* 2020; **23:** e25634.

20 WHO. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection. 2021. https://www.who.int/news/item/26-01-2021-who-recommends-the-dapivirine-vaginal-ring-as-a-new-choice-for-hiv-prevention-for-women-at-substantial-risk-of-hiv-infection (accessed Dec 20, 2022).

21 Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013; **29:** 384–90.

22 Anderson PL, Liu AY, Castillo-Mancilla JR, et al. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following directly observed therapy. *Antimicrob Agents Chemother* 2017; **62:** e01710-17.

23 Roberts ST, Mancuso N, Williams K, et al. Strategies to support effective use of the vaginal ring and oral PrEP among adolescent girls and young women in sub-Saharan Africa: qualitative findings from MTN-034/REACH. https://programme.aids2022.org/Abstract/Abstract/?abstractid=6840 (accessed Oct 10, 2023).

24 Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1, July 2017 and addendum 1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed Oct 10, 2023).

25 Celum CL, Bukusi EA, Bekker LG, et al. PrEP use and HIV seroconversion rates in adolescent girls and young women from Kenya and South Africa: the POWER demonstration project. *J Int AIDS Soc* 2022; **25:** e25962.

26 Haakenstad A, Angelino O, Irvine CMS, et al. Measuring contraceptive method mix, prevalence, and demand satisfied by age and marital status in 204 countries and territories, 1970–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **400:** 295–327.

27 Gaffield ME, Kiarie J. Setting global standards: the paramount importance of considering contraceptive values and preferences of clients and providers. *Contraception* 2022; **111:** 1–2.

28 Bekker LG, Pike C, Hillier SL. HIV prevention: better choice for better coverage. *J Int AIDS Soc* 2022; **25:** e25872.

29 Celum CL, Gill K, Morton JF, et al. Incentives conditioned on tenofovir levels to support PrEP adherence among young South African women: a randomized trial. *J Int AIDS Soc* 2020; **23:** e25636.