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Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

MTN-034

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Protocol Name:	A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population
Protocol Number:	MTN-034
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1. LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
AE	adverse event
CRF	case report form
DBS	dried blood spot
DPV	dapivirine
DVR	dapivirine vaginal ring
FTC	emtricitabine
GEE	generalized estimating equations
HIV-1	human immunodeficiency virus-1
LoA	letter of amendment
MTN	Microbicide Trials Network
SAP	Statistical analysis plan
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
VR	vaginal ring

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical analyses that will be conducted to compare safety profiles, adherence, acceptability, and participant product preference between the emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) oral tablet administered daily and the dapivirine (DPV) vaginal ring (VR) (25 mg) inserted once every 4 weeks. This SAP covers the final study analyses.

2.1 General Design Considerations

The following is a summary of the protocol.

Short Title: Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)

IND Sponsor: DAIDS

Funders: Division of AIDS, NIAID, NIMH, NICHD, US NIH

Protocol Chair: Gonasagrie Nair, MBChB, MPH

Protocol Co-Chairs: Connie Celum, MD, MPH
Kenneth Ngure, PhD

Sample Size: Approximately 300 participants

Study Population: Healthy, HIV-uninfected, sexually active adolescent and young adult females, 16 - 21 years old (inclusive)

Study Sites: Sites selected by the MTN Executive Committee

Study Design: Phase 2a, open-label, multi-site, two-sequence, crossover, randomized trial

Study Duration: Approximately 76 weeks of follow-up per participant with a projected accrual period of approximately 12 months at each site.

Study Product:

- Silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month
- Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) tablets to be taken orally daily

Study Regimen: Participants will be randomized (1:1) to one of two sequences of a vaginal ring (VR) containing 25mg of dapivirine to be inserted monthly for 24 weeks and 200 mg FTC/300 mg TDF oral tablets taken daily for 24 weeks. After completing the randomized sequence of two study product use periods, participants will then select between the two study products to use in the final 24 weeks of the trial. Participants will be able to choose either or neither study product at any time during the third product use period.

	N	Period 1 (24 Weeks)	Period 2 (24 Weeks)	Period 3 (24 Weeks)
Sequence A	150	Vaginal (dapivirine 25 mg VR)	Oral (Daily FTC/ TDF tablet)	Free choice (dapivirine 25 mg VR or daily FTC/TDF tablet or neither)
Sequence B	150	Oral (Daily FTC/ TDF tablet)	Vaginal (dapivirine 25 mg VR)	Free choice (dapivirine 25 mg VR or daily FTC/TDF tablet or neither)

2.2 Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
Safety: To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population	• Grade 2 or higher adverse events (AEs) as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])
Adherence: To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population	• Detectable drug levels in blood • Residual drug levels in returned VRs

Secondary Objectives	Secondary Endpoints
To compare the acceptability of the FTC/TDF oral tablet administered daily and the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population	• Participant report of acceptability
To compare study product adherence during the third study product use period when study product is chosen against the study product use period during which the study product is randomly assigned	• Detectable drug levels in blood • Residual drug levels in returned VRs
Participant preference between dapivirine VR and FTC/TDF oral tablets over the course of study participation	• Participant product selection during third product use period • Participant report of product preference

2.3 Randomization

Participants were randomized in a 1:1 ratio to one of two sequences; either a VR containing 25mg of DPV to be inserted monthly for 24 weeks followed by 200 mg FTC/300 mg TDF oral tablets taken daily for 24 weeks, or vice versa. Randomization was stratified by site.

2.4 Blinding

This was an open label study. Study staff and participants were blinded to the sequence prior to randomization of the participant.

2.5 Sample Size and Power

The following description of sample size and power for the primary endpoints reflects changes to the protocol (Letter of Amendment (LoA) #03, dated 30 June 2020) that were made in response to the COVID-19 pandemic (247 participants instead of the original target of 300 participants).

Sample size/power formulas for a parallel design (i.e., independent groups of participants on each treatment regimen) can be used to compute sample size/power. Sample size/power calculations assume the primary comparisons will be between the first and second periods of the study (randomized periods). The sample size resulting from the assumption of independent groups can then be adjusted to reflect that there will be intra-participant correlation in the crossover study design. This sample size adjustment is obtained using the formula: $N' = N(1-\rho)/2$ where N' is the sample size for the crossover study, N is the total number of participants necessary for a parallel design with two arms ($N/2$ in each arm) and ρ is the correlation between responses within a single participant during different study product use periods (intra-participant correlation).

Primary Endpoints

Safety: Based on previous studies we expect to observe rates of the primary safety endpoints between 2% to 10%. Table 1 shows the minimum detectable difference in rates of safety events assuming 80% power, $\alpha=0.05$, a two-sided test based on the Normal approximation of the Binomial distribution, varying

rates of safety events in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), and a sample size of 250.

Table 1: Minimum Detectable Difference in Rates of Safety Outcomes Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
Rate of Safety Event in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
2%	5.8%	4.8%	4.1%	3.2%
5%	7.5%	6.3%	5.3%	4.1%
10%	9.2%	7.7%	6.5%	5.0%

If there is no intra-participant correlation for safety outcomes, the study will have 80% power to detect a minimum difference of 5.8% to 9.2% depending on the rate of the safety event in the treatment regimen with the lower rate. If the intra-participant correlation is moderately high (0.5), this minimum detectable difference ranges from 4.1% to 6.5%.

Adherence: Based on previous studies we expect to observe a high rate of participants with at least 80% of their visits with detectable drug levels in plasma (for the oral regimen) and detectable drug levels in residual ring drug levels consistent with high adherence (for the DPV ring regimen). Table 2 shows the minimum detectable difference in rates of ≥80% adherence assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ≥80% adherence in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), and a sample size of 250.

Table 2: Minimum Detectable Difference in Rates of ≥80% Adherence Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
≥80% Adherence Rate in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
60%	11.9%	10.0%	8.4%	6.5%
70%	10.8%	9.0%	7.6%	5.9%
80%	9.0%	7.5%	6.4%	4.9%
90%	6.3%	5.3%	4.5%	3.5%

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

Primary Analysis Set: The analysis set for the primary safety, primary adherence, secondary adherence, and secondary acceptability analyses will consist of all randomized and enrolled participants.

Choice Period Analysis set: The analysis set for adherence during the third period will include all participants who completed visits in Period 3 (i.e., from Week 48/Visit 16 through Week 72/Visit 23).

3.2 Statistical Analysis Issues

MTN-034 follow-up consisted of three product use periods, with participants randomized to a sequence of product use in the first two periods (i.e., dapivirine ring in Period 1 followed by FTC/TDF oral tablets in Period 2, or vice versa) followed by Period 3 during which participants chose which, if any, product to use. During Period 3 participants could also choose to change their product choice. There was no washout period between product use periods.
During the first two product use periods participants will be analyzed according to the product the participant was randomized to receive (i.e., intent-to-treat).

The COVID-19 pandemic began while the study was in follow-up, affecting the ability of participants to attend follow-up visits. This in particular could affect the adherence data available differentially between the two products. Adherence to tablets was measured using dried blood spot (DBS) samples that could only be collected at an in-person visit; whereas, adherence to rings was measured using residual dapivirine remaining in a used ring that could be returned at any subsequent visit. Therefore, interruptions to scheduled visit due to pandemic restrictions restricted the study's ability to assess tablet but not ring adherence. However, because rings could be returned at any visit, it is possible that a ring returned during the Period 3 (Choice Period) might reflect use of rings from the Period 1 and 2 (Crossover Period).

Ring adherence is complicated due to the data used for that calculation being collected partly when rings were returned (i.e., residual amount of dapivirine remaining in ring, date ring was intended to be inserted, date ring was intended to be removed) and partly when the ring was provided (i.e., ring manufacturer lot), without there being a ring identifier that allowed direct linkage of returned and dispensed rings. The method for linking returned and dispensed rings is described in Appendix I.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No interim statistical analysis was planned or performed for MTN-034.

Safety monitoring committee (SMC) reviews were conducted during study follow-up, approximately every six months. Evaluation was based on descriptive tables with no formal statistical testing.

5. GENERAL ANALYSIS METHODS

Descriptive statistics will be used to summarize continuous (mean and standard deviation, median, quartiles, range and number of missing data values) and categorical (frequencies, relative frequencies, percentages, and number of missing data values) variables. Descriptive analyses will be summarized overall, and stratified by site and by randomization sequence unless otherwise noted noted. Summaries by site will use the site at which the participant was enrolled. A two-sided significance level of 0.05 will be used for all statistical tests unless otherwise noted.

Data from both regularly scheduled and unscheduled (referred to as "interim" visits will be used in analyses as appropriate. Unless otherwise noted, data from interim visits will not contribute to summaries by visit but will contribute to summaries that are combined across all visits.

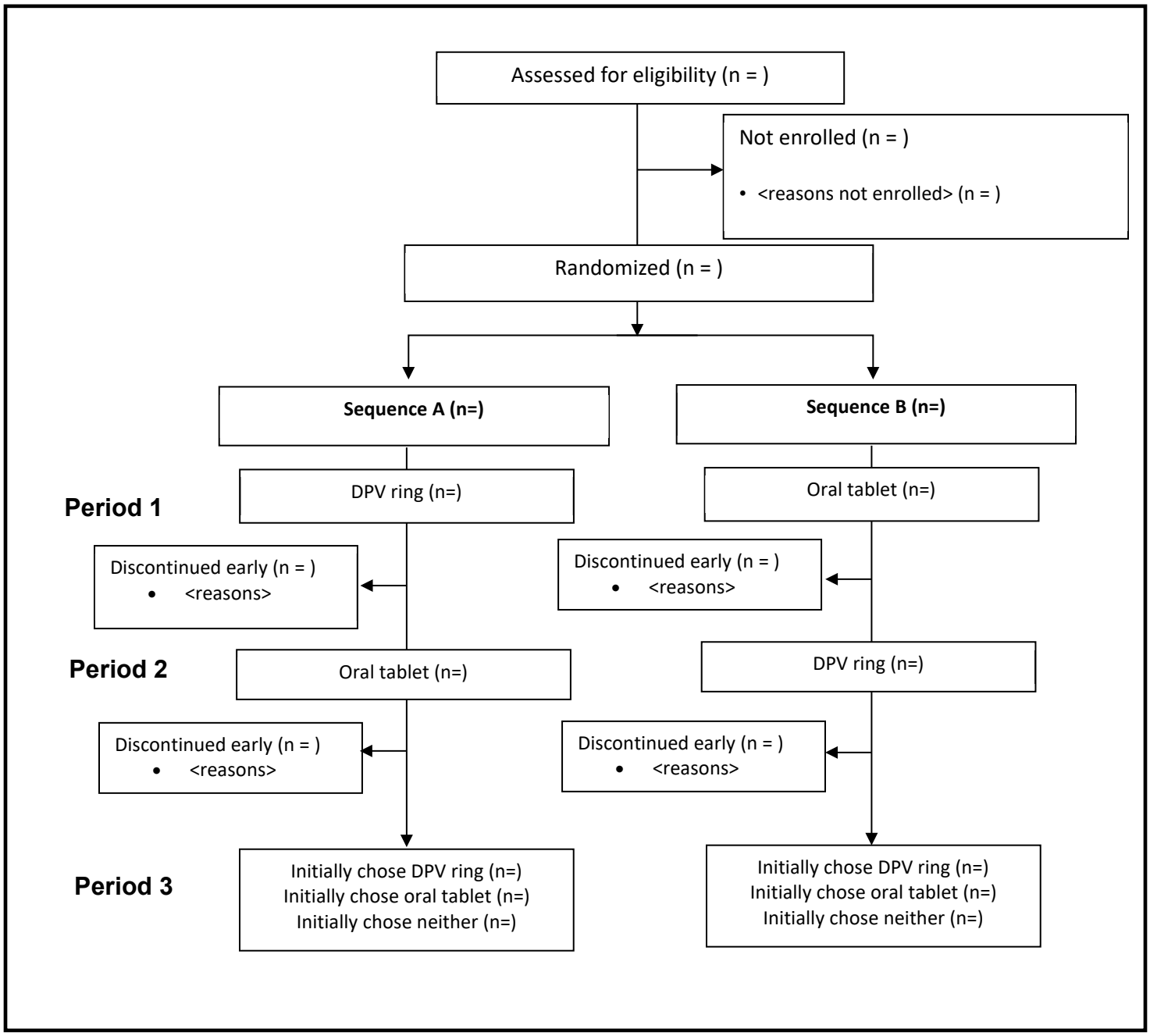
We expect little to no missing data. Data will be considered missing (no data on outcome measures) if a participant does not return for a follow-up visit. However, if the probability of missing measurements depends on either covariates or on the measurement outcomes of participants, then the methods described above may give biased inferences and point estimates. If a substantial amount of endpoint data is missing (e.g., follow-up data missing in at least 10% of participants), then secondary analyses of the endpoints will be conducted using methods that relax the missing completely at random assumption to a missing at random assumption. For a univariate binary and quantitative outcome, respectively, a

generalized linear model with a binomial or Normal error distribution will be used for estimation and testing. Sensitivity analyses will be conducted comparing the regimens using only the first study product use period data for all the outcomes.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

The number of participants screened, the number of participants who were enrolled and not enrolled, the number of participants with each reason for not enrolling, the number of participants randomized to each sequence, and the number of participants considered evaluable for each primary and secondary endpoint (e.g., the analysis sets defined in 3.1) will be displayed in a CONSORT flow diagram.



6.2 Protocol Deviations

The number of protocol deviations and number of each type of deviation will be summarized in a table by site, and presented in a listing of each deviation. Additional tables will summarize the protocol deviations that were and were not related to the COVID-19 pandemic (identified by whether the description of the deviation includes the text “COVID”).

7. BASELINE DATA

Unless otherwise specified, baseline characteristics will be summarized descriptively using appropriate summary statistics as described in Section 5. Other than the summary of screening (Section 7.1), summaries will only include participants in the Primary Analysis Set. No formal statistical testing will be performed.

7.1 Screening

The number of participants screened, enrolled, and the reasons why participants were not enrolled (including reasons for ineligibility) will be summarized by site, for all participants who were screened for enrollment into MTN-034.

7.2 Accrual

The site activation dates, first and last site enrollment dates, duration of accrual, total number of potential participants screened, total number of participants enrolled, and mean number of participants enrolled per week will be summarized by site. Accrual duration will not include the time while accrual was halted due to the COVID-19 pandemic, since the study did not resume accrual after the halt.

7.3 Demographics

Baseline demographics (taken from the Demographics Case Report Form (CRF)) will be summarized by sequence and by site. The items will include the following:

- Participant age (continuous)
- Participant age group (categorical; 16-17 years old, 18-19 years old, and 20-21 years old)
- Participant marital status (categorical)
- Whether participant is currently attending school (categorical)
    - If not currently attending school, whether participant ever attended school (categorical)
    - If not currently attending school, age when participant left school (continuous)
- Highest level of school attended (categorical)
- Whether participant earns an income of their own (categorical)
- How worried the participant is that they may get infected with HIV (categorical)

7.4 Contraception

Baseline contraception methods and days from the start date for that method to randomization (taken from the Family Planning CRF) will be summarized by randomization sequence and site. Days from contraception start to randomization will be summarized both as a continuous and as a categorical variable (0-70 days, 71+ days).

Baseline contraception methods are defined as methods with Date Regimen Started on or prior to randomization (including cases where the Date Regimen Started is incomplete but known to be prior to randomization, e.g., if a participant was randomized March 1, 2019 and the Date Regimen Started was an unknown date in February 2019) and a Date Regimen Stopped that is either a) on or after randomization or b) ongoing at the end of participant follow-up. If the Date Regimen Started was incomplete then the participant will not be included in the continuous summary, and will only be included in the categorical summary if the minimum and maximum possible days from contraception start both fall within only one category (e.g., if days from contraception start is known to be between 100 and 120 days then this participant would be categorized as having 71+ days from contraception start, but if the known range was 60 to 80 days then this participant would not be included in the categorical summary).

7.5 Sexually Transmitted Infections (STIs)

The number and percentage of participants diagnosed with syphilis, trichomonas, gonorrhea, or chlamydia at baseline, as well as the number and percentage diagnosed with any of those four STIs at baseline will be summarized by randomization sequence and site.

Baseline STIs will be summarized using the STI Test Results CRF collected at Screening/Visit 1. A positive result for trichomonas, gonorrhea, or chlamydia is defined as having a value of "Positive" for "Trichomonas test", "N. gonorrhea", or "C. trachomatis" respectively, and a negative result as having a value of "Negative". A positive result for syphilis is defined as having a value of "Reactive" for "Syphilis screening test" and a value of "Positive" for "Syphilis confirmatory test", and a negative result if the syphilis test was done but did not meet the above definition for positivity. If "Was a sample collected for Trichomonas testing?" is "No" or the response to "Trichomonas test" is "Not done" or missing the participant will not be counted in the denominator for trichomonas. If "Was a vaginal sample collected for NAAT for GC/CT?" is "No" or the response to "N. gonorrhea" is "Not done" or missing the participant will not be counted in the denominator for gonorrhea, and if "Was a vaginal sample collected for NAAT for GC/CT?" is "No" or the response to "C. trachomatis" is "Not done" or missing the participant will not be counted in the denominator for chlamydia.

A positive result for Any STI is defined as a positive result for any of the four STIs. Any participant with a baseline test result for at least one of the four STIs will be included in the denominator for Any STI.

7.6 Local Laboratory Results

Descriptive statistics for continuous variables (see Section 5 General Analysis Methods) will be calculated for creatinine clearance at baseline by randomization sequence and site. This will be taken from the "Calculated creatinine clearance" item on the Local Laboratory Results CRF collected at Screening/Visit 1.

8. PRIMARY ENDPOINT ANALYSES

8.1 Primary Safety Analyses

Objective: To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population.

Data Set: Primary Analysis Set

Strata: Intervention

Endpoint: Grade 2 or higher adverse events (AEs)

Analysis Details:

The primary safety endpoint is grade 2 or higher adverse events (AEs). The primary safety unit of analysis will be the participant-period. The study hypothesis is that the daily FTC/TDF tablets and DPV VR will be generally safe and well-tolerated.

For the primary analysis, adverse events will be classified into one of two participant-periods, based on the reported time on event onset. Events will be classified into Period 1 if the reported onset date is between the date of randomization and the date 30 days after the participant's Week 24/Visit 9 visit* (inclusive). Events will be classified into Period 2 if the reported onset date is between the date of the

participant's Week 24/Visit 9 visit and the date 30 days after the participant's Week 48/Visit 16 visit*. Note that AEs occurring within 30 days of Week 24/Visit 9 visits will be classified into both periods.

The number and percentage of participant-periods with at least one grade 2 or higher AE will be tabulated by product (combining the two product use periods) and by product and period. Each participant-period will contribute once (e.g., only the highest severity AE that was classified into the period).

To compare the proportion of participants experiencing an adverse event between products, we will fit a generalized estimating equation 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 period). Events in this analysis ascribed to a product will be limited to those that occur during the product use period.

Primary analyses will be further supported by a table that breaks out AE onset further as follows (and illustrated in the table below):

- Onset between date of randomization and at or before the participant's Week 24/Visit 9 visit.
- Onset between the participant's Week 24/Visit 9 visit and the date 30 days after the participant's Week 24/Visit 9 visit* (inclusive).
  Onset between the participant's Week 48/Visit 16 visit and the date 30 days after the participant's Week 48/Visit 16 visit*

** If the participant missed this visit, use the date 30 days after the close of the visit window.*

	Truvada						DVR					
	During product use period			One month post product use period			During product use period			One month post product use period		
AEs	1st period	2nd period	overall	1st period	2nd period	overall	1st period	2nd period	overall	1st period	2nd period	overall
Total # AEs												
Total # AEs related to study product				N/A	N/A	N/A				N/A	N/A	N/A
≥1 AE per participant												
Mean AEs per ppt (SD)												
Total SAEs												
Product-related SAEs				N/A	N/A	N/A				N/A	N/A	N/A
SAEs resulting in hospitalization or death												
# ppts with >1 SAEs												
# ppts with HIV												
Creatinine clearance decreased												
Grade 1												
Grade 2												
Grade 3												
Grade 4												

In addition, the five most common product-related AEs will be tabulated within each product (across all three product use periods).

8.2 Primary Adherence Analyses

Objective: To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

Data Set: Primary Analysis Set

This analysis will be restricted to blood and residual drug levels collected during the first two product use periods (i.e., collected after Enrollment/Visit 2 and on or prior to Week 48/Visit 16).

Strata: Randomization sequence, intervention

Endpoints:

- Detectable drug levels in blood (Truvada) during the randomization period
- Residual drug levels in returned VRs distributed during the randomization period

Analysis Details:

Histograms and density plots of drug levels will be presented by randomization sequence and further broken down by site. Boxplots over time will also be displayed by randomization sequence. To understand completeness of these measures, these plots will be accompanied by tables describing the completion of adherence assessments (number of rings returned vs dispensed and number of blood draws completed vs tablet bottles dispensed). The means, medians and interquartile ranges of the drug level measures will also be tabulated. These plots and tables will be calculated overall and by randomization sequence, with tables also presented by visit.

Number of rings returned vs. dispensed will be calculated only among rings that were returned and dispensed in the first two product use periods (e.g., a ring that was dispensed in Period 1 but not returned until Period 3 would be counted as a dispensed ring but not as a returned ring for this analysis).

CUTPOINT ANALYSES
Drug level will also be summarized (number and percent) by categories defined by the following cutpoints for each product. The summaries will be calculated overall and by randomization sequence. Because DPV ring release rates have not been verified against directly observed use, the only comparable category for the two products is no use.

DPV ring:
No use (rate ≤ 0.9mg/month)
Some release (0.9mg/month < rate ≤ 4.0mg/month)
High release (rate > 4.0mg/month)

Truvada:
No use (< 16.6fmol/punch)
Some use (16.6-699fmol/punch)
High use (≥700fmol/punch)

The first month of Truvada use (e.g.,dried blood spot (DBS) samples collected at Week 4/Visit 4 visit for participants randomized to Sequence B, Week 28/Visit 11 for participants randomized to Sequence A) will also separately be categorized as:
No use (< 16.6fmol/punch)
Some use (16.6-499fmol/punch)
High use (≥500fmol/punch)

DPV release rate is defined as the amount of DPV released from the ring divided by the duration of time during which the participant had the ring (or, if the participant had multiple rings at one time, the duration of time during which the participant reported they should have been using the ring). The amount of DPV released is calculated by subtracting the amount of residual DPV in a returned ring from the amount of DPV in control rings from the same lot number (provided by FARMOVS). See Appendix I for further details on this calculation.

A Generalized Estimating Equation model with a Poisson (log) link, an offset of the number of visits with drug levels measured per study product use period, an exchangeable correlation structure and robust errors will be used to compare non-adherence (no use) to the two regimens (controlling for study product use period) during the first two study product use periods. These comparisons will be done using: 1) plasma data for participants during the oral regimen, and 2) residual ring data for participants during the VR regimen. This analysis differs slightly from the protocol in two ways. First, since the protocol was written, dapivirine ring release has become the standard objective measure for vaginal ring use; therefore, dapivirine plasma levels have been removed from the definition. Second, the outcome will be "no use" since it is the only level comparable between the two measures of product use. This is also more standard in adherence analyses since the protocol was written.

9. SECONDARY ENDPOINT ANALYSES

9.1 Secondary Acceptability Analyses

Objective: To compare the acceptability of the FTC/TDF oral tablet administered daily and the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population**.**

Data Set: Primary Analysis Set

This analysis will be restricted to scheduled visits during Periods 1 and 2 where the ACASI was expected to be completed and the endpoint question expected to be answered (i.e., Week 12/Visit 6, Week 24/Visit 9, Week 36/Visit 13, and Week 48/Visit 16).

Strata: Site

Endpoint: Participant report of acceptability

Analysis Details:

The secondary acceptability endpoint is participant report of acceptability, defined as their response to the ACASI questions "please rate how much you like using the ring for HIV prevention" and "please rate how much you like using the tablets for HIV prevention". Two analyses will be completed to accommodate for social desirability bias:

- Responses will be collapsed into two categories; "like" (responses of "like" and "like very much") and "did not like" (responses of "dislike very much", "dislike", and "neither like nor dislike").
- Responses will be collapsed into two categories; "like" (responses of "like" and "like very much", and "neither like nor dislike") and "did not like" (responses of "dislike very much", "dislike").

To compare the proportion of participants liking the product for HIV prevention between products, we will fit a generalized estimating equations (GEE) model, adjusting for randomization arm and site, with repeated measures by participant assuming an independent correlation matrix, and using a binomial distribution with logistic link.

9.2 Secondary Adherence Analyses

Objective: To compare study product adherence during the third study product use period when study product is chosen against the study product use period during which the study product is randomly assigned

Data Set: Choice Period Analysis Set

Strata: Product choice in Choice Period

Outcomes:
- Detectable drug levels in blood
- Residual drug levels in returned VRs

Analysis Details:
A Generalized Estimating Equation model with a Poisson (log) link, an offset of the number of visits with drug levels measured per study product use period, an exchangeable correlation structure and robust errors will be used to compare non-adherence (no use) to each regimen separately between Crossover Period and the Choice Period. These analyses will be stratified by product. Participants will only be included in these product specific analyses if they chose to use the product in the Choice Period. Participants who selected both products will be included in both regression analyses. Participants who choose neither will not be included in either analysis. Sensitivity analyses will repeat these analyses restricted to participants who selected only one product in the Choice Period.

Cutpoint analyses for Truvada will use different cutoffs depending on whether the DBS sample is from the first month of Truvada use as in 8.2. The first month of use cutoff in Period 3 is defined as a visit where a participant chose to use Truvada following a visit where they did not choose Truvada (or, for the first month of Period 3, if the participant was randomized to receive the dapivirine ring during Period 2). Since samples are collected at the following visit, samples will use the first month cutoff if the participant did not choose/was randomized to receive Truvada at the scheduled visit two visits prior (e.g., for a sample collected at Week 60/Visit 20, the first month cutoff would be used if the participant had not chosen Truvada at Week 52/Visit 18). Note that Week 49/Visit 17 was a phone contact visit where product was not dispensed, so this visit should be omitted for these purposes (e.g., for a sample collected at Week 56/Visit 19, the relevant choice visit is Week 48/Visit 16, not Week 49/Visit 17).

9.3 Secondary Study Product Preference Analyses

Objective: Participant preference between dapivirine VR and FTC/TDF oral tablets over the course of study participation

Data Set: Choice Period Analysis Set for participant product selection during third product use period outcome. Primary Analysis Set for participant report of product preference outcome.

Strata: Randomization sequence

Outcomes:

- Participant product selection during third product use period
- Participant report of product preference

Analysis Details:
Questions about product preference were administered by ACASI and through face to face interview (captured by CRF) as follows:

Question	*ENR/ Visit 2*	*Visit 6/13/20 (M3/9/15)*	*Visit 9 (M6)*	*Visit 16 (M12)*	*Visit 23 (M18)*	*Early PUEV/ Discont.*
Preference for ring vs. tablets	ACASI			ACASI	ACASI, CRF	ACASI, CRF
Willingness to use non-preferred product if preferred product not available					ACASI	ACASI
Acceptability of current product	ACASI	ACASI*	ACASI, CRF	ACASI, CRF	ACASI*	ACASI*

* Skipped if ppt is not using a product in period 3

Product preferred
Participant report of product preference is defined as the participant's response to the question "would you prefer to use the ring or the tablets for HIV prevention?" on the Product Preference and Acceptability CRF completed at Week 72/Visit 23 (or, at an interim visit for visit 23 if visit 23 was missed). This question was also asked by ACASI at enrollment, the end of the product assignment periods, the end of the product choice period and at PUEV.

The proportion of participants stating a preference for each product will be calculated at each time point it is asked for both ACASI and CRF. This will also be shown by randomized arm.

Product selected
Participant product selection is defined longitudinally over their period of choice follow-up (third product use period). Participants will be categorized as always choosing ring, always choosing tablets, sometimes choosing one or the other (including switching between tablet, ring or none), or never choosing either.

Participants will be defined as "always choosing ring" if they meet any of the following criteria:

- Product Choice CRF, item "would you like to use the tablets or the ring?" has response of "ring" and participant does not have any Product Change CRFs.
- Product Choice CRF was not completed, but one Product Change CRF was completed and "what product does the participant want to start using at this visit?" is "ring" (i.e., participant does not have a subsequent Product Change CRF). This is treated as "always choosing ring" because if a participant had been randomized to receive tablets in Period 2, missed Week 48/Visit 16, and then attended a later visit and wanted to use rings the sites would complete a Product Change CRF.
- Neither Product Choice nor Product Change CRFs were completed, but participant did attend at least one visit in Period 3 and ring was dispensed (Pharmacy Dispensation CRF indicates vaginal ring was dispensed at a visit between Week 48/Visit 16 and Week 72/Visit 23, inclusive).

Participants will be defined as "always choosing tablets" using the same criteria as above, except for choice/dispensation of tablets instead of rings.

Participants will be defined as "switching between the two" if they have both a Product Choice CRF and a Product Change CRF, or at least two Product Change CRFs.

Participants will be defined as "never choosing either" if they had no Participant Choice or Participant Change CRF indicating choice of ring or tablets, and no product dispensed during Period 3 according to the Pharmacy Dispensation CRF.

Alluvial plots of product selected over time will be presented with the categories of oral PrEP, DPV ring and no product.

10. ADDITIONAL ANALYSES

10.1 Incident HIV-1 infections

Participants with HIV-1 infections will be summarized in a listing with randomization assignment, product choice, and adherence history (DPV release rate and Truvada levels in blood).

10.2 Follow-up Sexually Transmitted Infections (STIs)

The number and percentage of participants diagnosed with syphilis, trichomonas, gonorrhea, or chlamydia during follow-up, as well as the number and percentage diagnosed with any of those four STIs during follow-up will be summarized by randomization sequence and site.

Similar to the baseline STIs (see Section 7.5), follow-up STIs will be summarized using the STI Test Results CRF, with the only difference being that results from follow-up visits (e.g., Week 4/Visit 3 or later) will be used instead of screening visit. Participants will be counted as a positive result for trichomonas, gonorrhea, or chlamydia if they ever had a positive result during follow-up (e.g., participants will only be counted once per STI). Participants will be counted as a negative result for each if they had at least one test result during follow-up and no positive results.

A positive result for Any STI is defined as a positive result for any of the four STIs. Any participant with a follow-up test result for at least one of the four STIs will be included in the denominator for Any STI.

10.3 Local Laboratory Results

Descriptive statistics will be calculated for creatinine clearance at Week 24/Visit 9, Week 48/Visit 16, and Week 72/Visit 23, by randomization sequence and site. This will be taken from the “Calculated creatinine clearance” item on the Local Laboratory Results CRF collected at those visits.
For participants who had an adverse event of “creatinine renal clearance decreased” recorded on the Adverse Event Log CRF, descriptive statistics summarizing the change in calculated creatinine clearance will be provided by randomization sequence. This change will be the difference between the calculated creatinine clearance at Screening/Visit 1 and the calculated creatinine clearance at the visit at which the AE was first reported.

11. ADDITIONAL FOLLOW-UP DATA

11.1 Visit Retention

Visit retention summaries will include, for regularly scheduled visits, the number and proportion of participant-visits that were expected, not expected, completed (among expected visits), not completed (among expected visits), missed (among expected and not completed), and missed after early termination (among expected, not completed, and missed). These summaries will be provided by site and by randomization sequence.

See Appendix II for visit schedule and windows.

11.2 Study Termination

Reasons for study termination, derived from multiple items on the Study Termination CRF, and whether or not the study termination was associated with an adverse event will be summarized by site and by arm. The derivation is that any participants with a response of “yes” to the “did the participant complete the study?” item will be considered to have a reason for study termination of “completed study”, and any

participants without a response of "yes" will be considered to have the reason entered for the "primary reason for non-completion" item (e.g., "death", "withdrawal of consent by participant", etc.).

Time from randomization to study termination will be summarized in a Kaplan-Meier curve by randomization sequence, with participants censored at time of HIV-1 infection.

12. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
1.0	04/26/2022	All	Initial version

APPENDIX I

Calculation of DPV release rate

The DPV release rate per 28 days of use is calculated as:

$$rate = \frac{(conc_m - conc_r)}{days} \times 28$$

With $conc_m$ being the amount of residual drug in the manufacturer lot, $conc_r$ being the amount of residual drug in the returned ring, and *days* being the number of days the participant should have been using the ring.

An individual ring is identified in the lab residual DPV data using the `guspec` identifier, with each individual ring having it's own unique identifier. Some rings were tested multiple times and will have multiple observations with the same `guspec` value. Observations with censor values of "(A)X", "(B)X", "(B)Z", or "Z" should not be analyzed. The amount of residual dapivirine in the ring ($conc_r$ above) is indicated by the value of `conc`.

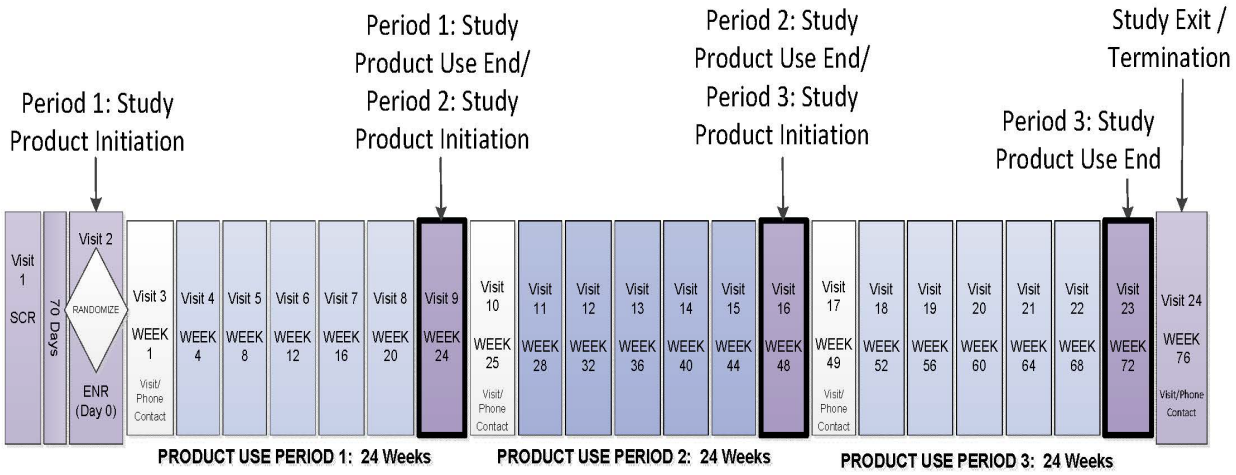
Rings from the lab residual DPV data are linked to the clinical data through the Ring Insertion and Removal CRF, using the participant ID (`ptid`) and specimen collection date (`spcdt`) from the lab data and participant ID and the "date of assessment" from the CRF data. For participants with multiple rings collected on the same date (i.e., two observations with same `ptid` and `spcdt` and different `guspec`), one ring needs to be assigned to correspond to "ring #1" in the Ring Return section of the CRF, and one to "ring #2". If the lab data `sec_id` is "1st IVR" or "Ring 1" (regardless of capitalization) then this ring should be linked to ring #1, and if `sec_id` is "2nd IVR" or "Ring 2" it should be linked to ring #2. If `sec_id` does not contain any of these values, then ring order is assigned arbitrarily, with the smallest value of `recnum` linked to ring #1, the second smallest linked to ring #2, etc.

The number of days (*days* in the above equation) is calculated by taking "date returned ring #1 was removed" – "date returned ring #1 was inserted" + 1 day (and similarly for returned ring #2). If the date ring was removed is marked as unknown, use "date of assessment" instead. If the date ring was inserted is marked as unknown, use "date returned ring #1 was provided" (similar for returned ring #2).

Ring lot number is determined by linking the "date returned ring #1/#2 was provided" to the Pharmacy Dispensation CRF "date study product dispensed" and taking the "vaginal ring #1 lot number" or "vaginal ring #2 lot number", as appropriate. That lot number is linked to the manufacturer record of the concentration for that lot ($conc_m$ above).

APPENDIX II

Visit schedule



Visit windows

All windows are in days; Enrollment date = Day 0 PUEV=Product Use End Visit

Visit	Visit Code	Target Day	Window Opens	Window Closes
Screening	1.0	NA	70 days prior to Enrollment	
Enrollment Period 1: Study Product Initiation	2.0	0	NA	70 days after Screening Visit
Visit 3: Visit/Phone Contact - Week 1	3.0	7	1	13
Visit 4 - Week 4	4.0	28	14	41
Visit 5 - Week 8	5.0	56	42	69
Visit 6 - Week 12	6.0	84	70	97
Visit 7 - Week 16	7.0	112	98	125
Visit 8 - Week 20	8.0	140	126	153

Visit 9 - Week 24 Period 1 Study Product Use End/ Period 2 Study Product Initiation	9.0	168	154	181
Visit 10: Visit/Phone Contact - Week 25	10.0	175	161	188
Visit 11 - Week 28	11.0	196	182	209
Visit 12 - Week 32	12.0	224	210	237
Visit 13 - Week 36	13.0	252	238	265
Visit 14 - Week 40	14.0	280	266	293
Visit 15 - Week 44	15.0	308	294	321
Visit 16 - Week 48 Period 2 Study Product Use End/ Period 3 Study Product Initiation	16.0	336	322	349
Visit 17: Visit/Phone Contact - Week 49	17.0	343	329	356
Visit 18 - Week 52	18.0	364	351	377
Visit 19 - Week 56	19.0	392	378	405
Visit 20 - Week 60	20.0	420	406	433
Visit 21 - Week 64	21.0	448	434	461
Visit 22 - Week 68	22.0	476	462	489
Visit 23 - Week 72 Period 3 Study Product Use End Visit (PUEV)	23.0	504	490	518
Visit 24: Visit/Phone Contact - Week 76 Study Exit/Termination	24.0	532	14 days after PUEV (Visit 23)	42 days after PUEV (Visit 23)