

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

MTN-014

DAIDS Protocol #:11885

**A Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1%
Gel in the Rectal and Vaginal Compartments in Women**

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/May 1, 2013**

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-014 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-014

Summary of Revisions

To ease in the review process, all revisions are displayed below. A summary of revisions is provided below:

- The Protocol Team Roster is updated to reflect current members. The roster format is also modified to list members by affiliation.
- The list of Abbreviations and Acronyms has been updated
- The study duration has been revised to extend accrual from approximately 6 months to 10 months per site
- The exploratory objectives and endpoints no longer include behavioral measures. Revisions have made to corresponding protocol text.
- The background section is updated to include rationale for the addition of directly observed dosing (DOD) and the collection of rectal biopsies in a subset of participants via flexible sigmoidoscope. Related sections have been updated accordingly.
- The inclusion criteria are updated for clarity and consistency
- Section 6, *Study Product*, has been modified to clarify study product administration, dispensing, retrieval of unused study product, assessment of study product dosing and adherence, and prohibited medications and practices
- In Section 7, *Study Procedures*, the formatting and organization has been revised. The study visit schedule has been updated to accurately reflect study visits and corresponding days. A *Study*

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Product Administration Visits table has been added for clarity and consistency throughout this section. The study procedures are comprehensively listed in table format. Appendix I, *Schedule of Study Visits and Evaluations*, and the Sample Informed Consent documents are updated accordingly.

- Section 10, *Statistical Considerations*, is modified to reflect the revised exploratory objectives and endpoints and study duration
- Section 13, *Human Subjects Protection*, has been revised to omit text regarding receiving and reporting to text messages and now includes risks related to DOD
- Appendix III: *Sample Informed Consent (Screening, Enrollment, Long-term Storage)*, has been updated to reflect modifications to exploratory objectives and endpoints and study procedures, and is revised to enhance participant understanding of the trial. Also, a checkbox is included for participants to indicate whether or not they agree to off-site visits by clinic staff, when necessary.
- Other minor updates, corrections, and clarifications are incorporated

Rationale

The primary purpose of this full version amendment is to incorporate a directly observed dosing (DOD) strategy to ensure complete compliance to the study product regimen, which is critical for this Phase 1 pharmacokinetic clinical trial. Rational for incorporating DOD has been provided in the protocol and modifications have been made to appropriate sections to account for participant safety and compliance with ethical and regulatory requirements. In addition, study product administration will be prioritized to occur at the clinic and participants will not be dosing at home (unless, a participant is not able to make it to the clinic due to unforeseen circumstances) and, therefore, behavioral exploratory objectives and endpoints originally in Version 1.0 of the protocol will not be assessed and have been removed.

Modifications throughout the protocol, including updates to the study duration, introduction, study product administration, the study visit schedule, study procedures, statistical considerations, and the sample informed consent have been incorporated for clarity and consistency. The overall scientific priorities, overall study design, study population, sample size, and primary and secondary objective and endpoint remain consistent with Version 1.0.

The proposed revisions enhance the scientific merit of MTN-014 that the integrity of the data generated is reinforced and ensures that the proper safeguards for participant safety remain intact.

Implementation

This amendment is now official MTN-014 protocol documentation. Prior to implementing the revisions listed below, MTN-014 study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs/ECs.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions). Unless otherwise stated section numbers reflect the current version of the protocol.

Detailed Listing of Revisions New to Version 2.0

1. The *List of Abbreviations and Acronyms* has been updated:

DOD	direct observed dosing
SMS	short message service

2. The Protocol Team Roster is updated to reflect current Protocol Team members and contact information:

The following individual is added to the protocol roster:

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The following individuals contact information has been updated:

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Fax: 212-342-1824
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The following individual is removed from the roster: Pamina Gorbach, MHS, DrPH.

3. Protocol Summary:

Study Duration: Accrual will require approximately **610** months per site. Each enrolled participant will be followed for approximately **44-10-13** weeks, **depending upon their menses schedule.**

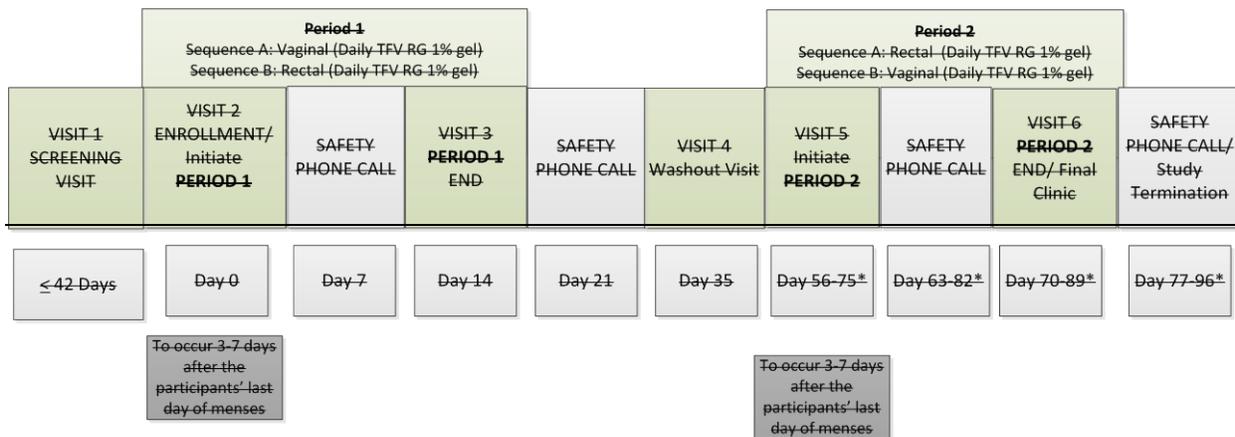
Exploratory Objectives:

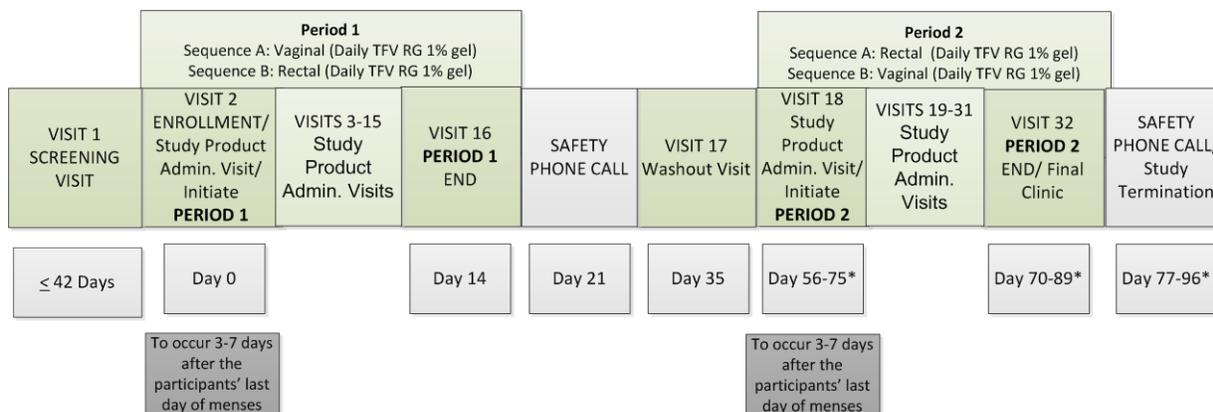
- ~~3. Determine the timing of vaginal and rectal intercourse around gel insertion among those participants who are heterosexually active.~~
- ~~4. Determine reports of partner response to vaginal and rectal gel use of the women who disclose product use to their partner~~
- ~~5. Determine the effect of daily gel use on vaginal and rectal non-sexual practices~~

Exploratory Endpoints:

- ~~• Participant self-reported timing of gel insertion in relation to vaginal and rectal intercourse~~
- ~~• Participant self-report of partner's response to vaginal and rectal gel use~~
- ~~• Participant self-report of vaginal and rectal non-sexual practices~~

Figure 1: *Study Visit Schedule*, has been updated:





4. Section 2.1, *Oral Pre-Exposure Prophylaxis and Microbicides in HIV/AIDS Prevention*, the second paragraph has been modified:

In 2010, the results of the first clinical trial to demonstrate effectiveness were released. The CAPRISA 004 study demonstrated a 39% reduction in HIV acquisition, incidence rate ratio (IRR) = 0.61, 95% CI: 0.4-0.94, among participants who used tenofovir (TFV) 1% gel in a pericoital regimen. However, the daily dosing regimen of TFV 1% gel used in the ongoing MTN-003 (VOICE) Phase 2B effectiveness study was shown not to reduce rates of HIV acquisition compared to the matching placebo. ~~The VOICE Data Safety Monitoring Board (DSMB) subsequently recommended that the TFV 1% gel arm of the VOICE study be stopped for futility.~~^{3, 4} These results speak to the daunting challenge of preventing HIV acquisition in females at high risk for HIV acquisition.

5. Section 2.2.1, *In vitro and Ex vivo Studies of TFV Gel (Various Formulations)*, the *Condom Integrity* section has been revised:

Condom Integrity

~~The compatibility of original TFV 1% gel was tested with three types of lubricated male latex condoms. A matched placebo gel and Universal HEC placebo were used as comparator gels. The condoms tested were representatives of leading brands on the US market (Trojan® and Durex®) with either silicone or aqueous lubricant. The airburst test was used to evaluate changes in film integrity (strength) and test specimens were measured before and after treatment with the gels to assess changes in strength properties following the application of the three gel preparations. All three gels (the original vaginal gel, matched placebo, and HEC Universal placebo gel) were shown to be compatible with the above condoms.~~

~~The TFV RG 1% gel is only slightly modified from the TFV 1% gel; therefore, it is expected to perform similarly to the TFV 1% gel. Nevertheless, similar condom testing is planned to be complete in the third quarter of 2012 using the same protocol (ASTM D7661-10). CONRAD's IND 73,382 will include the data for TFV RG 1% gel testing (authorization for review is stated in CONRAD's cross-reference letter).~~

Information regarding condom integrity can be found in the Investigator's Brochure.¹²⁴

6. Section 2.4.1, *TFV 1% Gel (Original Formulation)*, the *Rectal Administration* section, a final sentence has been added:

Rectal Administration

In a Phase 1 study, RMP-02/MTN-006, 12 men and women participants received sequentially: single-dose oral TDF, single-dose TFV 1% gel (original vaginal formulation) per rectum, 7 daily doses of TFV 1% gel (original vaginal formulation) per rectum. Blood, tissue, and luminal sampling followed each of these 3 dosing periods. At 30 minutes following single rectal, topical dosing, rectal tissue

concentrations were 100-times greater than 30 minutes after single oral dosing. Multiple rectal doses resulted in five times greater concentrations in tissue when compared to a single rectal dose with no significant increase in plasma concentrations. Peripheral blood mononuclear cell (PBMC) tenofovir-diphosphate (TFV-DP) concentrations were below limits of quantitation in the vast majority of specimens collected in the 24 hours following a single rectal dose.²²¹³ **In addition, tenofovir was detected in a proportion of vaginal samples collected from female participants.**

7. Section 2.4.1, *TFV 1% Gel (Original Formulation)*, the *Effectiveness for Prevention of HIV* section, *VOICE* subsection has been modified:

VOICE

The daily dosing regimen of TFV 1% gel (original vaginal formulation) used in the ~~ongoing~~ MTN-003 (VOICE) Phase 2B effectiveness study was not shown to be associated with reduced rates of HIV acquisition and the VOICE DSMB recommended that this arm of the VOICE study be stopped for ~~futility~~ **early for futility.**^{3, 294}

8. New Section 2.7, *Justification of Directly Observed Dosing Strategy*, has been added:

MTN-014 will employ a directly observed dosing (DOD) strategy to ensure complete compliance to the study product regimen.

This strategy is being employed given recently obtained data from MTN-003 VOICE where tenofovir gel adherence as reported via unused applicator counts and by participant self-reports, was high, 86% and 90%, respectively.²⁹ However, in a case-cohort subset, adherence was low as demonstrated by the detection of tenofovir in an average of 25% of available quarterly plasma samples among participants randomized to tenofovir gel.

DOD will guarantee that study participants receive the study product daily, ensuring that adherence does not serve as a confounding factor in the PK analysis. Protocol provisions have been made for study product administration outside of the clinic with/without DOD in the event that participants are unable to present to the clinic, See Section 6.0, *Study Product*, for additional details.

9. Section 2.8, *Other Protocol Considerations*, has been updated to include justification for the use of a flexible sigmoidoscope to collect rectal biopsies in a subset of participants:

Rectal biopsies will be collected in a subset of participants using a flexible sigmoidoscope. A flexible sigmoidoscope allows for the collection of a sufficient number of rectal biopsies (6) at the preferred distance from the anal verge (~15-20 cm). An anoscope cannot extend beyond 5-9 cm and will not be used to collect biopsy samples. Further, in a previously completed trial, RMP 002/MTN-006, samples were collected at ~15-20 cm, and the collection of samples at this location will allow for a comparison between data generated in MTN-014 and the former.

10. Section 3.3, *Exploratory Objective*, the following objectives were removed:

- ~~3. Determine the timing of vaginal and rectal intercourse around gel insertion among those participants who are heterosexually active.~~
- ~~4. Determine reports of partner response to vaginal and rectal gel use of women who disclose product use to their partner~~
- ~~5. Determine the effect of daily gel use on vaginal and rectal non-sexual practices~~

11. Section 4.4, *Time to Complete Accrual*, has been updated:

Accrual is expected to be complete in approximately ~~6~~**10** months per site.

12. Section 4.6, *Sequence and Duration of Participation*, has been updated:

~~The expected duration of participation for women enrolled is approximately 11 weeks, depending upon their menses schedule. The total duration of participation from the Enrollment Visit to Termination is anticipated to be 410-13 weeks, depending participants' menses schedule; this includes two two-week study product use periods and one six-week washout periods plus a one-week follow-up safety phone call after the Period 2 End Visit. Visits may be completed within specified windows around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-014 SSP Manual.~~

13. Section 5.2, *Inclusion Criteria*, number 11, 14 and 15 have been updated to account for the new study visits:

11) Per participant report at Screening, states a willingness to refrain from inserting any non-study vaginal or rectal products or objects into the vagina or rectum, including but not limited to, spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal/rectal douches, enemas, non-study approved lubricants, sex toys (vibrators, dildos, etc.), and tampons for the duration of the study product use periods and for 24 hours prior to ~~each scheduled study clinic visit.~~**Period Initiation Visits and Period End Visits.**

14) Willing to abstain from inserting ~~anything~~**any non-study products** into the vagina or rectum for 72 hours prior to and following the collection of ~~these samples, including vaginal and rectal intercourse biopsies.~~

15) Willing to abstain from vaginal and rectal intercourse 72 hours prior to and following the collection of biopsies.

14. Section 5.3, *Exclusion Criteria*, number 1 letter g, has been revised to include PrEP use:

1) Participant report of any of the following:
g.) Post-exposure prophylaxis (PEP) ~~for possible HIV infection~~ **or Pre-exposure prophylaxis (PrEP)** within the 6 calendar months prior to Enrollment

15. Section 5.4, *Co-enrollment Guidelines*, the bullet has been modified to remove the restrictive language:

- Participants may take part in ~~ancillary~~ studies approved by MTN-014 Protocol Chair and/or Co-Chair

16. Section 6.1, *Regimen*:

Each participant will be randomized to one of two ~~study gel~~ administration sequences **of TVF RG 1% gel**:

17. Section 6.2, *Administration*:

~~TFV RG 1% Gel~~

~~StudyClinic staff will instruct participants in the proper method of study product~~**attempt to observe each administration and storage of study gel.** Participants will ~~receive pre-filled applicators of TFV RG 1% gel at Visit 2 (Enrollment Visit). Study participants will be instructed to insert one dose (the~~

~~entire contents of one applicator) daily into the vagina or rectum depending upon their randomization sequence. They will also be instructed to insert the gel as close to the same time each day as possible. After an approximate 6-week washout period, participants will return~~**present** to the clinic to receive pre-filled applicators of TFV RG 1% gel and instructions and initiate the next period of study product use.**daily for each 14-day period for direct observed dosing (DOD). Administration of study product will be performed either by participants or by study staff, depending upon site and/or participant preference. If a daily dose participant is missed not able to attend a clinic visit, the participant will be instructed to administer the missed dose as soon as possible a dose at home at approximately the same time of day as all other daily doses, unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled. Participants will receive two pre-filled applicators of TFV RG 1% gel at Visit 2 (Enrollment Visit) and Visit 18 (Initiate Period 2 Visit) in the event that they cannot attend their clinic visit. Participants will be instructed to insert one dose (the entire contents of one applicator) into the vagina or rectum depending upon their randomization sequence only on the day(s) they are unable to attend the clinic. Study staff will instruct participants in the proper method of study product administration and storage.**

18. Section 6.4.1, *Supply*:

~~The TFV RG 1% gel will be supplied by CONRAD (Arlington, VA, USA).~~ **will supply the TFV RG 1% gel.** Under direction from CONRAD, DPT Laboratories LTD (San Antonio, TX) which is a contract manufacturing facility, will manufacture the TVF RG 1% gel and analyze/release the gel under cGMP.

19. Section 6.4.3, *Study Product Dispensing*:

~~Study product (TFV RG 1% gel pre-filled applicators) will be dispensed by the pharmacist to enrolled study participants or to study staff on behalf of the participant, upon~~**Following** receipt of a written prescription from an authorized prescriber, **one pre-filled applicator of study product (TFV RG 1% gel) will be dispensed at each study product administration visit for DOD.** An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the United States (US) Food and Drug Administration (FDA) 1572 Form.

~~Pre~~**Participants will receive two pre-filled applicators of TFV RG 1% gel for at home use for each study period. These doses** will be dispensed at **both** Visit 2, the beginning of Period 1, and at Visit ~~5~~**18**, the beginning of Period 2. ~~Participants will receive 14 pre-filled applicators, sufficient to last until~~**Details regarding the Period End Visits. dispensation of additional doses will be provided in the MTN-014 Study Specific Procedures (SSP) Manual available at www.mtnstopshiv.org.** No study product will be dispensed during the study washout phase. ~~In the event that additional study product is needed between visits, participants will be instructed to contact the study site. A Study Product Request Slip from the clinic to the pharmacy will be used in the event that additional product is needed.~~

20. Section 6.4.5, *Retrieval of Unused Study Product*, the first, third, fifth and sixth paragraphs have been edited:

Study participants will be instructed to return all unused study product ~~back~~ to the site at Visit ~~3~~**15 (the last Study Product Administration Visit of Period 1-End)** and Visit ~~6~~**31 (the last Study Product Administration Visit of Period 2-End/Final Clinic Visit).**

[...]

Study product retrieval will occur ~~either~~ by the participant returning the product to study staff within the specified timeframe ~~or~~. **Attempts** by study staff ~~conducting outreach to retrieve the unused study product from the participant (e.g., at her home).~~**must be documented.**

[...]

For each participant, unused study product ~~remaining in the participant's possession should not~~**previously returned must** be retrieved at the Period 2 End/~~Final Clinic (Visit 6)~~**(Visit 32)**. If the

participant does not bring her remaining unused study product to the Final Clinic Visit, study staff must arrange to retrieve the unused study product within 7 days. If the study product(s) are not retrieved within that timeframe, the MTN-014 PSRT must be informed.

The PoR will document all product returns and store **(quarantine)** returned **unused** study product in designated areas within the study pharmacy.

21. Section 6.5, *Study Product Dosing Assessment and Study Product Adherence Counseling*:

~~Adherence~~ **Study Product Dosing** Assessment and **Study Product Adherence** Counseling:

Data on adherence to ~~self-administration of a study gel~~ will be collected **recorded** at Period 1 End and at Period 2 End via case report form (CRF). ~~Short message service (SMS) will be employed for participants who opt-in to receive and to reply to daily text messages during their product use periods.~~

Product adherence counseling will be provided to study participants upon enrollment into the study, and every visit when study product is dispensed thereafter to help ensure high rates of study product use. Counseling will be provided in accordance with standard study methods ~~that~~. **Participants will address such topics as participant be counseled to return to the clinic daily during the product use periods for directly observed gel administration. Participant-centered strategies to remember to use the study gel daily and to ensure the use and availability of the study product both in the home and away from home. will also be provided.** Counseling also will include reminders to contact study staff with questions about study product use.

For participants who have adherence problems **and/or issues presenting to the clinic for the administration of study product**, every effort will be made to identify adherence strategies to increase their rates of study product use **and attendance to daily clinic visits** throughout the course of the study.

22. Section 6.7, *Prohibited Medications and Practices*, has been modified:

All participants will be counseled to avoid the use of non-study vaginal or rectal products, ~~during for the duration of~~ the product use periods and 24 hours prior to ~~each scheduled study visit. Period Initiation Visits and Period End Visits.~~ Concomitant use of prohibited non-study vaginal products or other devices including, but not limited to: spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), vaginal/rectal douches, enemas, non-study approved lubricants, sex toys (vibrators, dildos, etc.), and tampons will be assessed. These products will be recorded on forms designed for that purpose. Participants who report use of ~~these~~ **prohibited** products during study product use periods will be counseled regarding the use of alternative methods. Condoms provided by study staff will not be coated with any type of spermicide.

Furthermore, a subset of participants will also be counseled not to use NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection. Should a participant report the use of such drugs within 72 hours prior to a biopsy visit, collection of biopsies at that visit ~~will~~ **would** be performed at IoR discretion. **Participants are to abstain from inserting any non-study products into their vagina or rectum for 72 hours prior to and following the collection of biopsies. Further, they are to abstain from vaginal and rectal intercourse for 72 hours prior to and following the collection of biopsies.** Participants will be appropriately counseled regarding the potential risks **associated with biopsy collection** and documentation of the decision process will be included in the participants' study documents. Rapid PSRT consultation can be requested at IoR discretion, if needed.

23. Section 7.1, *Screening Visit*, first paragraph and Table 2: *Screening Visit*, the note at the bottom of the table have been updated:

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A Screening Visit may take place up to 42 days prior to the Visit 2: Enrollment/**Study Product Admin. Visit**/Initiate Period 1 Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent will be obtained before any study procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

[...]

* If indicated, *To be collected/performed during the screening process at the US site on all women who have not already had their screening terminated due to ineligibility. **(samples to be collected are for gene expression only).**

24. Section 7.2, Visit 2: *Enrollment (Day 0)/ Study Product Administration Visit/ Initiate Period 1*, has been updated:

Visit 2: Enrollment (Day 0)/ **Study Product Administration Visit**/ Initiate Period 1

Once ineligibility is determined at Visit 2: Enrollment (Day 0)/ **Study Product Administration Visit**/ Initiate Period 1 all procedures will discontinue.

Table 43: Enrollment (Day 0)/ **Study Product Administration Visit**/ Initiate Period 1

Visit 2: Enrollment Visit/ Study Product Administration Visit / Initiate Period 1	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> • Schedule next visit and follow-up safety phone call • SMS training*
Behavioral/Counseling	<ul style="list-style-type: none"> • Administer baseline behavioral assessment
Clinical	<ul style="list-style-type: none"> • Vaginal/Rectal dose observation

25. Section 7.3, *Visits 3-15: Study Product Administration Visits*, has been added:

7.3 Visits 3-15: Study Product Administration Visits

Table 4: **Visits 3-15: Study Product Administration Visits**

Visits 3-15: Study Product Administration Visits	
Component	Procedures
Administrative and Regulatory	Review/update locator information Reimbursement Schedule next visit*
Clinical	Collect AEs Review/update concomitant medications Vaginal/Rectal dose observation Treat for UTIs/RTIs/STIs or refer*
Study Product Supply	<ul style="list-style-type: none"> • Provide study product • Provision of panty liners* • Provision of lubricant* • Provision of condoms* • Collect unused study product ▲

* If indicated, ▲ to be performed at the final study product administration visit

26. Section 7.4, *Visit 16: Period 1 End (Day 14)*, has been updated:

Table 45: Visit 316: Period 1 End (Day 14)

Visit 316: Period 1 End (Day 14)	
Component	Procedures
Behavioral/Counseling	<ul style="list-style-type: none"> Administer adherence assessment Complete Study Product Dosing Assessment
Study Product Supply	<ul style="list-style-type: none"> Collect unused study product*

* If indicated, ■ All participants at the US site only. See Section 7.124 for additional details.

27. Section 7.6, *Visit 5: 18: Study Product Administration/Initiate Period 2 (Day 56-75*)*, has been updated:

The PSRT must be consulted regarding progression into the next dosing period prior to the initiation of study product for Period 2, for any participant who has unresolved abdominal–or, genital, or **anorectal** AEs of any Grade or unresolved Grade 3 or 4 AEs regardless of organ system.

Table 67: Visit 5-18 Study Product Administration/Initiate Period 2 (Day 56-75)

Visit 5-18: Study Product Administration/Initiate Period 2 (Day 56-75*)	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> Schedule next visit and follow-up safety phone call SMS training*
Clinical	<ul style="list-style-type: none"> Vaginal/Rectal dose observation

28. Section 7.7, Study Product Administration Visits, has been added:

Section 7.7, Visits 19-31: Study Product Administration Visits

Table 8: Visits 19-31: Study Product Administration Visits

Visits 19-31: Study Product Administration Visits	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> Review/update locator information Reimbursement Schedule next visit*
Clinical	<ul style="list-style-type: none"> Collect AEs Review/update concomitant medications Vaginal/Rectal dose observation Treat for UTIs/RTIs/STIs or refer*
Study Product Supply	<ul style="list-style-type: none"> Provide study product Provision of panty liners* Provision of lubricant* Provision of condoms* Collect unused study product ▲

* If indicated, ▲ to be performed at the final study product administration visit

29. Section 7.8, *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89*)*, has been updated:

Visit **632**: Period 2 End/Final Clinic Visit (Day 70-89*)

* Visit schedule will vary based upon participants' menses.

Table ~~79~~: Visit **632**: Period 2 End/Final Clinic Visit (Day 70-89)*

Visit 632 : Period 2 End/Final Clinic Visit (Day 70-89)*	
Component	Procedures
	•
Behavioral/Counseling	<ul style="list-style-type: none"> • Adherence assessment • Conduct in-depth interview • Complete Study Product Dosing Assessment • Provide counseling <ul style="list-style-type: none"> ○ HIV pre-and post-test[‡]
Study Product Supply	• Collect unused study product*

* If indicated, [‡] All participants at the US site only. See Section 7.124 for additional details.

30. Section 7.9, *Safety Phone Calls*, visit numbering has been updated:

Approximately one week following Visit ~~2~~, ~~Visit 3~~, ~~Visit 516~~ and Visit **632**, study staff will contact participants to inquire about AEs that they might have experienced as a result of the study product or procedures performed during the previous visits. The phone call that follows the Visit **632** is Study Termination.

Table 2: Safety Phone Calls

Safety Phone Calls	
Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> • Reimbursement~ • Locator information • Schedule interim visit*
Clinical	• Record/update AEs

~ Sites to reference SOPs regarding participant reimbursement, * If indicated

31. Section 7.10.3, *Participants Who Permanently Discontinue for Other Reasons*, the second paragraph has been revised and the first bullet has been added:

In the event site study follow-up visits and procedures are continued, all protocol-specified study **visits and** procedures will continue except the following:

- **Study Product Administration Visits/Procedures**

32. Section 7.11, *Participants Who Temporarily Hold Study Product*, the first sentence has been revised and the following has been added as the first bullet:

All protocol-specified study **visits and** procedures will continue except the following:

- **Study Product Administration Visits/Procedures**

33. Section 7.13, *Pharmacokinetics/Pharmacodynamics*, visit titles have been updated:

All study participants will have the following samples collected to assess PK and PD.

Table 3: PK/PD Specimen Collection Schedule

Visit	Specimens Collected for PK	Specimens Collected for PD
Visit 2: Enrollment/ Study Product Admin. Visit/ Initiate Period 1 (Day 0)		<ul style="list-style-type: none"> ● Rectal fluid ● CVL
Visit 316 : Period 1 End	<ul style="list-style-type: none"> ● Blood ● Vaginal fluid ● Rectal fluid ● CVL ● Cervical cytobrush 	<ul style="list-style-type: none"> ● Rectal fluid ● CVL
Visit 518 : Study Product Admin. Visit/ Initiate Period 2	<ul style="list-style-type: none"> ● Blood ● Vaginal fluid ● Rectal fluid ● CVL 	<ul style="list-style-type: none"> ● Rectal fluid ● CVL
Visit 632 : Period 2 End	<ul style="list-style-type: none"> ● Blood ● Vaginal fluid ● Rectal fluid ● CVL ● Cervical cytobrush 	<ul style="list-style-type: none"> ● Rectal fluid ● CVL

34. Section 7.14, *Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset*, the second paragraph, fourth paragraph and Table 12 have been modified:

[...]

Biopsy procedural counseling will precede each biopsy collection. Counseling will include, but not be limited to the following information: Participants will be asked to refrain from the use of NSAIDs, aspirin and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours prior to and following mucosal biopsy collection. During the counseling session participants will be instructed to abstain from inserting ~~anything~~**any non-study product** into the vagina or rectum, including abstaining from sexual activity ~~and gel use~~, for 72 hours before and after the collection of samples. All heterosexually-active participants will be reminded of the importance of using male condoms with each sex act, as all biopsy subset participants will be at increased risk of HIV/STI transmission following biopsy collection. In the event that a participant reports prohibited medication/practices the site should reference Section 6.7.

~~Should~~**At the time of biopsy collection, if** a pelvic or rectal exam finding ~~at the time of biopsy~~ **is** suggestive of cervicitis, vaginitis, proctitis or another inflammatory condition, the IoR ~~should~~**will** use discretion ~~as to whether~~**with regard** to proceeding with the biopsy collection.

[...]

Table 412: Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset Sample Collection

Visit	Specimens Collected for PK	Specimens Collected for Microarray
Visit 1: Screening		<ul style="list-style-type: none"> ● 1 Vaginal Biopsy [■] ● 1 Rectal Biopsy [■]
Visit 316 : Period 1 End	<ul style="list-style-type: none"> ● 2 Vaginal Biopsies ● 4 Rectal Biopsies 	<ul style="list-style-type: none"> ● 1 Vaginal Biopsy ● 2 Rectal Biopsies
Visit 632 :	<ul style="list-style-type: none"> ● 2 Vaginal Biopsies 	<ul style="list-style-type: none"> ● 1 Vaginal Biopsy

Period 2 End	• 4 Rectal Biopsies	• 2 Rectal Biopsies
--------------	---------------------	---------------------

Former section X.X, Behavioral Measures has been removed:

Quantitative

~~A quantitative behavioral assessment conducted at baseline will be structured around the following topics:~~

~~History of anal intercourse and practices~~

~~Partnership status~~

~~Intra-vaginal practices~~

Qualitative

~~The primary behavioral study aims will be addressed in an in-depth qualitative interview, to be conducted at the end of Period 2 that addresses use of study product during the trial. This interview will be conducted by a trained study interviewer and will follow a structured interview guide. The interview will last approximately 30 minutes and will be modeled off of previously completed and/or ongoing MTN studies with in-depth interviews. The interview will be audio recorded and transcribed.~~

~~The interview guide will be structured around the following topics:~~

~~Intra-vaginal practices~~

~~Reasons for product non-use~~

~~Sexual activity*~~

~~Timing of sexual activity in relationship to study product use*~~

~~Male condom use (frequency and in combination with study product)*~~

~~Experiences using study product, including obstacles to use, side effects and partner involvement*~~

~~*The interview may be modified based upon participant's sexual activity~~

35. Section 7.15, *Clinical Evaluations and Procedures*, minor edits have been made to the *Pelvic Examination* section and the *Rectal Examinations and Specimen Collection* section:

Pelvic Examination and Specimen Collection

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>. The required sequence of procedures and specimen collection to be performed during **the** pelvic exams will be specified in the MTN-014 SSP Manual.

Rectal Examination and Specimen Collection

~~Rectal examinations~~ **and specimen collection** will be conducted per guidelines provided in the SSP. The required sequence of procedures and specimen collection to be performed during the rectal exam will be specified in the MTN-014 SSP.

36. Section 7.17, *Specimen Collection and Processing*, the reference to the MTN Network Laboratory Manual has been removed from the first paragraph:

~~Each study site will adhere to the standards of good clinical laboratory practice, the MTN Network Laboratory Manual (www.mtnstopshiv.org), in accordance with current DAIDS Laboratory Requirements, MTN-014 Study Specific Procedures Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory.[...]~~

37. Section 9.3, *General Criteria for Temporary Hold and Permanent Discontinuation of Study Product*, the fourth bullet has been modified to include PrEP use:

- Report of use of post-exposure prophylaxis (PEP) or **Pre-exposure prophylaxis (PrEP)** for HIV exposure-(permanent discontinuation)

38. Section 9.7, *Pregnancy*, the first and third paragraphs have been updated to designate the appropriate visit names:

All study participants are required to be using an effective method of contraception according to Section 5.2 at Visit 2: Enrollment/**Study Product Admin Visit**/Initiate Period 1 (Day 0). Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

[...]

A participant who is pregnant at the ~~Termination~~**Final Clinic** Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes are reported on relevant CRFs; outcomes meeting criteria for EAE reporting also are reported on EAE forms.

39. Section 10.2.3, *Exploratory Study Endpoints*, the behavioral endpoints have been removed:

Consistent with the exploratory study objectives, the following exploratory endpoints will be assessed:

- Inhibition of HIV by drug in rectal and genital fluids
- Changes in pH, microflora, biomarkers and gene expression
- ~~Participant self-reported timing of gel insertion in relation to vaginal and rectal intercourse~~
- ~~Participant self-report of partner's response to vaginal and rectal gel use~~
- ~~Participant self-report of vaginal and rectal non-sexual practices.~~

40. Section 10.4, *Randomization Procedures*, the sixth sentence has been removed as the language is no longer appropriate:

~~In an unblinded product trial, special care needs to be taken to assure that the study staff cannot control or guess the sequence assignment.~~

41. Section 10.5, *Participant Accrual and Retention*, the first paragraph has been modified:

The accrual period is expected to require approximately ~~6~~**10** months. The study will enroll 28 women.

42. Section 13.4.1, *Risks*, in the *General* section, the fourth and fifth paragraphs have been modified:

Site staff will make every effort to protect participant privacy while in the study. Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection), **off site visits may allow for participants study involvement to become known to others**). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

~~Receiving and Replying to Text Messages~~

~~For participants who opt-in to receiving text messages, it is possible that others may become aware of her participation in this study and she may be treated unfairly or discriminated against. Language used in the text messages will help to ensure that participant's study participation is kept confidential.~~

43. Section 13.4.1, *Risks*, a new section pertaining to directly observed therapy has been added:

Directly Observed Dosing

Participants may experience embarrassment or nervousness while being observed inserting the study product or while the study product is being inserted.

44. Appendix I: *Schedule of Study Visits and Evaluations*, has been updated:

	Visit 1 SCR	Visit 2 ENR Study Product Admin. Visit/ Initiate Period 1 Initiate/ENR (Day 0)	Safety Phone Call Visits 3-15, Study Product Admin Visits	Visit 316 /Period 1 End. (Day 14)	Safety Phone Call	Visit4 Visit 17 Washout Visit (Day 35)	Visit 18 Study Product Admin Visit/ Initiate Period 2 Initiate (Day 56- 75))*	Safety Phone Call Visits 19-31 Study Product Admin Visits	Visit 632 Period 2 End/ Final Clinic: (Day 70-89)*	Safety Phone Call/ Termination (Day 77- 96)*
ADMINISTRATIVE AND REGULATORY										
Reimbursement	X	X	-X	X	~	X	X	-X	X	~
SMS training										
BEHAVIORAL/COUNSELING										
Behavioral assessment		X								
Adherence assessment				X					X	
In-depth Interview									X	
Study Product Dosing Assessment				X					X	
HIV pre- and post-test counseling	X	X		*		*	X		*X	
Product use instructions and adherence counseling		X					X			
CLINICAL										
Concomitant medications	X	X	X	X		X	X	X	X	
Vaginal/Rectal dose observation		X	X				X	X		
Treatment for UTI/RTI/STIs or refer	*	*	*	*		*	*	*	*	
LABORATORY (vaginal and cervical swabs as required)										

CVL for PK, PD and biomarkers		X (PD and biomarkers only) ◊		X			X		X	
Vaginal biopsies for PK and gene expression microarray	∞ (for gene expression only)			■					■	
Rectal fluid for PK, PD and biomarkers		X (PD and biomarkers only) ◊		X			X		X	
Rectal biopsies for PK and gene expression microarray	∞ (for gene expression only)			■					■	
STUDY PRODUCT/SUPPLIES										
Provision of study condoms	*	*	*	*		*	*	*	*	
Provision of panty liners		*	*				*	*		
Provision of study product		X	X				X	X		
Provision of lubricant		*	*				*	*		
Collect unused study product			▲	X*				▲	X*	

*= If indicated ∞=To be collected at the US site on all women who have not already had their screening terminated due to ineligibility, (samples to be collected for gene expression only), ■= To be collected on a subset of approximately 14 US participants, ~=Sites to reference SOPs regarding participant reimbursement, ◊= PD and biomarkers only, ▲= to be performed at the final

45. The following modifications have been made to Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*:

The cover page of the Sample Informed Consent Form now includes all funders:

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, **NICHD, NIMH, NIH**

The *Do I have to join this study?* section has been revised:

You do not have to join this study if you do not want to. It is also possible that if you want to join this study you may not be able to. It is important that you know that regardless of whether or not you join this study, your relationship with this clinic or the staff will not change. You may still get the care you need, or be referred for care. You can change your mind later if you decide to join today. You may be asked to supply the reason why you changed your mind about participating in the study. Once you read this form and ~~understand~~ **are aware of** the study **and required procedures**, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

The *Why is this research being done?* section has been revised:

If you agree and are eligible to participate in this study, you will be asked to ~~use~~ **come to the clinic to use** a study gel for 14 days vaginally and for 14 days rectally. The study gel contains an antiretroviral drug called tenofovir. **An oral tablet form of this drug, called Viread[®], is licensed, as part of a combination therapy, for the treatment of HIV, and hepatitis B in individuals 12 years of age and older. HIV is the virus that causes AIDS.** Antiretroviral drugs stop or slow the activity of retroviruses such as HIV. ~~HIV is the virus that causes AIDS.~~

The main purpose of this study is to see where the study drug (tenofovir) goes, when it is applied **in a gel form** vaginally vs. when it is applied **in a gel form** rectally. We are studying the “pharmacokinetics” of tenofovir. Pharmacokinetics is the study of the way a drug enters and leaves the blood and tissue over time. For example, we will measure how much tenofovir passes from the gel and goes into the blood when used vaginally vs. rectally.

This study gel is experimental. While the gel has been tested before in men and women rectally, this is the first time the **reduced-glycerin tenofovir** gel will be tested vaginally. ~~When~~ **As part of the gel was MTN-007 study 65 healthy men and women at 3 trial sites in the US inserted the gel rectally, and it was found to be safe. As a follow-up to the MTN-007 study, MTN-017 will further test the safety of the reduced-glycerin tenofovir gel among 186 men and transgender women at clinical trial sites in Peru, South Africa, Thailand and the United States.**

It is important that you know that a gel very similar to this one has been tested ~~vaginally in over one thousand women~~ **several studies** and it has been found to be safe **when used vaginally.** ~~This study gel is~~ **For example, in CAPRISA 004 when 445 women used tenofovir gel before and after sex, it was found to be safe and effective in preventing HIV infection amongst women from KwaZulu-Natal, South Africa. Currently, former CAPRISA 004 participants are being invited to join the CAPRISA 008 Study in which they will use gel before and after sex. This study will continue to assess the safety and effectiveness of tenofovir gel when provided through family planning clinics in KwaZulu-Natal, South Africa. An additional study, the FACTS 001 study, is currently enrolling 2900 women across sites in South Africa and will provide more information on the safety and effectiveness of tenofovir gel. Results of FACTS 001 are expected mid-2015. It is important to note that the gel also appeared to be safe when used by 1007 women during the VOICE trial conducted in South Africa, Zimbabwe and Uganda, however few women used tenofovir gel as instructed (daily). The study did not show that tenofovir gel prevented women from becoming HIV infected.**

The gel in this study, MTN-014, is expected to be as safe as, or safer ~~than~~ **for vaginal use than** the other gel, ~~which has already been tested vaginally, but~~ **however** we cannot be sure until it has been tested in a clinical trial. If you want additional information about studies that have completed, or those that are currently ongoing, please ask a study staff member for this information and they will provide it to you.

Who will be in this research study and what will I be asked to do if I join? section has been revised:

Each participant will be randomly assigned (chosen “by lot” [or other equivalent local term, for example, flipping a coin]) to the order in which study product will be used, ~~but regardless.~~ **Regardless** of the order assigned, all participants will use the study gel vaginally for two weeks and rectally for two weeks. Neither you nor the study staff can choose or change the order in which you will use the products.

Screening Procedures, Study Staff Will, section the second bullet and final bullet have been modified:

[...]

- Talk with you about the requirements of this study, such as the need to abstain from inserting ~~anything~~ **any non-study products** into your vagina or rectum for 24 hours prior to your study visits and you must refrain from inserting any non-study vaginal or rectal products or objects into your vagina or rectum during your product use periods. These products include spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps, vaginal/rectal douches, enemas, lubricants, sex toys and tampons. Study provided lubricant may be used to assist in **the rectal** insertion of the study applicator. In addition, you must not take part in other research studies involving drugs, medical devices, or vaginal/rectal products for the whole time you are in this study.

[...]

- Results of tests listed above will be available within [site to specify timeframe] of your visit. The study staff will review your test results ~~when they are available. You may return when the results are available. The study staff will review the study again with you and answer any questions you may have, at that time we will schedule next visit if you are eligible and willing.~~ **with you when they are available.**

In the *Tissue Samples* section the *[Sites participating in the Rectal and Vaginal Tissue Subset please insert the following language:]* section has been updated:

At ~~other~~ **Screening, Visit 316** and **Visit 632** more biopsies will be collected, see below:

Visit	Number of biopsies collected	
	Vaginal	Rectal
Screening	1	1
Visit 316 : Period 1 End Visit (Day 14)	3	6
Visit 632 : Period 2 End Visit (Day 70-89)	3	6
Total	7	13

Study staff will talk to you about a few of important things to avoid doing prior to and following the collection of your biopsies. It is important that you do not put ~~anything~~ **any non-study product** in your rectum or vagina for 3 days before the collection of the biopsies or for 3 days after, this includes having vaginal sex and anal sex, because you may be at higher risk for getting or spreading an infection until the biopsy sites have healed. It is important that you continue to use condoms every time you have sex, regardless of how many days it has been since your biopsies were collected. If you have inserted anything into your rectum or vagina in the past 3 days it is important that you tell a member of the study staff. You should also not take medicine that may cause you to bleed easily for 3 days prior to the collection of these samples and for 3 days after the collection of the samples. Study staff can tell you which medicines to avoid.

Enrollment and Follow-up Procedures section has been modified:

If you are eligible, your next visit will be within 42 days of today's visit. That visit is called, Enrollment/**Study Product Admin./Initiate Period 1 Visit (Visit 2)**.

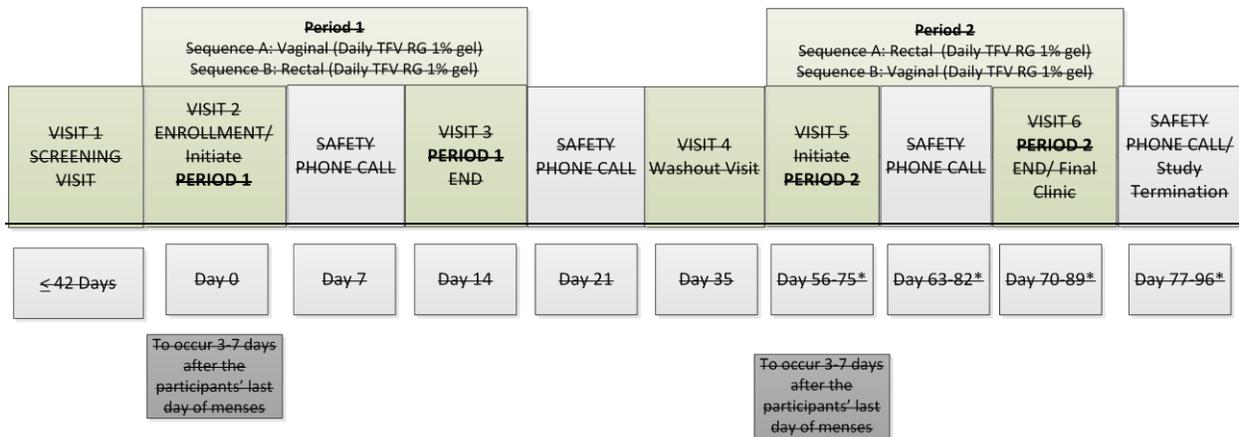
This study has 2 periods and each period lasts about two weeks. **You will begin using study product at the Enrollment/Study Product Admin./Initiate Period 1 Visit (Visit 2). Your Period Start Visits will need to fall approximately 3-7 days after the last day of your period. You will use the study product rectally for 14 days and vaginally for 14 days. During the two periods you will be asked to come into the clinic every day, including Saturdays and Sundays to insert the study gel in the clinic. The insertion of this gel will be observed. This means that study staff will watch you insert the gel [Site to insert as appropriate: or will assist you with inserting the gel, if needed].**The periods are separated by an approximately 6 week washout period. A washout period can be described as a period of time when participants do not take study product. This period of time will ensure that the study drug

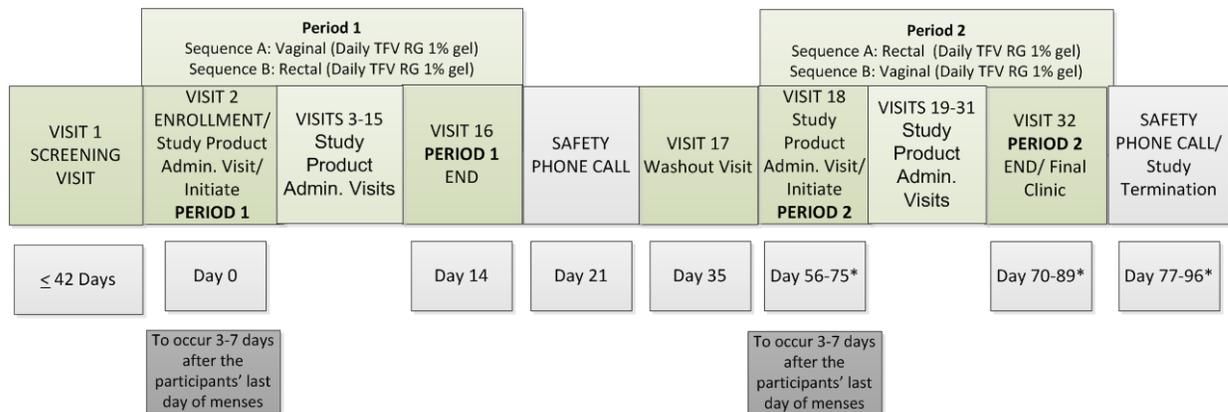
has time to leave your body before you begin using study product in Period 2. **You will come into the clinic once during this washout period.**

You will be in the study for approximately ~~4-10-13~~ **10-13** weeks, **depending upon the timing of your menstrual cycle**, from the time you enter the study up until your follow-up phone call at the end of the study.- The study visit schedule may change and be longer depending upon your menstrual cycle, because it is important that you start using the product around the same time in your cycle for both periods. You will use the study gel for a total of 28 days. ~~You will never use the study product more than 14 days.~~ ~~Most of the visits will take [insert approximate of time]~~ **You will never use the study product more than 14 days in a row, and it is important that you come into the clinic for each dose. You will be given extra doses during each period in the event that you are not able to make it to the clinic [Site to insert as appropriate: or able to make alternative arrangements with study staff to bring you study gel and observe the administration of the product]. When gel is administered at home, it should be applied at approximately the same time of day as all other doses, if possible.**

~~You will begin using study product at the Enrollment/~~ **The visits when you come to the clinic to insert your gel will take [insert approximate of time]. The other visits will take [insert approximate of time].**

The visit schedule is shown below:





At your Enrollment Visit, you will have the following study procedures: section has been updated:

- At your Enrollment Visit/ Period 1 Start, you will answer questions to confirm that you are able to join the study including whether you are using an effective method of contraception and intending to use that method for the entire time that you are in this ~~trial~~**study**. Acceptable methods of contraception for this study include:
[...]
- ~~In addition, you must agree to abstain from inserting anything into your vagina or rectum for 24 hours prior to your scheduled study clinics, and you~~**You must agree to refrain from inserting in any non-study vaginal or rectal products or objects into the vagina or rectum during ~~the~~your study product use periods. In addition, 24 hours before the Enrollment Visit, Study Product Administration/Initiate Period 2 Visit, and Period End Visits you must agree to abstain from inserting any non-study product or object into your vagina or rectum.**
- Also at the Enrollment Visit, if you are found to be eligible, you will be told the order in which you will use the **study** product.
- **Study product will be inserted in the clinic. You will be asked to come into the clinic [or meet with study staff at an alternative location] every day for the next 13 days to use study gel, this same visit schedule will be repeated during the second period.**
[...]
- ~~Answer questions about your vaginal and rectal practices, including answering questions about your partner, if you have one. These questions may be asked on a computer, study staff will teach you how to use the computer, if needed.~~

The following clinical procedures will be performed: section has been modified:

The following clinical procedures will be performed **at some visits (but not the visits when you only come into the clinic to insert the gel)**:

- ~~At some visits a~~**A** blood sample [sites to insert amount] will be taken to test:
[...]
- You must receive your HIV test results to stay in the study. You will talk with study staff about the meaning of your tests and about feelings you may have about the results. If your HIV test is positive, you may be offered additional blood tests, [sites to insert blood volumes per local regulatory requirements- XX mL] if the study doctor and researchers think that it would benefit you. ~~Additional tests include, but are not limited to, a test to find out how changes in HIV may affect how well some HIV drugs work (HIV drug resistance) and a CD4-positive T cell count. The CD4-positive T cell count will measure the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections.~~ **Study**

staff will provide you more information about additional blood tests if the tests are determined to be needed. You will be referred to available sources of medical care and other services that you may need.

[...]

- A rectal exam will be performed at **all period initiation and period end visits**, ~~except at the Washout Visit~~. To collect these samples the clinician and/or designee will need to insert a short hollow tube called an anoscope inside your rectum. The clinician will insert swabs and/or sponges through the hollow tube to test:
[...]
- A pelvic ~~examination~~ **exam** will be performed at **all period initiation and period end visits**, ~~except at the Washout Visits~~. Vaginal and/or cervical fluid will be taken and may be used to test:
[...]
- A cervicovaginal lavage (CVL) will be performed ~~at period initiation and period end visits~~. For CVL, a clinician rinses your vagina and cervix with about 2 teaspoons [SITES TO INSERT LOCAL EQUIVALENT] of sterile fluid and collects that fluid into a tube for testing. This fluid will be used to look for proteins and cytokines. Researchers will also use this fluid to see how it protects against HIV in the laboratory and how much of the study drug is in your vaginal fluids

You will be asked to use study product for 2 weeks vaginally and for 2 weeks rectally; as part of using study product you will;, section has been revised:

[...]

- **Be asked to come into the clinic to insert your study gel. [Site allowing off-site visits: Alternatively, you can make arrangements with study staff to meet you at a location that is convenient for you and the study staff.]**
[...]
- Be asked to bring unused gel applicators with you to your **period end visits** ~~so that they can be counted by study staff~~
- Be called by study staff about one week after ~~starting study product~~ **Period 1 end visit** and one week after ~~ending study product use~~ **Period 2 end visit**, so that you can report any health problems or other problems since your last visit. You can always call study staff if you have any problems related to the study product or your participation in this study.
~~Talk with study staff in an interview at the end of the study (after using the product for 14 days vaginally and after using the product for 14 days rectally). Study staff will ask you questions about your vaginal practices, sexual activity, condom use and various questions about your experience using the study gel. This session will be audio-recorded and transcribed. The session will take about 30 minutes.~~

Optional Study Activities, section has been removed:

~~Optional Study Activities:~~

~~The following procedure is an optional study activity. You do not have to agree to participate in this activity to join this study.~~

~~If you agree to participate, you will answer a few short questions by cell phone via text message that will ask about your use of the study product. Language used in the text messages will help to ensure that your study participation is kept confidential. These messages will be sent daily during the two product use periods. We will schedule you to receive a text during a specified block of time and you can answer at your convenience within 24 hours. You will receive instructions on how to reply to these messages and how to delete them. In addition, you will be reimbursed for the costs associated with each text message. Text messages will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded.~~

Risks:

~~We will make every effort to protect your privacy, however when you send and receive text messages, it is possible that others may see the information on your phone and find out about your participation in this study. This is unlikely as questions will be asked in a way that keeps your study participation confidential, however it is still possible. Because of this they may treat you unfairly or discriminate against you. You will be shown how to erase the text messages from your cell phone by study staff.~~

~~_____ Yes, I agree to receive and reply to text messages asking about my product use.
Initials & Date~~

~~_____ No, I do not agree to receive and reply to text messages asking about my product use.
Initials & Date~~

*Other possible risks:*section has been updated:

[...]

- **You may become embarrassed or nervous while study product use is being observed.**

[...]

- ~~● When staff talk with you about how and when you used the study products they will audio record the discussion using a digital audio recorder. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. The audio recordings will be destroyed as soon as they have been put into writing, usually this is about three months after your interview. The person in charge at this site will make sure that these records have been destroyed. You should NOT identify anyone in the in-depth interviews and any names that might be mentioned on the recording will NOT be noted. Instead a generic description will be used in the transcript (i.e., if you refer to a friend's name, "FRIEND1" will be noted).~~

[...]

- We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. ~~Finding out your HIV status could also cause problems between you and your partner.~~ Also, you could face problems in your relationships associated with study product use. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

[...]

- ~~● It is possible that your participation in this study could become known to others. This may cause you problems. You are encouraged to tell study staff about any issues you have as a result of taking part in this study.~~

[...]

~~We will make every effort to protect your privacy while you are having the study visits, exams, and tests. Reports via computer will be stored in computers that are password-protected and will not include personal information that could identify or link information to you; only your study ID number will be recorded.~~

Is it possible that I may be taken out of the study without my consent? New final paragraph has been added:

If you stop using the study product, but continue to come in for follow-up visits, your visit schedule and procedures may be modified. Study staff will provide you with more information as changes in your schedule and procedures, as needed.

Will there be any payments if I take part in this research study? section has been modified:

[Site to insert information about local reimbursement:] You will receive [Site to insert amount xx] for your time, effort, and travel to and from the clinic at each scheduled visit. You will receive [Site to insert amount xx] for any visits which occur in between your normally scheduled visits, these are called interim visits. For phone calls you will receive [Site to insert amount xx]. You will not receive payment for costs associated with your pregnancy, if you become pregnant or for your HIV-related care, if you become infected with HIV. ~~[Sites to insert if applicable:] If you are in the subset, you will receive [Site to insert reimbursement amount \$xx] for short message service (SMS)/text messages.~~

[US Sites to insert the following US Internal Revenue Service reporting, as applicable: This compensation for your time, effort and travel is taxable income. If the amount paid to you exceeds \$600 within a calendar year, [your site] will file an IRS form 1099 with the Internal Revenue Service and will mail you a copy.]

What other choices to I have besides this study? section has been updated:

You do not have to participate in this study, if you choose not to do so. ~~[Sites to include/amend the following, if applicable: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about these places if you wish.]~~ Please talk to your doctor about these and other choices that may be available to you.

Can my private health information and samples collected by this study be used for future studies? section has been updated:

There might be a small amount of your biological specimens, such as **urine**, blood, vaginal, cervical and rectal samples, left over after we have done all of the study-related testing after your study visits. We would like to ask your permission to store these samples and health data related to these samples for use in future studies. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. ~~[Non-US site(s) to insert: Some of these research facilities may be outside of your country.]~~ Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have these samples stored for future studies. If you do not want the samples stored, we will destroy the leftover specimens. ~~[[Site outside the US please insert the following language:] Some of the facilities that will store your samples are outside of your country.~~ Any future studies that may be done will also have to be approved by an IRB/EC. ~~[Sites to specify institutional policy:]~~ There is no time limit on how long your samples or health data will be stored or when these leftover specimens may be tested.

CONSENT FOR OFF-SITE VISITS, section has been added:

[Sites to include/amend the following, if applicable:]

CONSENT FOR OFF-SITE VISITS

Members of the research team at this clinic may be able to visit you at a location other than the study clinic as part of the study. Some of the scheduled study visits (Study Product Administration Visits) may take place at a location other than the study clinic, if you agree. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the duration) and procedures to ensure confidentiality. However it is important that you know that off site visits may affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

To conduct visits outside of the clinic we will need your consent. Please read carefully the following statement and initial and date one option. You can choose to not to be visited outside of the study clinic and still participate in this study. You can withdraw your consent for off site visits at any time by providing your request in writing to the person in charge of this study.

_____ I DO agree to be visited at a location other than the study clinic by clinic staff, when necessary
Initials and Date

_____ I DO NOT agree to be visited at a location other than the study clinic by clinic staff, when necessary
Initials and Date

- 46. Rectal exam has been changed to rectal examination throughout the protocol.
- 47. The protocol title, version number and date are updated throughout the protocol document.
- 48. Correction of minor editorial and typographical edits and updates, including updates to table numbers and referenced sections, are made throughout the protocol document.