SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:
MTN-011

DAIDS Protocol #:11825

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/September 30, 2013

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-011 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-011.

Summary of Revisions

- In an effort to afford greater scheduling flexibility, the visit windows and washout periods for Group 1 and Group 2 participants have been lengthened. As a result, the potential maximum study duration has been adjusted. To ensure participant safety, in the event a period of more than 42 days has passed since the couple was last seen in the clinic, HIV and STI testing is required to occur and negative test results must be obtained before study product can be dispensed.
- The sample size has been redefined as 20 evaluable couples per matched-pairs set, rather than 40 couples overall.
- The study duration has been revised to allow accrual to continue for 18 months per site. Throughout the protocol, emphasis has been placed on the completion of matched-pair visit sets and thus provisions have been made to allow for the enrollment of couples within specific matched-pair sets, as needed, in the event that all other sets within a group have been accrued.
- In Section 7, *Study Procedures,* the formatting and organization has been revised. The study visit schedule has been updated to accurately reflect study visits, washout periods and visit windows. Two new tables were added that outline the required visits for participants who are completing specific matched paired visits in Group 1 and Group 2. Section 7.6.4, *Follow-up Procedures for Participants Who Do Not Adhere to the Study Protocol and/or Study Product Regimen* was modified to highlight which procedures should be omitted in the event that participants have not adhered to the study protocol and/or study product regimen, or if they are not able to complete the study visit. Appendix I, *Schedule of Study Visits and Evaluations,* and the Sample Informed Consent documents have been updated accordingly.
- Section 10, *Statistical Considerations*, is modified to reflect the revised study duration and definition of an evaluable matched-pair set.
- Section 6, *Study Product*, has been modified to clarify that, at the discretion of the PSRT, additional study product may be dispensed.
- Appendix IV-VI: *Sample Informed Consents (Screening, Enrollment, Long-term Storage)*, have been updated to reflect modifications to the main protocol.
- Revisions previously included within Letter of Amendment #01 have been incorporated.
- Updates to the protocol version number, date, and roster, as well as minor editorial and typographical edits, including updates to table numbers and referenced sections have been included.

Rationale

The primary purpose of this full version amendment is to expand flexibility of the timing of study visits within the MTN-011 protocol in order to decrease participant burden, and to clarify the criteria that determines evaluability.

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, and primary and secondary objective and endpoint remain consistent with Version 1.0.

The proposed revisions enhance the scientific merit of MTN-011, reinforcing the integrity of all the data generated, and ensures that proper safeguards are in place for participant safety.

Implementation

This amendment is now official MTN-011 protocol documentation. Prior to implementing the revisions listed below, MTN-011 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 the exception of the removal of figures, 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

1. Provision for greater flexibility in scheduling study visits: to allow for greater flexibility regarding the timing of study visits, the elapsed time between visits has been extended throughout the protocol and sample informed consent documents. Specifically, the washout period between visits in a matched-pair set has been extended to a maximum of 56 days and the washout period between sets of matched-pair visits has been extended to a maximum of 90 days. The maximum number of days a female participant may return to the study clinic for Visit 2a for Group 1 and Visit 2 for Group 2 after the last day of her menstrual period has been extended to 12 days. Due to the extension in washout periods, the overall expected duration of study participation from the date of enrollment has been lengthened to approximately 7-55 weeks for Group 1 participants and approximately 14-34 week for Group 2 participants throughout the protocol. In order to ensure participant safety, HIV and STI testing will be required for couples who return to the clinic more than 42 days after their last clinic visit. All of these changes have been updated throughout the protocol and sample informed consent documents.

2. Within the *Protocol Summary*, the Sample Size, Figure 1: Study Design, Table 1: Group 1 Study Visit Schedule, and Table 2: Group 2 Study Visit Schedule have been updated.

Sample Size: Approximately ~~40~~**20 evaluable** couples **per matched-pair visit**

Figure 1, the Study Groups Figure has been removed and it has been replaced by a new study design figure:

Figure 1: Study ~~Groups~~**Design**

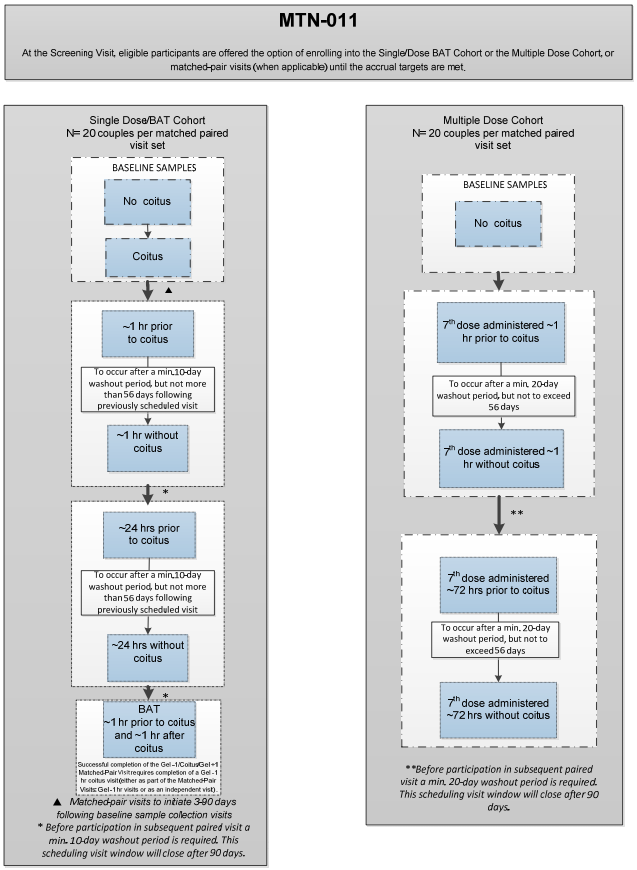

Table 1: *Group 1 Study Visit Schedule* has been updated:

Group 1- Single Dose/BAT Cohort				
Gel	Visit	Visit Name	Coitus (following the visit)	Study Product Dispensed
	1 ♂♀	Screening		
	2a ♂♀	Enrollment/ No Gel/ Coitus	X	
	2b♀	Post-Coital Sampling		
-1 hr	3a ♂♀	Gel -1/Coitus	X	X
	3b♀	Post-Coital Sampling		
	4a ♀	Gel -1/No Coitus		X
	4b ♀	Sampling		
-24 hr	5a ♂♀	Gel -24/Coitus	X	X
	5b ♀	Post-Coital Sampling		
	6a ♀	Gel -24/No Coitus		X
	6b ♀	Sampling		
BAT	7a ♂♀	Gel -1/Coitus/ Gel +1	X	X
	7b/ Final ♂♀	Post-Coital Sampling		

♀= female ♂= male, *scheduling guidance, including guidance for participants who are amenorrhoeic and for participants completing specific matched-pair visits, can be found in the SSP Manual.

Table 2: *Group 2 Study Visit Schedule* has been updated:

Group 2- Multiple Dose Cohort				
Gel	Visit	Visit Name	Coitus (following the visit)	Study Product Dispensed
	1 ♂♀	Screening		
	2 ♂♀	Enrollment- Provision of Study Product		X
-1 hr	3a ♂♀	Gel -1/Coitus	X	X
	3b ♀	Post-Coital Sampling		
	4 ♀	Provision of Study Product		X
	5 ♀	Sampling for Gel -1/No Coitus		X
-72 hr	6 ♀	Provision of Study Product		X
	7a ♂♀	Gel -72/Coitus	X	
	7b ♀	Post-Coital Sampling		
	8 ♀	Provision of Study Product		X
	9/ Final ♂♀	Sampling for Gel -72/No Coitus		

♀= female ♂= male *scheduling guidance, including guidance for participants who are amenorrhoeic and for participants completing specific matched-pair visits, can be found in the SSP Manual.

3. Modifications have been made to the following sections to clarify information regarding enrollment in matched-pair sets, the required clinic visits for the completion of matched-pair sets, and definition of an evaluable couple for a matched-pair set.

   Sections 7.3.2, 7.4, 7.5.2, and 10.4

   Section 7.3.2, *Group 1 – Required Clinic Visits for the Completion of Matched-Pair Sets*
   […]
   For the Matched-Pair Visit Set -1 hr, -24 hrs, Gel -1/Coitus/ Gel +1 (BAT), the following study clinic visits and above-mentioned procedures are to be completed, see the MTN-011 SSP for additional details.

Table 10: Group 1-Required Clinic Visits for the Completion of the Matched-Pair Sets

Gel	Visit	Visit Name	Matched-Pair Visit Set -1 hr	Matched-Pair Visit Set -24 hrs	Matched-Pair Visit Set Gel -1/Coitus/ Gel +1
	1 ♂♀	Screening	X		
	2a ♂♀	Enrollment/ No Gel/ Coitus	X		
	2b♀	Post-Coital Sampling	X		
-1 hr	3a ♂♀	Gel -1/Coitus	X		X
	3b♀	Post-Coital Sampling	X		X
	4a ♀	Gel -1/No Coitus	X		
	4b ♀	Sampling	X		
-24 hr	5a ♂♀	Gel -24/Coitus		X	
	5b ♀	Post-Coital Sampling		X	
	6a ♀	Gel -24/No Coitus		X	
	6b ♀	Sampling		X	
BAT	7a ♂♀	Gel -1/Coitus/ Gel +1			X
	7b/ Final ♂♀	Post-Coital Sampling			X

Note: Visits previously completed need not be repeated, i.e., Screening and Enrollment, provided that participants have not exceeded the allowable visit windows. Washout periods are required as described in Table 5.

Section 7.4, *Group 2 (Multiple Dose Cohort)- Screening Visit (Visit 1), Table 11* omits Baseline CVL at Screening:
[…]
♀= female ♂= male, *-scheduling guidance**, including guidance*** for participants who are amenorrhoeic **and for participants completing specific matched-pair visits,** can be found in the SSP Manual.

~~*Note: All follow-up*~~***Note: The Targeted Visit Schedule applies to participants completing all Group 2- Multiple Dose Cohort visits, the schedule will be adjusted for participants completing matched-pair visits, see SSP Manual.***

Section 7.5.2, *Group 2– Required Clinic Visits for the Completion of Matched-Pair Sets*

Upon completion of accrual for specific matched-pair sets, subsequent enrollments will be closed for that specific set and potential participants will only be allowed to screen/enroll into the matched-pair sets with remaining accrual slots.

For the Matched-Pair Visit Set -1 hr and -72 hrs, the following study clinic visits and above-mentioned procedures are to be completed, see the MTN-011 SSP for additional details.

Table 17: Group 2-Required Clinic Visits for the Completion of the Matched-Pair Sets

Gel	Visit	Visit Name	Matched-Pair Visit -1 hr	Matched-Pair Visit -72 hrs
	1 ♂♀	Screening	X	
	2 ♂♀	Enrollment- Provision of Study Product	X	
-1 hr	3a ♂♀	Gel -1/Coitus	X	
	3b ♀	Post-Coital Sampling	X	
	4 ♀	Provision of Study Product	X	
	5 ♀	Sampling	X	
-72 hr	6 ♀	Provision of Study Product		
	7a ♂♀	Gel -72/Coitus		X
	7b ♀	Post-Coital Sampling		X
	8 ♀	Provision of Study Product		X
	9/Final ♂♀	Sampling		X

Note: Visits previously completed need not be repeated, i.e., Screening and Enrollment, provided that participants have not exceeded the allowable visit windows. Washout periods are required as described in Table 11.

Section 10.4, *Sample Size and Power Calculations*:

The sample size of ~~40~~**20** evaluable couples~~, with 20 couples in~~ **for** each ~~group (Single Dose /BAT Cohort and Multiple Dose Cohort),~~**matched-pair visit set (see Section 10.1 for additional details regarding matched-pair visit sets)** was determined with respect to the primary PK endpoints. […]

Section 10.5, *Participant Accrual, Follow-up and Retention*:

A couple is considered evaluable **for a specific matched-pair set** if ALL of the following have been achieved **for that set**:

- The primary pharmacokinetic endpoints (tenofovir levels from cervicovaginal lavage (CVL) and ~~vaginal/cervical tissue biopsies) are provided~~**plasma) were obtained** at ~~both the~~**all** visits ~~where the female participants dose with gel and engage in coitus and the visits where female participants dose with gel and do not engage~~ in ~~coitus,~~**the set** and
- ~~At each Gel/Sex Visit, the~~**The** couple has completed coitus **at any required coital visits for that set**, and
- ~~In Group 2, gel has been used daily~~**Minimum gel dosing was completed for all visits in the set (Group 1, single dose of gel; Group 2,** at least 5 of the 7 days~~ prior to the study visits~~**).**

~~Couples in Group 1 will be followed for approximately 8 weeks and couples in Group 2 will be followed for approximately 14 weeks.~~

As stated above in the definition of an evaluable couple, to adequately assess the primary PK objective of this study, it is important for each couple to provide complete data throughout follow-up. Thus, target retention should be set at 100%. Once a couple is enrolled in the study, the study site will make every reasonable effort to retain the couple~~ for the entire study period so that they are evaluable~~.

4. In order to provide clarity the following paragraph has been added to Sections 5.1.1, 7.3.2, 7.5.2, and 10.4:

   Upon completion of accrual for specific matched-pair sets, subsequent enrollments will be closed for that specific set and potential participants will only be allowed to screen/enroll into the matched-pair sets with remaining accrual slots.

5. Section 5.1.3, *Other Screening Considerations*, a new third and fourth paragraph have been added.

   Further, a 30 day minimum washout period is required prior to enrollment into the opposite group.

   See the MTN-011 SSP Manual for additional details.

6. Section 5.2, *Inclusion Criteria* and 5.3, Exclusion Criteria, respectively, and throughout the protocol document, the time frame for participants to remain in monogamous relationships was changed from "the next 4 months" to "the duration of study participation".

7. Restriction of the use of systemic immunomodulators, resulting in permanent discontinuation of study product, has been clarified to apply only to female participants; participants who report the use of PrEP within the 6 months prior to Screening will be excluded, further, participants who use PrEP for HIV prevention during study participation will be permanently discontinued from study product.

   Section 5.3, *Exclusion Criteria:*
   1. c. Pre-exposure prophylaxis (PrEP) for HIV prevention within 6 months prior to Screening

   ~~1. g. Currently using or planning to use pharmacologic immune modulator(s)~~

   7a.vi. Currently using or planning to use systemic immune modulator(s) for duration of the study

   Section 6.9, *Prohibited Medication and Practices*:
   […]~~Participants~~ The use of **systemic** immune modulators **by female participants** is prohibited**. Women** requiring the use of these agents should not be included in the trial~~.~~ **and will be permanently discontinued from study product (see Section 9.3).**

   Section 9.3, *General Criteria for Permanent Discontinuation of Study Product*:
   - Report of **PrEP for HIV prevention**

8. Clarification regarding study product administration, dispensation and procedures for missed study product dose and/or study visits has been updated.

   Section 6.2, *Administration,* the second paragraph has been updated:

   ~~When~~**If the female participant fails to administer the minimum number of doses during a study dosing period (Group 1: a single dose, Group 2: five doses), or if the female or male participant is unable to attend a clinic visit, or when** product use is associated with the act of coitus ~~if~~**and** coitus does not occur, the ~~visit will be rescheduled after~~**IoR/designee must consult with the MTN-011 PSRT. Following** a sufficient washout period~~ and~~**,** additional study product ~~will be dispensed.~~**may be provided and visits will be rescheduled at the PSRT's discretion. See Section 7.0 for additional information regarding modifications to the study visit schedule and procedures in the event the minimum numbers of doses are not administered**

   Section 6.5, *Study Product Dispensing*:

   […] The dose in Group 1 and Group 2 that is to be self-administered at the hotel (or comparable site) just prior to coitus will be dispensed ~~on that day~~ at the clinic. Group 2 participants will receive 6 pre-filled applicators of tenofovir 1% gel ~~at the clinic visit just prior to each of the~~ **for** at home administration periods at Visit 2 and Visit 4 **and the seventh dose will be provided at Visit**

3a and Visit 5, respectively.[…] Group 2 participants will receive 7 pre-filled applicators of tenofovir 1% gel ~~at~~**for** the~~ clinic visit just prior to each of the~~ at home administration periods at Visit 6 and Visit 8. This will provide participants with applicators for doses 2-7. […]

Additional study product may be provided at the discretion of the MTN-011 PSRT.

Section 7.6, *Follow-up Procedures for Participants Who Permanently Discontinue Study Product* **or Who Do Not Adhere to the Study Protocol and/or Product Regimen**
[…] ~~Note: IoR discretion will be used for participants suspected of non-monogamy.~~

Section 7.6.4, Follow-up Procedures for Participants Who Do Not Adhere to the Study Protocol and/or Study Product Regimen, added:

If the female participant fails to administer the minimum number of doses during a study dosing period (Group 1: a single dose, Group 2: five doses), or if the female or male participant is unable to complete a clinic visit, or if coitus is not completed (when applicable) study procedures are to be modified.

Modifications to the study visit procedures are as follows:

- **Samples for PK, PD and biomarkers are to be omitted**
- **Behavioral assessments are to be omitted**
- **Pelvic exam and related procedures may be omitted, unless required for AE follow-up**
- **All other safety evaluations are to be omitted, unless required for AE follow-up**
- **Provision of study product and related procedures are to be conducted, if indicated**
- **Coitus and coital related procedures are to be omitted, when applicable**

Further, additional study product may be provided and visits rescheduled at the PSRT's discretion.

If any study product was administered, a minimum washout period of 10-days should be used for Group 1 and 20-days for Group 2.

Section 7, *Study Procedures*:

An overview of the study visit and evaluations schedule is presented in Appendices I and II. Presented in this section is additional information on visit-specific study procedures. **If a couple fails to comply with protocol requirements, the IoR/designee may consult the study PSRT for study product provision guidance.**

9. Section 6.6, *Retrieval of Unused Study Products,* first sentence has been removed.

   ~~It is anticipated that for participants in Group 2 unused applicator will be returned to the study site following each consecutive administration at home, unless a replacement applicator is needed by the participant.~~

10. Section 6.2.1, *Group 1 (Single Dose/BAT Cohort Group),* Table 3 has been revised to include the Screening and Enrollment visits. Within Section 6.2.1, *Group 1 (Single Dose/BAT Cohort Group)* Table 3 and Section 6.2.2, *Group 2 (Multiple Dose Cohort)* Table 4 the *Location of Use* column was removed. Finally, the notation of the collection of baseline CVL at Screening within Table 4 was removed.

11. Section 6.7, *Study Product Counseling and Adherence,* new third paragraph added.

    In the event a participant reports any of the aforementioned prohibited practices, continuation of the study visit procedures will be performed at the IoR's discretion.

12. The following tables have been updated to clarify that modified physical exams will be performed if indicated for male participants, specifies at which study visits HIV/STI risk reduction counseling will be performed, and permits the provision of study product use and study product instructions at Visit 5, Sampling, for Group 2 participants.

    Table 7: Group 1- Visit 2a: Enrollment No Gel/Coitus, Visit 3a: Gel -1/Coitus, Visit 4a: Gel-1 /No Coitus, Visit 5a: Gel -24/Coitus, Visit 6a: Gel -24/No Coitus, Visit 7a: Gel -1/Coitus/ Gel +1

    Table 13: Group 2- Visit 2: Enrollment- Provision of Study Product, Visit 4: Provision of Study Product, Visit 6: Provision of Study Product, Visit 8: Provision of Study Product

    Table 14: Group 2- Visit 3a: Gel -1/Coitus, Visit 7a: Gel -72/Coitus

    Table 15: Group 2- Visit 3b: Post-Coital Sampling, Visit 5: Sampling, Visit 7b: Post-Coital Sampling

    Appendix I, *Schedule Of Study Visits And Evaluations: Group 1*

    Appendix II, *Schedule Of Study Visits And Evaluations: Group 2*

13. Section 7.11, *Laboratory Evaluations,* has been updated to allow for Network Laboratory to confirm HIV-1 seroconversion.

Network Laboratory

- Blood
  - **Confirmation HIV-1 serology for seroconversion**

14. Section 9.5, *Other Clinical Events,* the second paragraph has been updated.

    If any participant has **symptomatic BV, candidiasis or** a symptomatic UTI the participant will be referred for treatment and the visit will be rescheduled after treatment is complete and symptoms have resolved. Further details regarding management of Other Clinical Events will be provided in the SSP (www.mtnstopshiv.org/).

15. Section 13.6, *Participant Confidentiality*, second paragraph has been updated.

    All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. ~~All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.~~ All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

16. The following modifications have been made throughout all *Sample Informed Consent (Screening and Enrollment)* documents (Appendices IV, V, VI, and VII).

    The *Study Product and Procedure Overview* Section, third paragraph has been added:

    > **Toward the end of this study, enrolled couples may be asked to complete a subset of the visits below, rather than the full visit schedule. If this is the case for you and your partner, study staff will provide you with a revised visit schedule at your Enrollment Visit.**

    The *Benefits* Section, last paragraph has been removed:

    > ~~There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about individuals' sexual behaviors.~~

    The *Storage and Future Testing of Specimens* Section has been updated:

    > STORAGE AND FUTURE TESTING OF SPECIMENS **AND ASSOCIATED HEALTH INFORMATION**
    >
    > There might be a small amount of blood, vaginal and cervical fluids and/or tissue 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 your leftover blood, vaginal and cervical fluids and/or tissue **along with associated health information** for ~~testing in~~ future ~~studies.~~**research. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range.** You can still enroll in this study if you decide not to have blood, vaginal and cervical fluids and/or tissue **and associated health information** stored for future studies. If you do not want blood, vaginal and cervical fluids and/or tissue stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

17. The following modifications have been made to Appendix IV: *Sample Informed Consent Document, Group 1 Female (Screening and Enrollment)* and Appendix V: *Sample Informed Consent Document, Group 2 Female (Screening and Enrollment).*

    The following clinical procedures will be performed bullet in the *Enrollment and Study Procedures* Section within Appendix IV and V has been revised as follows:

    Appendix IV, first bullet:

    - The following clinical procedures will be performed:
      - A physical exam will be completed ~~prior~~ at visits when you receive study product and/or before **you** have **sex** with your partner.

    Appendix IV and V, second bullet, first sub-bullet:

    - You will be asked to provide blood samples [INSERT AMOUNT] :
      - To be ~~kept frozen and~~ used~~, only~~ if needed to check on your health or if there are questions about your lab tests, at Visit 2 only

18. The following modifications have been made to Appendix VI*: Sample Informed Consent Document, Group 1 Male (Screening and Enrollment)* and Appendix VII*: Sample Informed Consent Document, Group 2 Male (Screening and Enrollment)*.

    The *What do I have to do if I take part in the Screening Exams and Tests* Section, *Study Staff Will* Section, fourth bullet:

    - ~~Ask you to provide~~**Provide** a semen sample.

    Within *the Enrollment and Study Procedures* Section, the third bullet, second sub-bullet has been updated:

- Have a genital exam~~, if needed~~ **at some visits**

19. Modifications from the MTN-011 Letter of Amendment (LoA) #01 have been incorporated throughout the protocol.

20. Throughout the protocol document the following have been included: updates to the protocol version number, grant numbers, inclusion of an additional funding agency “US Eunice Kennedy Shriver National Institute of Child Health and Human Development”, date, and roster, including the addition of Robert Bucklew, JD, as well as minor editorial and typographical edits, including updates to table numbers and referenced sections.