

## **HIV Prevention Trials Network**

### **AMENDMENT #1**

#### **HPTN 035**

#### **Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women, Version 1.0, dated 24 September 2004**

**Amendment Date: 2 August 2004**

**IND #62,366**

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#### **Rationale for Modifications**

The primary rationale for the modifications included in this protocol amendment is to address questions and comments received during regulatory and ethical review of protocol Version 1.0 (dated 24 September 2003) pertaining to differences in study design and procedures across US and non-US study sites. In addition, the recent finalization of revised DAIDS definitions and procedures for expedited reporting of adverse events, which will be adopted for HPTN 035, requires certain protocol modifications. Finally, ongoing efforts to prepare for study implementation have identified certain aspects of the protocol that require updating, correction, or clarification to ensure consistent interpretation of, and adherence to, protocol specifications and DAIDS and HPTN policies and procedures across study sites.

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#### **Summary of Modifications**

- The total number of study participants is increased to approximately 3220 (320 US and 2900 non-US). The randomization scheme for US participants is modified to 1:1:1:1, such that 80 US participants will be assigned to each of the four study treatment groups. Protocol specifications related to participant accrual and statistical power are updated accordingly.
- The specification for at least four study sites (one US and three non-US) to initiate the study concurrently is removed. A cap on the number of Phase II participants to be accrued at non-US sites is added.

- References to the “DAIDS Serious Adverse Event Reporting Manual for the HPTN” are replaced with references to the newly available “Manual for Expedited Reporting of Adverse Events to DAIDS.” References to “serious adverse events” are replaced with references to “adverse events meeting criteria for expedited reporting” where applicable. The Manual for Expedited Reporting of Adverse Events to DAIDS is added as protocol Appendix VI and the formal title of the DAIDS toxicity table is updated. Clarification of expedited reporting requirements across the four study treatment groups is added.
- References to the Protocol Safety Review Team are added, per standard HPTN safety monitoring procedures.
- Specification of the frequency of DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB) reviews during the Phase IIb portion of the study are updated to correspond with the routine DSMB meeting schedule.
- Clarification of study product packaging and storage conditions is added; references for product ordering procedures are added.
- Clarification of the timing of screening procedures, and the screening procedures to be completed when Enrollment does not take place on the same day as Screening Part 2, is added.
- Clarification of contraindicated contraceptive products and devices is added.
- Procedural specifications are modified to allow all study sites to perform colposcopy on all Phase II participants during the Phase II portion of the study and to discontinue investigational product use among participants who become infected with HIV during follow-up.
- Procedural specifications are modified such that hematology and coagulation testing will be performed at all sites during the Phase IIb portion of the study.
- Procedural specifications for HIV testing at screening are updated to allow the US site to perform an enzyme immunoassay (EIA), since two different rapid tests are not currently available in the US.
- Procedural specifications for HIV testing during follow-up are updated to allow study sites to perform an additional rapid test or EIA if required by local HIV counseling and testing guidelines or regulations and/or if approved by the HPTN Central Laboratory. Clarification of Western blot testing requirements in this context is added.
- Procedural specifications for HIV testing during follow-up are further updated to specify that, for participants who test HIV-positive on their first post-enrollment HIV test, HIV antibody testing will be performed on plasma archived at enrollment to confirm that the participant was HIV-uninfected at enrollment.

- Procedural specifications to perform urine culture are removed.
  - The protocol version number, version date, pagination, and table of contents are updated.
  - The sample informed consent forms in Appendices VII-XIII are updated to reflect other protocol modifications as needed.
  - Other updates, corrections, and clarifications are incorporated.
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### Implementation of Modifications

Prior to implementing the procedures described below, HPTN 035 study sites will submit this amendment, the corresponding protocol Version 2.0, and updated site-specific informed consent forms to all relevant regulatory authorities and Institutional Review Boards and Ethics Committees (IRBs/ECs). The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application #62,366.

Upon receipt of all required regulatory and IRB/EC approvals, completion of protocol registration procedures with the DAIDS Regulatory Compliance Center, and activation by the HPTN Coordinating and Operations Center, the protocol modifications listed below will be implemented. Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

At all sites, the study will be will be activated under protocol Version 2.0. No sites will be activated under protocol Version 1.0 and no participants will document provision of informed consent for screening or enrollment by signing or marking Version 1.0 informed consent forms.

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### Detailed Listing of Modifications

1. Throughout the protocol, the protocol version number and version date are updated, to FINAL Version 2.0 and 2 August 2004, respectively. The list of abbreviations and acronyms, document pagination, and table of contents are updated.
2. On the protocol cover page, Salim Abdool Karim's affiliation is updated. In the Protocol Team Roster, Muzala Kapina Kanyanga replaces Stephen Weiss as the Protocol Co-Chair for Lusaka, Zambia. Zeda Rosenberg is deleted, JoAnn Kuruc is added, and contact details are updated for all team members except Saidi Kapiga.
3. In accordance with the detailed text modifications listed below, the Schema, Figures 1-3, and Appendix I are updated to reflect a total of approximately 3220 study participants (2900 non-US and 320 US) with random assignment in a 1:1:1:1 ratio to each of the four study treatment groups. Figures 1-2 are clarified to specify up to 30 months follow-up for all study participants.

4. In Section 1.1, first paragraph: The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that ~~42~~ **37.8** million adults and children were living with HIV/AIDS at the end of ~~2002~~ **2003**, and that about ~~14,000~~ **13,000** new infections are occurring each day **in 2003** [1].
5. In Section 1.2.2, Pre-Clinical Research, second paragraph: ~~In repeat-dose intravaginal toxicity studies, concentrations up to 4% were reasonably well tolerated for six months in rats and four and a half months in rabbits. No adverse effects were associated with exposure to 0.5% PRO 2000/5 Gel (P) in either species, though the 2% and 4% concentrations were associated with microscopic signs of vaginal irritation in both. Excess mortality was seen in rabbits treated with 4% PRO 2000/5 Gel (P), though some of the deaths were judged to be unrelated to PRO 2000/5 exposure. The relatedness of the others has not yet been determined.~~ **repeat-dose toxicity studies of six months' duration in rats and nine months' duration in rabbits. Signs of genital tract irritation were associated with the 2% and 4% PRO 2000/5 Gel (P) concentrations in both studies, however these findings were considered to be within acceptable limits. The 4% concentration was associated with decreased survival in two rabbit intravaginal toxicity studies conducted concurrently by the same laboratory, but the circumstances of the deaths suggest that the method of gel administration may have been a factor. Intravaginal 4% PRO 2000/5 Gel (P) was not associated with unexpected deaths in other repeat-dose toxicity studies in rabbits, nor in a six month repeat-dose toxicity study in rats.**
6. In Section 1.2.2, Pre-Clinical Research, fourth paragraph: Likewise, ~~repeated intravaginal application of up to 4% PRO 2000/5 Gel (P) for four and a half months in rabbits, six months in rats, and 10 days in dogs had no significant effect on blood coagulation times, indicating negligible systemic absorption~~ **there was no indication of systemic absorption or toxicity in dogs treated intravaginally with 10 doses of 2% or 4% PRO 2000/5 Gel (P).** Low levels of PRO 2000/5 were ~~reported~~ **apparent** in plasma samples collected from pregnant rats after 12 intravaginal gel applications. **However, PRO 2000/5 was not detected in plasma specimens collected after repeated intravaginal administration of up to 4% PRO 2000/5 Gel (P) for six months in rats and nine months in rabbits.** PRO 2000/5 at concentrations up to 4% had no effect on the growth of vaginal lactobacilli.
7. In Section 2.3.1, first paragraph, second sentence (added): **Participants will be assigned to the four study treatment groups in a 1:1:1:1 ratio.**
8. In Section 2.3.1, third paragraph: The study design is summarized in the Schema, Overview Figures 1-3 (on pages 11-13), and Appendices I-III. ~~For both the Phase II and Phase IIb portions of the study, non-US participants will be assigned at random to the four study treatment groups in a 1:1:1:1 ratio. US participants will be assigned in a 4:4:1:1 ratio, such that four times as many US participants will be assigned to the candidate microbicide groups as to the control groups, in order to provide a relatively larger amount of candidate product safety information among the US participant population.~~

9. In Section 2.3.1, fourth paragraph: ~~Accrual will begin after the US site and at least three non-US sites have obtained all applicable required regulatory approvals~~ **are obtained and a site-specific study activation notice is issued** ~~are activated to begin study implementation by the HPTN Coordinating and Operations Center (CORE; see also Section 10.1). Depending on the timing of activation across sites, it is possible that some not all non-US sites will not take part in the Phase II portion of the study. Activated sites each will accrue up to 25 Phase II participants per month until a total of 800 (100 US and 700 non-US) Phase II participants are enrolled (see also Section 7.1). For non-US sites, accrual of Phase II participants will be capped at a maximum of 350 per site, to ensure adequate cross-site representation in the Phase II data. At all sites, Phase II~~ **These participants will complete three monthly follow-up assessments for Phase II study endpoints.**
10. In Section 2.3.1, fifth paragraph: The DSMB **routinely** meets ~~approximately~~ **routinely** every four months and will review the Phase II data at its first meeting after the data have been compiled and analyzed.
11. In Section 2.3.1, sixth paragraph: However, prior to the DSMB review, accrual into the Phase IIb portion of the study will be capped at a maximum of ~~25~~ **20 US and 175 non-US** participants ~~per site per month~~.
12. In Section 2.3.1, seventh paragraph: Assuming a favorable DSMB review of the Phase II data, accrual into the Phase IIb study will continue for approximately nine additional months, such that approximately ~~3100~~ **3220** participants total will be enrolled over approximately 18 months total.
13. In Section 2.3.2, first paragraph: In addition, all US Phase II participants (n=100) and **at least** the first 150 ~~non-US~~ Phase II participants **enrolled across at selected non-US** sites will undergo colposcopic examination as part of their pelvic exams during each of their first three months in the study. **In contributing participants to the colposcopy subset, non-US sites may perform colposcopic exams either among a subset of their Phase II participants or among all of their Phase II participants.**
14. In Section 2.3.2, second paragraph: As described more fully in Section 3.3, potential study participants will be screened for eligibility and enrolled in the study over the course of up to 30 days, and over the course of at least **two visits** ~~one Screening Part 1 Visit and one Screening Part 2/Enrollment Visit~~. Eligible participants who provide informed consent to take part in the study will be assigned at random to one of the four study treatment groups ~~according to the randomization schemes described above~~.
15. In Section 2.3.2, third paragraph: At each **of these** visits, participants will complete an interval medical and menstrual history and undergo pregnancy testing.

16. In Section 2.3.2, fifth paragraph: Colposcopic evaluations also will be performed for the **100** US Phase II participants and **at least** the first 150 **Phase II non-US Phase II** participants enrolled across selected **non-US** sites, in accordance with the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update ~~2000~~ **2004**.
17. In Section 2.3.2, sixth paragraph: Follow-up hematology and coagulation testing will be performed ~~quarterly at the US site~~ **for all participants at Months 3, 12, and 24, at study exit, and additionally if clinically indicated**. Follow-up HIV (see Appendix V) testing will be performed quarterly, and additionally if clinically indicated. Follow-up chlamydia, gonorrhea, and syphilis testing will be performed annually, and additionally if clinically indicated. HSV-2 testing will be performed on specimens obtained at enrollment and at study exit, however since information on HSV-2 serostatus is not required for clinical management, this testing will be performed in batches in the final year of study implementation at each site. ~~STD and~~ HIV testing will be performed in the context of pre-test, risk reduction, and post-test counseling.
18. In Section 2.3.2, eighth paragraph: Participants who are found to have an STD or other reproductive tract infection will be provided ~~counseling, treatment, and follow-up care~~ in accordance with World Health Organization (WHO) guidelines, free of charge. Observed single-dose treatment will be provided whenever possible. Participants with STDs will be encouraged to refer their partners for testing and treatment if applicable. Participants who become pregnant during the study will discontinue product use while they are pregnant, however they will remain in follow-up and may resume product use 42 days after birth or other termination of the pregnancy. Participants who become infected with HIV will be ~~maintained~~ **offered the option to continue in follow-up through their originally scheduled study exit date for ascertainment of secondary endpoints. Unless not permitted by site regulatory authorities or Institutional Review Boards (IRBs)/Ethics Committees (ECs), participants who become infected with HIV who were assigned to one of the three study product groups also will be offered the option to continue product use through their originally scheduled study exit date. At all sites, participants who become infected with HIV** They will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons.
19. In Section 3, first paragraph: The study will include approximately ~~3400~~ **3220** sexually active women from the study sites listed in the Schema and in Section 2.3.1.
20. In Section 3, second paragraph: Ideally 415 women will be enrolled at each of the non-US sites and ~~200~~ **320** women will be enrolled at the US site.
21. In Section 3.1, fourth bullet: Sexually active, defined as having had vaginal intercourse at least once in the three months prior to **Sscreening Part 1**.
22. In Section 3.1, fifth bullet: HIV-uninfected based on testing performed by study staff **at Screening Part 1**.

23. In Section 3.2, second bullet: History of non-therapeutic injection drug use in the 12 months prior to **Sscreening Part 1**.
24. In Section 3.2, third bullet: History of vaginal intercourse more than an average of two times per day in the two weeks prior to **Sscreening Part 1**.
25. In Section 3.2, fourth bullet: For Phase II participants, Grade 3 or higher laboratory abnormality, as defined by the DAIDS **Table for Grading Adult and Pediatric Adverse Events Toxicity Tables**, based on hematology, liver and renal function, and coagulation testing performed by study staff **at Screening Part 1; for Phase IIb participants, Grade 4 or higher laboratory abnormality based on hematology and coagulation testing performed by study staff at Screening Part 1**.
26. In Section 3.2, italicized note below fourth bullet (added): **Note: Otherwise eligible participants with a Grade 3 (Phase II) or 4 (Phase IIb) exclusionary test result may be re-tested during the screening process. If the participant is re-tested and a non-exclusionary result is documented within 30 days of providing informed consent for screening, the participant may be enrolled.**
27. In Section 3.2, fifth bullet: Plans any of the following during the ~~next~~ 30 months **following Screening Part 1**:
28. In Section 3.2, italicized note following the ninth bullet: If resolution is documented within 30 days ~~after~~ **of** providing informed consent for screening, the participant may be enrolled.
29. In Section 3.2, italicized note following the tenth bullet: Participants will undergo laboratory testing for chlamydia, gonorrhea, and syphilis at ~~their~~ Screening Part 1 visits, and wet mount testing for BV, candidiasis, and trichomoniasis at ~~their~~ Screening Part 2/~~Enrollment~~ visits; all results will be available by the time of enrollment/randomization. Otherwise eligible participants diagnosed during screening with infection(s) requiring treatment per WHO guidelines (other than asymptomatic candidiasis) will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 30 days ~~after~~ **of** providing informed consent for screening, the participant may be enrolled.

30. In Section 3.3, first paragraph and second (added) paragraph: **Ideally, Eligibility for the study will be assessed in a step-wise manner at the study over the course of two screening visits, on two separate days, and — for women who are found to be eligible — enrollment/randomization will take place on the same day as the second screening visit. Required screening and enrollment procedures are listed in Sections 5.2, Screening Part 1, and 5.3, Screening Part 2/Enrollment Visits. Although ideal, it is not necessary that all Screening Part 1 and Screening Part 2/Enrollment required procedures may be completed in as few as two visits. Additional visits may be conducted if needed. For example, a participant may want more time to consider whether to participate in the study, may require treatment for an STD or other reproductive tract infection, or may not be able to undergo a pelvic exam due to menstruation. Regardless of the number of visits required, all screening and enrollment procedures must be completed within a 30-day period, beginning on the day the participant provides informed consent for screening. If a participant is not enrolled/randomized within 30 days of providing informed consent for screening, the screening process must be repeated. In cases such as these, required procedures may be performed over the course three or more visits, and enrollment/randomization may take place one or more days after screening procedures are completed.**

**Regardless of the number of screening visits required, once eligibility vis-à-vis each study eligibility criterion is determined, it is not necessary to re-assess each criterion on the day of Enrollment. However, when Enrollment does not take place on the same day as Screening Part 2, the following criteria must be re-assessed on the day of Enrollment: participation in any other study of a vaginally-applied product, within 42 days of last pregnancy outcome, current pregnancy.**

31. In Section 3.3, third paragraph: ~~At their Screening Part 1 Visits, after providing written informed consent for screening, potential study participants will be assigned an ID number and asked to provide demographic information, behavioral eligibility information, and locator information. They will undergo testing for urine pregnancy, testing and HIV, and STD (chlamydia, gonorrhea, and syphilis) counseling and testing. All Phase II study participants also will undergo hematology, liver and renal function, and coagulation testing; Phase II participants additionally will undergo liver and renal function testing.~~ Presumptively eligible participants will be provided educational materials about the study to review prior to ~~their~~ Screening Part 2/Enrollment visit, which will be scheduled to take place approximately 7-14 days later, when all Screening Part 1 test results are expected to be available.
32. In Section 3.3, italicized note: For study screening purposes HIV infection status will be ascertained using two different rapid enzyme immunoassay tests **at non-US sites and using an enzyme immunoassay (EIA) at the US site;** ~~in the event that~~ **At non-US sites, if the results of from the two rapid tests are discordant, a Western blot (WB) test will be performed. At the US site, a WB will be performed to confirm reactive EIAs.**

33. In Section 3.3, fourth paragraph: At ~~their~~ Screening Part 2/Enrollment Visits, **elements of behavioral eligibility (participation in any other study of a vaginally-applied product, within 42 days of last pregnancy outcome) will be confirmed.** Potential participants will be informed of their Screening Part 1 test results, ~~in the context of post-test counseling,~~ and again undergo testing for pregnancy. Those who test negative will undergo a physical exam and pelvic exam with pH assessment, **assessment for homogenous discharge,** and wet mount testing for BV, candidiasis, and trichomoniasis; colposcopy will be performed for the first 250 participants enrolled at selected sites.
34. In Section 3.3, fifth paragraph: If treatment is completed and symptoms have resolved within 30 days ~~after~~ of providing informed consent for screening, screening procedures need not be repeated.
35. In Section 3.3, sixth paragraph: If resolution is documented within 30 days ~~after~~ of providing informed consent for screening, screening procedures need not be repeated.
36. In Section 3.3, eighth paragraph (added): **Regardless of the number of visits required, all screening and enrollment procedures must be completed within a 30-day period, beginning on the day the participant provides informed consent for screening. For example, a potential participant who provided informed consent for screening on January 1 could be enrolled/randomized on any day up to and including January 30. If a participant is not enrolled/randomized within 30 days of providing informed consent for screening, the entire screening process, including the screening informed consent process must be repeated.**
37. In Section 3.6: The site Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the **Protocol Safety Review Team (PSRT; see Section 6.1) Protocol Chair, SDMC Protocol Statistician, DAIDS Medical Officer, and CORE Protocol Specialist.** Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or site ~~Institutional Review Boards (IRBs)/Ethics Committees (ECs)~~ terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation (see Section 5.4 and Appendices II and III) of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff will record the reason(s) for all withdrawals in participants' study records. **In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date.**
38. In Section 4.3, first paragraph: All three products will be ~~provided in~~ identically packaged **in** single-use opaque plastic applicators **that will be further packaged in cartons containing 10 (pre-filled) applicators each.**

39. In Section 4.3, second paragraph: Site pharmacists will obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) **by following** ~~according to ordering procedures instructions provided in the~~ **Study Product Control section of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks study specific procedures manual.** All three study products will be stored **at room temperature (15-30 degrees C)** in a secure, limited-access area at the site.
40. In Section 4.3, third paragraph: Study product **cartons** will be dispensed only to enrolled study participants, upon receipt of a written prescription from an authorized prescriber, in quantities expected to be sufficient until the participant's next monthly follow-up visit (up to a maximum of **six cartons** (60 applicators) per month, which corresponds to the maximum frequency of exposure — twice per day — evaluated in Phase I studies of the candidate products).
41. In Section 4.3, fourth paragraph: Site pharmacists are required to maintain complete records of all study product **supplies** received from the CRPMC and subsequently dispensed. Instructions and sample forms will be provided in ~~the study specific procedures~~ **the HPTN 035 Pharmacist Study Product Management Procedures Manual to be provided by the DAIDS Pharmaceutical Affairs Branch.**
42. In Section 4.6, first paragraph: Study participants will be discontinued from product use by the study site Investigator or designee in the event that they become pregnant or experience an **AE that meets criteria for expedited reporting to DAIDS** ~~serious adverse event~~ (SAE, see Section 6 **and Appendix VI**) that is judged by the site Investigator or designee to be probably or definitely related to product use. **With approval from the PSRT, participants who discontinue product use due to a probably or definitely related AE that meets criteria for expedited reporting may resume product use after the AE resolves (returns to baseline) or stabilizes at a non-reportable severity grade.** Participants who become pregnant may resume product use 42 days after giving birth or other termination of the pregnancy.
43. In Section 4.6, second paragraph (added): **Participants who become infected with HIV will be offered the option to continue product use unless continued use is not permitted by site regulatory authorities or IRBs/ECs. At sites where continued product use is not permitted, product use will be discontinued after HIV infection is confirmed per the algorithm in Appendix V.**
44. In Section 4.6, fourth paragraph: Investigators/designees also may ~~at their discretion~~ discontinue product use, ~~—temporarily or permanently—~~ **pending consultation with the PSRT**, among participants who:
45. In Section 4.6, first bullet following the fourth paragraph: Experience an ~~SAE~~ **AE that meets criteria for expedited reporting to DAIDS that is** judged possibly related to product use.

46. In Section 4.7, first paragraph: Enrolled study participants may continue use of all concomitant medications, including prescription, non-prescription, traditional, and other preparations during this study. However, **spermicides, diaphragms, and contraceptive vaginal rings should not be used during this study. Participants who report current use of these contraceptive products and devices during screening will be counseled regarding the use of alternative methods and referred to family planning services for provision of alternative methods should they enroll in the study.** In addition, as noted in Section 4.2, participants will be encouraged to avoid douching and the use of vaginally-applied medications/preparations within one hour before and one hour after having vaginal intercourse.
47. In Section 4.7, second paragraph: All concomitant medications used by participants throughout the course of the study, beginning at **Screening Part 2**, ~~the time of randomization/enrollment~~ will be reported on applicable case report forms.
48. In Section 5.2, section title: Screening Part 1 ~~Visit~~
49. In Section 5.2, first paragraph: Unless otherwise noted, the ~~following~~ procedures **listed in this section** are performed at ~~Screening Part 1 Visits~~ for both Phase II and Phase IIb participants. Multiple visits may be conducted to complete all required procedures if necessary. **If more than one visit is needed to complete all required procedures, procedures not completed at the first visit may be performed on the same day as Screening Part 2 procedures.** Written informed consent for screening will be obtained before any screening procedures are initiated. ~~For potential participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.~~
50. In Section 5.2.1, fifth and sixth (added) bullets:
- HIV pre-test ~~and post-test~~ counseling.
  - **HIV post-test counseling (for non-US participants, based on rapid test results).**
51. In Section 5.2.3, third bullet: Dipstick urinalysis if clinically indicated; ~~urine culture if dipstick is positive for leukocyte esterase or nitrites.~~
52. In Section 5.2.3, sixth bullet: Complete blood count (~~Phase II participants only~~).
53. In Section 5.2.3, eighth bullet: Coagulation tests (~~Phase II participants only~~).
54. In Section 5.3, section title: Screening Part 2/~~Enrollment Visit~~
55. In Section 5.3, first paragraph: Unless otherwise noted, the ~~following~~ procedures **listed in this section** are performed at ~~the study Screening Part 2/Enrollment Visit~~ for **both** Phase II and Phase IIb participants. Multiple visits may be conducted to complete all required procedures if necessary. Written informed consent for study participation will be obtained before any Enrollment (or “on-study”) procedures are conducted. ~~For participants whose eligibility is not confirmed at this visit, the screening and enrollment process will be discontinued when ineligibility is determined.~~

56. In Section 5.3, second paragraph (added): **The procedures listed in Sections 5.3.1-5.3.3 apply when Screening Part 2 and Enrollment take place on the same day. In the event that Enrollment does not take place on the same day as Screening Part 2, the screening procedures listed in Section 5.3.4 must additionally be completed on the day of Enrollment to confirm participant eligibility prior to Enrollment.**
57. In Section 5.3.1, Screening Part 2, first bullet: HIV ~~pre-test and/or~~ post-test counseling ~~if needed~~ **(for US participants, based on EIA/WB results from sample collected at Screening Part 1; also for non-US participants requiring WB testing due to discordant rapid test results at Screening Part 1).**
58. In Section 5.3.2, Screening Part 2, second bullet: Blood collection if genital ulcer **indicative of syphilis infection** is observed.
59. In Section 5.3.2, Screening Part 2, fifth bullet, first sub-bullet: colposcopy (US Phase II participants and **at least the first 150 non-US** Phase II participants from selected **non-US sites only**)
60. In Section 5.3.2, first italicized note: If resolution is documented within 30 days ~~after of~~ providing informed consent for screening, the participant may be enrolled.
61. In Section 5.3.2, second italicized note: If treatment is completed and symptoms have resolved within 30 days ~~after of~~ providing informed consent for screening, the participant may be enrolled.
62. In Section 5.3.3, Screening Part 2, third bullet: Dipstick urinalysis if clinically indicated; ~~urine culture if dipstick is positive for leukocyte esterase or nitrites.~~
63. Protocol Section 5.3.4 (added): **Screening Procedures to be Completed When Enrollment Does Not Take Place on the Same Day as Screening Part 2**
- **Review of all prior screening documentation, with update of medical and menstrual history and/or current medications if applicable.**
  - **Re-confirmation (by participant self-report) that participant is not currently participating in any other study of a vaginally-applied product.**
  - **Re-confirmation (by participant self-report) that the participant has not been pregnant, given birth, or had a pregnancy terminated in the last six weeks.**
  - **Urine pregnancy test.**
  - **Any other clinically indicated behavioral, clinical, or laboratory assessments.**
64. In Section 5.4, italicized note: For example, ~~pregnancy testing~~ **quarterly pelvic exams** will be discontinued ~~and~~ after 24 weeks of pregnancy ~~quarterly pelvic exams may be discontinued and blood collection may be limited to fingersticks for HIV serology only.~~ **Use of study gels will be discontinued if continued use is not permitted by site regulatory authorities or IRBs/ECs.**

65. In Section 5.4.1, italicized note following the ninth bullet, second sentence (added): **Also not done for participants who become infected with HIV at sites where continued product use is not permitted by site regulatory authorities or IRBs/ECs.**
66. In Section 5.4.2, second bullet, fourth sub-bullet: Additionally with colposcopy:  
-At Months 1, 2, and 3 for **US Phase II participants and at least the first 250 150** Phase II participants from selected **non-US** sites.
67. In Section 5.4.3, second bullet: Urine SDA for chlamydia and gonorrhea:  
-Annually (**Months 12 and 24**) and at study exit.
68. In Section 5.4.3, third bullet: Dipstick urinalysis; ~~urine culture if dipstick is positive for leukocyte esterase or nitrites:~~
69. In Section 5.4.3, italicized note following seventh bullet (added): **Note: For participants who test HIV-positive on their first post-enrollment HIV test, HIV antibody testing will be performed on archived plasma to confirm that the participant was HIV-uninfected at enrollment. If additional testing (e.g., RNA PCR, p24 antigen) is required to clarify participants' HIV status at enrollment, such testing will be undertaken in consultation with the HPTN Central Lab.**
70. In Section 5.4.3, ninth bullet: Complete blood count:  
-At Months 1, **and 2,** ~~and 3~~ for Phase II participants only.  
-**At Month 3, annually (Months 12 and 24), Quarterly** and at study exit for all participants ~~at the US site only.~~  
-**Additionally when clinically indicated.**
71. In Section 5.4.3, eleventh bullet: Coagulation tests:  
-At Months 1, **and 2,** ~~and 3~~ for Phase II participants only.  
-**At Month 3, annually (Months 12 and 24), Quarterly** and at study exit for all participants ~~at the US site only.~~  
-**Additionally when clinically indicated.**
72. In Section 6.1, first paragraph: The study site Investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. **A sub-group of the Protocol Team, including the Protocol Chair, Medical Officer, and Protocol Statistician, will serve as the PSRT.** ~~In addition, the~~ The HPTN SDMC will prepare routine **AE and clinical data reports** ~~study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment) for review by the PSRT, Protocol Team. Protocol Team members~~ **which** will meet via conference call **approximately at least once per month or as needed** throughout the period of study implementation **to review safety data, discuss product use management (see Section 4.6), and address any potential safety concerns** ~~additional ad hoc calls will be convened if required.~~

73. In Section 6.1, third paragraph: ~~These~~ **The DSMB routinely meets approximately every four months, and it is expected that** reviews will take place approximately every ~~six~~ **eight** months.
74. In Section 6.2, third paragraph: All AEs will be graded using the DAIDS Table for Grading **Adult and Pediatric Severity of Adverse Events** (also referred to as the “Toxicity Table”). The investigator or designee will assess the relationship of all AEs to the study product based on the ~~DAIDS SAE Reporting Manual for~~ **Expedited Reporting of Adverse Events to DAIDS**, the HPTN, the Investigator’s Brochures, and his/her clinical judgment. ~~Both the The DAIDS SAE expedited Rreporting Mmanual for the HPTN and are provided in the study specific procedures manual and are~~ **provided in Appendix VI. The Toxicity Table is** available at the following web sites:
75. In Section 6.3, section title: ~~Serious~~ **Expedited** Adverse Event Reporting Requirements
76. In Section 6.3, first paragraph: Site staff ~~also~~ will report to ~~the~~ DAIDS, **through its** Regulatory Compliance Center, all AEs **experienced by that participants assigned to one of the three investigational study products that** meet **expedited** ~~serious~~ adverse event (SAE) reporting requirements ~~according to the procedures set forth in~~ **per the Manual for Expedited Reporting of Adverse Events to DAIDS. DAIDS SAE Reporting Manual for the HPTN.**
77. In Section 6.3, second paragraph (added): **For each study participant, expedited AE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., through completion of the participant’s study exit visit. Thereafter, only pregnancy outcomes that meet criteria for expedited AE reporting (e.g., fetal losses) occurring among participants known to be pregnant at study exit will be reported.**
78. In Section 6.3, third paragraph: Information on all AEs will be included in reports to the FDA, and other applicable government and regulatory authorities. Site staff will report information on ~~all AEs and SAEs~~ to their IRBs/ECs in accordance with all applicable regulations and local IRB/EC requirements.

79. In Section 7.1, first paragraph: In particular, a multi-site Phase II study among 800 participants will “lead in” to the Phase IIb study which will include the Phase II study participants plus approximately ~~2300~~ **2420** additional women. By capping, rather than stopping, enrollment during the transition between Phase II and Phase IIb, continuity of study operations is maintained without exposing more women than necessary to the candidate microbicide products. Specifically, with a cap ~~at of 25 participants enrolled per site per month, and assuming the Phase II accrual rates shown in Appendix I~~ **(10 US participants and 70 non-US participants in Month 1, 15 US participants and 105 non-US participants in Month 2, etc)** and three months of Phase II follow-up, plus two additional months for Phase II data cleaning, analysis, and DSMB review, approximately ~~390~~ **372** women will be exposed to each candidate microbicide prior to the data cut-off for the DSMB safety review. This includes the ~~215~~ **200** Phase II participants assigned to each of these products. These ~~780~~ **745** participants constitute less than half of the total number of participants planned to be exposed to a candidate microbicide during the full Phase II/IIb study.
80. In Section 7.3.1, first paragraph: A total of 800 women (**700 non-US and 100 from the US site and 700 from at least three non-US sites**) will be enrolled in the Phase II portion of the study over a period of approximately six months, and each woman will be followed monthly for three months in the Phase II portion of the study.
81. In Section 7.3.1, second paragraph: ~~Consistent with recommendations received from the FDA, non-US p~~ Participants will be assigned at random to the four study treatment groups in a 1:1:1:1 ratio, ~~whereas US participants will be assigned in a 4:4:1:1 ratio, such that four times as many US participants will be assigned to the candidate microbicide groups as to the control groups.~~ Assuming a five percent significance level for a two-sided test (i.e., a 2.5 percent false-positive error rate), and five percent loss-to-follow-up over the Phase II study period, ~~51 and 44~~ **47.5** person-years (p-y) of follow-up will be accumulated in **each treatment** ~~the active and control groups, respectively, of~~ **during** the Phase II portion of the study.
82. In Section 7.3.1, third paragraph: Assuming each candidate microbicide will be compared separately to the placebo gel and to no treatment, **and assuming a five percent significance level for a two -sided test (i.e., a 2.5 percent false positive rate)**, Table 7-1 presents the power of the Phase II study to detect various differences in rates of epithelial disruption for given baseline rates of this outcome (i.e., rates in the placebo and no treatment groups).
83. In Section 7.3.1, Table 7-1:

Baseline Rate (per 100 p-y)	Power to Detect a:			
	two-fold Difference	three-fold difference	five-fold difference	ten-fold difference
5	.15	<del>.41</del> <b>.39</b>	<del>.88</del> <b>.86</b>	>.99
10	.26	<del>.68</del> <b>.67</b>	>.99	>.99
15	<del>.37</del> <b>.36</b>	<del>.85</del> <b>.83</b>	>.99	>.99
20	<del>.47</del> <b>.46</b>	<del>.93</del> <b>.92</b>	>.99	>.99
25	<del>.55</del> <b>.54</b>	.97	>.99	>.99

84. In Section 7.3.1, fourth paragraph: If this same rate is observed among placebo and no treatment participants in this study, the Phase II portion of the study will have at least 90 percent power to detect a difference between a candidate microbicide group and a control group if epithelial disruption is observed at a rate of at least ~~58~~ **60.5** per 100 p-y in the candidate microbicide group.
85. In Section 7.3.2, first paragraph: The Phase IIb study will enroll a total of approximately ~~3100~~ **3220** women, with enrollment ending approximately nine months after the DSMB review of the Phase II data, resulting in a total enrollment period of approximately 18 months for the Phase II/IIb study.
86. In Section 7.3.2, second paragraph: The US site will enroll a total of ~~200~~ **320** women.
87. In Section 7.3.2, fifth paragraph: Sample size calculations are based on ~~the equal randomization schemes described in Section 7.4~~ **to the four study treatment groups** and the following assumptions:
88. In Section 7.3.2, seventh paragraph: Given the above assumptions, and assuming a 33 percent effect of the candidate products, a total of approximately ~~1000~~ **1085** p-y of follow-up are expected to be accrued in each study treatment group, and approximately 192 incident HIV infections are expected to be observed throughout the course of the study.
89. In Section 7.4, first paragraph: Enrolled participants will be assigned at random to one of the four study treatment groups **in a 1:1:1:1 ratio**. The randomization scheme will be stratified by site **and** ~~. At non-US sites, participants will be assigned to the four study treatment groups in a 1:1:1:1 ratio. At the US site, participants will be assigned in a 4:4:1:1 ratio, such that four times as many participants are assigned to the candidate microbicide groups as to the control groups. The randomization code will be generated and maintained by the HPTN SDMC.~~
90. In Section 7.4, second paragraph: The clinic envelopes will contain an assignment to “gel” or “~~no gel/~~ condoms only (**no gel**).” Clinic staff will assign these envelopes in sequential order by envelope number to eligible study participants. **For participants assigned to “gel,”** ~~t~~The corresponding pharmacy envelopes will contain coded (blinded) information indicating the specific product to which participants ~~in the three study gel groups~~ are assigned. ~~or “no gel/condoms only.”~~
91. In Section 7.4, third paragraph: For participants assigned to “~~no gel/~~ condoms only (**no gel**)” in the clinic, in lieu of a “prescription” per se, documentation of the random assignment will be forwarded to the pharmacy, however pharmacy staff will not open a corresponding envelope or dispense product for these participants.
92. In Section 7.5, fourth paragraph: If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the ~~PSRT Protocol Chair, Protocol Biostatistician, and DAIDS Medical Officer (or designees)~~ **PSRT Protocol Chair, Protocol Biostatistician, and DAIDS Medical Officer** (or designees) to consider and ~~jointly~~ rule upon the request.

93. In Section 7.6, third paragraph: DSMB reviews of study safety data will be conducted after the Phase II portion of the study is completed, and approximately every ~~six~~ **eight** months during the Phase IIb portion of the study.
94. In Section 7.6.2, Primary Analyses, first paragraph: To assess safety throughout the Phase IIb portion of the study, analyses of epithelial disruption observed on pelvic examination and reported genital signs and symptoms will be performed for DSMB review approximately every ~~6~~ **eight** months, including data from all sites, using the same methods described above for the Phase II analysis.
95. In Section 8.1, first paragraph: This protocol and the template informed consent forms contained in Appendices ~~VI-X~~ **VII-XIII** — and any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.
96. In Section 8.2, second paragraph: Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices ~~VI-X~~ **VII-XIII**, that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.
97. In Section 8.4, second paragraph: Study participants will receive **HIV/STD risk reduction counseling**, HIV and STD ~~counseling and~~ testing, a physical exam, and pelvic exams.
98. In Section 9.1, fourth bullet: Urine for **dipstick urinalysis**, pregnancy testing, and chlamydia and gonorrhea SDA
99. In Section 9.4: In addition, study participants will be asked to provide written informed consent for **additional their** plasma specimens to be ~~collected at study entry and exit and~~ stored after the end of the study for possible future research testing.
100. In Section 10.2, second paragraph: This manual — which will contain reference copies of the **protocol**, DAIDS SOPs for Source Documentation and Essential Documents, ~~as well as the DAIDS SAE Reporting Manual for the HPTN and DAIDS Toxicity Tables~~ — will outline procedures for conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations.
101. In Section 10.2, fourth paragraph: The ~~PSRT Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, and CORE Protocol Specialist~~ will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

102. In Section 11, Reference 1: Joint United Nations Programme on HIV/AIDS and World Health Organization (July 2004). **2004 Report on the Global AIDS Epidemic Update: December 2002.**
103. Appendices II and III are updated to reflect all procedural modifications listed above.
104. In Appendix IV, Appendix Title: **Phase II** Safety Laboratory Evaluations ~~to be Performed Among Phase II Participants at Screening and at Study Months 1, 2, and 3~~
105. In Appendix IV, Coagulation Tests, third bullet (added): **INR**
106. Appendix V is updated to allow study sites to perform an additional rapid test or EIA if required by local HIV counseling and testing guidelines or regulations and/or if approved by the HPTN Central Laboratory. Clarification of Western blot testing requirements in this context is added.
107. Appendix VI, Manual for Expedited Reporting of Adverse Events to DAIDS, is added.
108. Appendix VII, sample screening informed consent form for Phase II/IIb participants not undergoing colposcopy, is added.
109. In Appendix VIII, form title: **SCREENING ONLY / PHASE II/IIb / WITH COLPOSCOPY**
110. In Appendix VIII, Procedures, first paragraph: If you agree to have the screening tests, you will have 2 visits here over about ~~2~~**4** weeks.
111. In Appendix VIII, Procedures, Visit 1, fourth paragraph: **[For non-US sites:]** If you are prepared to have an HIV test, study staff will draw about [1-~~2~~**2**] teaspoon[s] [or local equivalent] of blood from your arm with a needle. They will test your blood for HIV. It will take about ~~15-20~~**40** minutes to get your test result. You will be told your result as soon as it is available, on the same day you give blood and have the test. You will talk with the study staff about the meaning of your result and how you feel about it. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will ~~draw your blood again and repeat the~~ **do more** tests until we know the result for sure.
112. In Appendix VIII, Procedures, Visit 1, fifth paragraph: **[For non-US sites:]** If the test shows that you have HIV, you will not be eligible for the research study.
113. In Appendix VIII, Procedures, Visit 1, sixth paragraph: **[For non-US sites:]** If the test shows that you do not have HIV, the study staff will test your blood for syphilis.

114. In Appendix VIII, Procedures, Visit 1, seventh paragraph (added): ***[For the US site:] If you are prepared to have an HIV test, study staff will draw about [1-2] teaspoon[s] [or local equivalent] of blood from your arm with a needle. They will test your blood for HIV and syphilis. They also will do tests to find out how healthy your blood, liver, and kidneys are, and test your urine for gonorrhea and chlamydia. These tests take 1-2 weeks. You will come back for another visit when your results are available.***
115. In Appendix VIII, Procedures, Visit 2, first paragraph (added to end of paragraph): ***[For the US site: If the tests show that you have HIV, you will not be eligible for the research study. The study staff will tell you about other studies you may be eligible for, if any. They will refer you to available sources of medical care and other services you may need. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will do more tests until we know the result for sure. You must receive your HIV test results to be in the research study.]***
116. In Appendix VIII, Procedures, Visit 2, fourth paragraph: ~~*[At selected sites only: During this exam, the study staff will look through a lens called a “colposcope.” The lens works like a magnifying glass to help the nurse or doctor see any abnormalities. The lens also is attached to a camera that will*~~ ***may be used to take a picture of the inside of your vagina if any abnormalities are seen.]***
117. In Appendix VIII, Procedures, Visit 2, fifth paragraph: ***If you join the research study, and then the Pap test shows a serious abnormality, you will be asked to stop using the gels until after you receive treatment and the abnormality has resolved.***
118. In Appendix VIII, Benefits, first paragraph: You will have tests of your blood; ***cells and how well your blood clots. You will have tests of your liver, and kidneys.***
119. In Appendix IX, Procedures, first paragraph: If you agree to have the screening tests, you will have 2 visits here over about ***2-4*** weeks.
120. In Appendix IX, Procedures, Visit 1, fourth paragraph: ***[For non-US sites:] If you are prepared to have an HIV test, study staff will draw about [1-2] teaspoon[s] [or local equivalent] of blood from your arm with a needle. They will test your blood for HIV. It will take about ~~15-20~~40 minutes to get your test result. You will be told your result as soon as it is available, on the same day you give blood and have the test. You will talk with the study staff about the meaning of your result and how you feel about it. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will draw your blood again and repeat the do more tests until we know the result for sure.***
121. In Appendix IX, Procedures, Visit 1, fifth paragraph: ***[For non-US sites:] If the test shows that you have HIV, you will not be eligible for the research study.***
122. In Appendix IX, Procedures, Visit 1, sixth paragraph: ***[For non-US sites:] If the test shows that you do not have HIV, the study staff will test your blood for syphilis. They also will do tests to find out how healthy your blood is. They will test your urine for gonorrhea and chlamydia.***

123. In Appendix IX, Procedures, Visit 1, seventh paragraph (added): *[For the US site:]* **If you are prepared to have an HIV test, study staff will draw about [1-2] teaspoon[s] [or local equivalent] of blood from your arm with a needle. They will test your blood for HIV and syphilis. They also will do tests to find out how healthy your blood, liver, and kidneys are, and test your urine for gonorrhea and chlamydia. These tests take 1-2 weeks. You will come back for another visit when your results are available.**
124. In Appendix IX, Procedures, Visit 2, first paragraph (added to end of paragraph): *[For the US site:* **If the tests show that you have HIV, you will not be eligible for the research study. The study staff will tell you about other studies you may be eligible for, if any. They will refer you to available sources of medical care and other services you may need. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will do more tests until we know the result for sure. You must receive your HIV test results to be in the research study.]**
125. In Appendix IX, Procedures, Visit 2, fourth paragraph: **If you join the research study, and then the Pap test shows a serious abnormality, you will be asked to stop using the gels until after you receive treatment and the abnormality has resolved.**
126. In Appendix IX, Benefits, first and second paragraphs: You may get no direct benefit from the screening tests. However, you will have a physical exam and a genital exam. **You will have tests of your blood cells and how well your blood clots. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.** ~~You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you.~~ *[For selected sites only:* your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].]
- You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you.** You will get counseling and testing for other infections. If you have these infections, you will get medicine to treat them, if needed. You can bring your partner here for tests and treatment for these infections if he needs them.
127. In Appendix X, sample enrollment informed consent form for Phase II/Ib participants not undergoing colposcopy, is added.
128. In Appendix XI, form title: ENROLLMENT / PHASE II/Ib / **WITH COLPOSCOPY**
129. In Appendix XI, Purpose of the Study, third paragraph: About ~~3400~~ **3200** women from Africa, India, and the United States will be in the study. About [200/~~300~~/**400**] women will be in the study here at [study site].

130. In Appendix XI, Study Groups, second paragraph: ~~[For Non-US Sites:—You have an equal chance of being placed in each group.] [For the US Site:—You have an 8 out of 10 chance of being placed in a group that will get either BufferGel or PRO 2000 Gel. You have a 1 out of 10 chance of being placed in the group that gets the placebo gel and a 1 out of 10 chance of being placed in the group that gets no gel.]~~
131. In Appendix XI, Study Procedures, In your first three visits, first bullet: ~~[At selected sites only:—~~ During this exam, the study staff will look through a lens called a “colposcope.” The lens works like a magnifying glass to help the nurse or doctor see any abnormalities. The lens also is attached to a camera that ~~will~~ **may be used to** take a picture of the inside of your vagina **if any abnormalities are seen.**
132. In Appendix XI, Study Procedures, Every 3 months, fifth bullet: Talk with study staff about the HIV test and give about [1-2] teaspoon[s] [or local equivalent] of blood from your arm for the test. When we do HIV testing for this study, we first do a test that gives results in ~~15–20–40~~ minutes. You will get the result of that test when it is available, on the same day you give blood and have the test. If the test shows that you may have HIV infection, we will do another different test to confirm this result. This test takes about 1-2 weeks, so you will have to come back here at that time to get the results. If that test shows that you have HIV, we will draw your blood again and repeat the test one more time. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will ~~draw your blood again and repeat the~~ **do more** tests until we know the result for sure. You must receive your HIV test results to stay in the study.
133. In Appendix XI, Study Procedures, Every 3 months, sixth bullet (deleted): ~~[For the US site only:—Give about 1 teaspoon [or local equivalent] of blood from your arm for tests of your blood cells and how well your blood clots.]~~
134. In Appendix XI, Study Procedures, Every 12 months, first bullet (added): **Have tests of your blood cells and how well your blood clots.**
135. In Appendix XI, Study Procedures, At your last study visit, first paragraph: You will have final tests **of your blood cells and how well your blood clots. You also will have final tests** for HIV, syphilis, gonorrhea, and chlamydia. The study staff will make arrangements with you to give you your test results when they are available.
136. In Appendix XI, Study Procedures, At any time in the study, fifth paragraph: If you become infected with HIV, you can stay in the study [[and keep using the gel (if you are in a gel group)] **OR [but you cannot keep using the gel (if you are in a gel group)]**].
137. In Appendix XI, Study Procedures, Other blood tests, second paragraph: The study staff also would like to ~~draw~~ **keep your leftover** blood ~~from you to keep~~ after the study is over.
138. In Appendix XI, Risks and/or Discomforts, Risks of the Study Gels, first paragraph: We do not yet know all the effects of the gels, but **some** women who used the gels in other studies have had:

139. In Appendix XI, Benefits, fourth paragraph: You will have tests of your blood, **cells and how well your blood clots.** You will have tests of your liver, and kidneys.
140. In Appendix XII, Purpose of the Study, third paragraph: About ~~3400~~ **3200** women from Africa, India, and the United States will be in the study. About [200/~~300~~/400] women will be in the study here at [study site].
141. In Appendix XII, Study Groups, second paragraph: ~~{For Non-US Sites:—You have an equal chance of being placed in each group.} [For the US Site:—You have an 8 out of 10 chance of being placed in a group that will get either BufferGel or PRO 2000 Gel. You have a 1 out of 10 chance of being placed in the group that gets the placebo gel and a 1 out of 10 chance of being placed in the group that gets no gel.]~~
142. In Appendix XII, Study Procedures, At your third visit (added between Every month and Every 3 months): **At your third visit, you also will:**
- **Have tests of your blood cells and how well your blood clots.**
143. In Appendix XII, Study Procedures, Every 3 months, fifth bullet: Talk with study staff about the HIV test and give about [1-2] teaspoon[s] [or local equivalent] of blood from your arm for the test. When we do HIV testing for this study, we first do a test that gives results in ~~15–20–40~~ minutes. You will get the result of that test when it is available, on the same day you give blood and have the test. If the test shows that you may have HIV infection, we will do another different test to confirm this result. This test takes about 1-2 weeks, so you will have to come back here at that time to get the results. If that test shows that you have HIV, we will draw your blood again and repeat the test one more time. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will ~~draw your blood again and repeat the~~ **do more** tests until we know the result for sure. You must receive your HIV test results to stay in the study.
144. In Appendix XII, Study Procedures, Every 3 months, sixth bullet (deleted): ~~{For the US site only: Give about 1 teaspoon [or local equivalent] of blood from your arm for tests of your blood cells and how well your blood clots.}~~
145. In Appendix XII, Study Procedures, Every 12 months, first bullet (added): **Have tests of your blood cells and how well your blood clots.**
146. In Appendix XII, Study Procedures, At your last study visit, first paragraph: You will have final tests **of your blood cells and how well your blood clots.** You also will have **final tests** for HIV, syphilis, gonorrhea, and chlamydia. The study staff will make arrangements with you to give you your test results when they are available.
147. In Appendix XII, Study Procedures, At any time in the study, fifth paragraph: If you become infected with HIV, you can stay in the study [[and keep using the gel (if you are in a gel group)] **OR [but you cannot keep using the gel (if you are in a gel group)]**].

148. In Appendix XII, Study Procedures, Other blood tests, second paragraph: The study staff also would like to ~~draw~~ **keep your leftover** blood ~~from you to keep~~ after the study is over.
149. In Appendix XII, Risks and/or Discomforts, Risks of the Study Gels, first paragraph: We do not yet know all the effects of the gels, but **some** women who used the gels in other studies have had:
150. In Appendix XII, Benefits, fourth paragraph, first and second sentences (added): **You will have tests of your blood cells and how well your blood clots. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.**
151. In Appendix XIII, How Will You Get The Blood From Me?: ~~The research doctors want to take blood from you at your first study visit and your last study visit for storage. If you agree to this, you will have you will have about 2 teaspoons [or local equivalent] of blood drawn at each of these visits. This blood will be kept and used for future research.~~ **You have agreed to have blood drawn, tested, and stored as part of the HPTN 035 study. During the study, your stored blood may be tested to check on your health. It also may be tested for HIV. The research doctors would like to keep any blood that is leftover, after the HPTN 035 study is done, to use for research in the future. If you agree to this, no additional blood will be taken from you. Only leftover blood will be kept and used for future research.**