SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-004
DAIDS Document ID 10492

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women
Version 1.0 / 8 January 2007

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0 / 15 May 2007

IND # 62,482

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-004 study and must be forwarded to your Institutional Review Boards (IRBs) 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 document files for MTN-004.

Summary of Revisions

This amendment incorporates the following protocol revisions:

- Updates to the Protocol Team Roster
- Updates to Introduction, including pre-clinical and clinical data
- Clarification of laboratory measures
- Modifications to Clinical Data Safety Review
- Modification of quorum for the Protocol Safety Review Team
- Deletion of Behavioral Questionnaire as an Appendix to the protocol
- Other minor editorial and typographical updates and corrections

Rationale

The text of the amended protocol (Version 2.0) has been updated to reflect new information available in the most recent version (CIB-001-06) of the Investigator's Brochure for SPL7013 Gel (VivaGel™), dated April 20, 2007.

With regard to laboratory measures, new information has become available from the MTN Network Laboratory regarding interference of SPL7013 Gel with the Strand Displacement Assay on urine for Chlamydia and gonorrhea. The protocol has been modified to permit a different type of analysis (Genprobe Aptima) for Chlamydia and gonorrhea testing as needed at participant follow-up visits. The amended protocol (Version 2.0) clarifies the allowance for confirmatory testing for syphilis and HIV as needed. The collection of RBC and hematocrit has been removed, as there is consensus among the MTN safety physicians and NIH medical officers that monitoring hemoglobin will be sufficient to monitor safety in study participants. The pharmacokinetic assay for SPL7013 will be performed as a plasma level, not a serum level, as was previously noted in Version 1.0.

With regard to Clinical Data Safety Review, generation of a safety report on WBC/differential has been omitted for this protocol, as there is consensus among members of the Protocol Safety Review Team (PSRT) that safety among participants will be sufficiently monitored without generation or review of this report. With agreement of the PSRT, the quorum for a conference call meeting of the PSRT has been modified to allow for calls to occur with fewer members of the PSRT available, thus decreasing the possibility that a call would be canceled or delayed.

The Behavioral Questionnaire has been removed from the protocol as an appendix, as its continued inclusion as an appendix was deemed by the protocol team to be unnecessary.

The Female Genital Toxicity Table has been recently developed by a collaborative scientific effort to better define and standardize the identification and grading of adverse

events in microbicide studies. The addition of this table to the protocol will help to make comparisons regarding tolerability and safety across different microbicide studies.

Implementation

This amendment is official MTN-004 protocol documentation. Prior to implementing the revisions listed below, MTN-004 study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs. Starpharma Pty Ltd will submit this amendment to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application #62,482.

Upon receipt of all required regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions

1. Throughout the amended protocol, the protocol version number and version date are updated to Version 2.0 and 14 May 2007, respectively. The table of contents is updated to reflect current document pagination.

2. The Protocol Team Roster has been updated to include the current contact details of current team members from participating study sites and organizations. The following persons have been added to this roster: **Wendy Brown**, **Elena Cyrus-Cameron**, **Kailazarid Gomez**, **Marla Husnik**, **Edward Livant**, and **Clare Price**. The following persons have been removed from this roster: Michael Cooney, Robin Fisher, and Fang Gai.

3. In the Schema, Sixth Bullet: The proportion of participants who at their **Two-**Week ~~2~~ Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future.

4. In the Schema, Eleventh Bullet: Detection of SPL7013 in blood samples at Day 0 and **Two-**Week ~~2~~ Clinic Visit (Target Day 14).

5. Section numbers have been reformatted throughout the protocol as needed to clarify and incorporate new information.

6. In Section 1.5, first listing: ~~Central~~ **Network** Laboratory: MTN ~~Central~~ **Network** Laboratory.

7. In Section 2.1: According to UNAIDS, an estimated ~~38.6~~ **39.5** million (~~33.4~~ **34.1** million–~~46.0~~ **47.1** million) people worldwide were living with human immunodeficiency virus (HIV) in 2006. An estimated ~~4.1~~ **4.3** million (~~3.4~~ **3.6** million–

~~6.2~~ **6.6** million) became newly infected with HIV and an estimated ~~2.8~~ **2.9** million (~~2.4~~ **2.5** million–~~3.3~~ **3.5** million) lost their lives to acquired immunodeficiency syndrome (AIDS) [1].

8. In Section 2.4.3, first sentence: SPL7013 Gel has been shown to be stable in the vaginal applicators for up to ~~6~~ **9** months at 40°C (104°F).

9. A new Section 2.5 was added: **Effect of SPL7013 on Condom Integrity**.
   The effect of SPL7013 Gel on latex condoms has been assessed in a number of studies. SPL7013 Gel did not compromise the integrity of non-lubricated, silicone lubricated, and aqueous lubricated condoms, as assessed by burst pressure, time to burst, burst volume, and tensile strength. The dimensions of the condoms after exposure to the gel also appeared to be unchanged.

10. In Section 2.9.3: Studies of repeat-dose toxicity in rats, rabbits, dogs, and macaques also found a lack of evidence for systemic toxicity. A study of rats (10 animals/group, 5 groups, up to 25 mg/kg/day, single daily 0.1 mL dose, 14-day exposure) found minimal vaginal irritation in all dose groups, with no systemic toxicity noted (NOEL >25 mg/kg). Rabbits receiving vaginal SPL7013 Gel (5 animals/group, 5 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >12.5 mg/kg). **Dogs receiving vaginal SPL7013 Gel (2 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >5% w/w SPL7013 Gel). A dose-related increase in the severity of subacute inflammation was noted in the cervix and vagina (proximal, mid, and distal sections) of the dogs. This occurred in all animals from all groups, including the vehicle control.**

    Mice, rats and dogs have been treated vaginally with placebo, 1, 3, or 5% w/w SPL7013 Gels for up to 90 days. The 90-day data in rats and dogs represent data from an interim sacrifice in 6- and 9-month chronic toxicity studies, respectively, which are ongoing. In all three species, no evidence of systemic toxicity was observed. In addition, no detectable levels of SPL7013 have been measured in the plasma. Minor microscopic changes were noted such as a dose-related increase in the incidence and severity of glandular dilatation of the cervix and uterus, and dose-related vaginal changes (distal, mid, and proximal portions) that included minimal to mild epithelial cell hyperplasia and minimal single cell necrosis in mice, minimal to mild epithelial hyperplasia, minimal cervical vacuolation and minimal to mild luminal exudate in the vagina in rats, and test article-related microscopic observations limited to the cervix and vagina in dogs, including vacuolated macrophages in the submucosa and subacute inflammation. In all three species, the NOEL was determined to be 5% w/w SPL7013 Gel.

11. In Section 2.9.7: SPL7013 was not detected in plasma samples drawn from those animals that were dosed vaginally with SPL7013 Gel in the rat ~~and~~, rabbit **and** dog repeat dose studies and rabbit teratology study that are described above. The identified lower limit of quantification (LLOQ) of SPL7013 in these plasma samples was **0.2 to** 0.5 µg/mL (**12 to** 30 nM).

12. A new Section 2.9.8 was added:
    Contraceptive Activity
    The effect of 3% w/w SPL7013 Gel, or 3% w/w of the active ingredient, SPL7013, in hydroxyethylcellulose (HEC) gel, on contraception in female New Zealand White rabbits has been studied. Animals were artificially inseminated with 0.5mL of sperm 5 minutes after vaginal administration of 2mL of the gels containing SPL7013. HEC gel was used as a placebo control. Contraceptive efficacy was determined 15 days post insemination by assessing whether or not the animal became pregnant, and by comparing the number of implanted embryos in pregnant animals.

    Out of 8 rabbits pre-treated with 3% w/w SPL7013 Gel, only 2 became pregnant, with 6 and 7 embryos counted in each of the pregnant does. Out of 8 rabbits pre-treated with 3% w/w SPL7013 in HEC Gel, again only 2 became pregnant. There was only one embryo in each of the pregnant does. In contrast, 9 of 11 rabbits in the HEC placebo control group became pregnant with a total of 75 embryos. Preliminary observations were also made to determine the duration of contraceptive effect. The combined results demonstrated that 3% w/w SPL7013 Gel was a highly effective contraceptive approximately 24 hours after application. The results also suggest that contraceptive efficacy diminished 2 days after application, and was no longer present at 7 days.

13. In Section 2.10, first paragraph, first sentence: Currently there is one completed **and fully reported** clinical trial of the safety of SPL7013 Gel.

14. In Section 2.10, fourth and fifth paragraphs (added): **A second Phase 1 safety study to investigate the safety, tolerability and systemic absorption of 3.0%w/w SPL7013 Gel when administered to the penile epithelium once daily for 7 days has recently been completed and is in the analysis stage. A total of 37 healthy male subjects aged 18 years or older were enrolled in the study and a total of 36 subjects completed all aspects of the study. Although the data has yet to be unblinded, an ongoing review of the safety data indicates that the product was well tolerated. The most commonly reported AEs with a potential causal relationship to the study product were penile itch (three subjects), penile redness (three subjects) and headache (three subjects) – all of which were mild in intensity. Three AEs were reported of moderate intensity (epistaxis, viral illness and folliculitis on face), but each was considered unlikely to be related to the study product. All other AEs were mild in intensity and only occurred in one subject. No SAEs were reported.**

As with the study in females, no discernible trends in AEs were observed in this study, and no SPL7013 was detected in any plasma sample analyzed during the study.

15. In Section 2.10, sixth paragraph (added): A Phase I safety study of 3.0% w/w SPL7013 Gel in sexually abstinent women ~~was recently initiated~~ **is ongoing** within the Sexually Transmitted Infections Clinical Trials Group under the IND for HSV-2 prevention. Safety ~~will be~~ **is being** measured by clinical symptoms and adverse events, pelvic exam with colposcopy and measurement of innate immunological factors in the genital tract; tolerability ~~will be~~ **is being** measured by standardized questionnaire. **Data reviewed as part of the ongoing safety assessment indicate that the product is being well tolerated, and no SAEs have been reported to date.** This trial is expected to complete enrollment in 2007.

16. In Section 2.12.2, second paragraph, fifth sentence: A Phase 1 study of the safety of 3% w/w SPL7013 Gel in male volunteers ~~is currently enrolling participants~~ **has completed enrollment and is in the analysis stage; a review of safety data has indicated that the product was well-tolerated** (Protocol Number SPL7013-002).

17. In Section 4.2, sixth bullet: The proportion of participants who at their **Two-**Week ~~2~~ Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;

18. In Section 4.2, eleventh bullet: Detection of PL7013 in blood samples at Day 0 and **Two-**Week ~~2~~ Clinic Visit (Target Day 14).

19. In Section 6.2.3, first paragraph, third sentence: SPL7013 Gel has been shown to be stable in the vaginal applicators for up to ~~6~~ **9** months at 40°C (104°F).

20. In Section 6.2.6: Study participants will be instructed to bring all unused study products back to the enrollment site at the **Two-**Week ~~2~~ **Clinic** Visit.

21. In Section 6.3, first paragraph, second sentence: Data on adherence to self-administration of a study gel will be collected at the **Two-**Week ~~2~~ Clinic Visit via a web-based questionnaire (see acceptability and adherence questionnaire in **S**~~s~~ection 7.2, **B**~~b~~behavioral **M**~~m~~easures).

22. In Section 6.3, second paragraph, fourth sentence: For participants who anticipate or report adherence difficulties at the **One-**Week ~~1~~ Clinic Visit, every effort will be made to identify strategies that will help increase their rates of correct product use throughout participation in the study.

23. In Section 6.4, first paragraph: Applicators will be tested in the MTN ~~Central~~ **Network** Laboratory using the Population Council dye-based applicator test noted in Section ~~7.4.2~~ **7.4.3**.

24. In Section 7.3, sixth bullet:
    - Complete blood count (hemoglobin, ~~hematocrit, RBC,~~ WBC with differential, platelets)

25. In Section 7.3, tenth bullet:
    - ~~Serum~~ **Plasma** SPL7013 level

26. In Section 7.3, twenty-first bullet:
    - As clinically indicated: urine culture and sensitivity, herpes culture, **Genprobe Aptima,** rapid plasma reagin (RPR)**, treponemal confirmation, HIV Western blot**

27. In Section 7.4, first paragraph, first sentence: Each study site will adhere to the standards of good clinical practice, the MTN ~~Central~~ **Network** Laboratory Manual, the study-specific procedures manual, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory.

28. In Section 7.4, second paragraph: The MTN ~~Central~~ **Network** Laboratory has confirmed that the study gels ~~which may contaminate specimens collected for pregnancy, gonorrhea, and Chlamydia testing~~ do not inhibit or otherwise interfere with the pregnancy test **and dipstick urinalysis** methodology selected for this study. **The study gel has been determined to interfere with SDA testing for Chlamydia and gonorrhea. Chlamydia and gonorrhea testing is only done at Screening, unless indicated at follow-up visits; in these cases, the testing will be done via Genprobe Aptima, which has been determined to be unaffected by the study gel.**

29. In Section 7.4.1, first paragraph: The following types of specimens will be collected at the study site and tested at the local laboratory: urine, vaginal, cervical, ~~and~~ blood**, and (as needed) other pelvic swabs**.

30. In Section 7.4.1, fifth paragraph (added):
    Other Pelvic Samples
    The Local Laboratory will test pelvic swabs for HSV-2 via culture as needed.

31. In Section 7.4.3, first paragraph: Vaginal and cervical specimens listed below will be collected at the study site and tested at the MTN ~~Central~~ **Network** Laboratory. These include: vaginal gram stain, quantitative vaginal cultures, cervical cytokines, cervical innate factors, **and** urine SDA for *C. trachomatis* and *N. gonorrhoeae* testing~~, and genital ulcer swabs for multiplex PCR~~. **As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.**

32. In Section 7.4.3, third paragraph: Gram-stained vaginal smears will have ~~neutrophils~~ **leukocytes** quantified according to ~~Central~~ **Network** Laboratory SOP.

33. In Section 7.4.3, fourth paragraph, third sentence:
Cytokines will be measured according to ~~Central~~ **Network** Laboratory SOP via the Luminex® 100TM Instrument (Luminex Co., Austin, TX), using concentrations extracted from an 8-point standard curve via the Luminex® 100TM IS software.

34. In Section 7.4.3, fifth paragraph:
Urine Specimens
C. trachomatis and *N. gonorrhoeae* will be detected using an amplified DNA (SDA) assay and measured according to policies outlined in the SSP. **As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.**

35. In Section 7.4.3, sixth paragraph, second sentence:
Applicators with visible remaining product will be emptied of product by the MTN Senior Pharmacist or their delegate before they are transferred to the MTN ~~CL~~ **NL** for dye-based testing similar to that described by Wallace et al. [18].

36. In Section 7.4.3.1: ~~Central~~ **Network** Laboratory staff will conduct periodic visits to both sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

37. In Section 7.4.3.2, first sentence: Plasma and cervical specimens will be stored at the MTN ~~Central~~ **Network** Laboratory for possible future research testing.

38. In Table 10:

Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • Rapid Plasma Reagin/***Confirmatory testing** • HIV-1 Antibody Test/***Confirmatory testing**

Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with ~~neutrophil~~ **leukocyte** quantification • ***Herpes culture** • Pap smear (if no written report from prior year)

39. In Table12:

Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level • *Rapid Plasma Reagin**/*Confirmatory testing**

	• Plasma archive
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with ~~neutrophil~~ **leukocyte** quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix

40. In Table 13:

Urine	• Pregnancy test • *Urinalysis • *Culture and sensitivity • *~~SDA~~ **Genprobe Aptima** for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • *Rapid Plasma Reagin**/*Confirmatory testing**
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with ~~neutrophil~~ **leukocyte** quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture

41. In Table 14:

Urine	• Pregnancy test • *Urinalysis • *Culture and sensitivity • *~~SDA~~ **Genprobe Aptima** for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level • *Rapid Plasma Reagin**/*Confirmatory testing** • Plasma archive
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with ~~neutrophil~~ **leukocyte** quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix • *Herpes culture

42. In Table 15:

Urine	• Pregnancy test

	• *Urinalysis • *Culture and sensitivity • *~~SDA~~ **Genprobe Aptima** for GC/CT
Blood	• *Complete blood count • *Liver function panel • *Creatinine level • *Coagulation panel • *Rapid Plasma Reagin/***Confirmatory testing**
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears for ~~neutrophil~~ **leukocyte** quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture

43. In Section 7.9, first paragraph, second sentence: If the results are not available at the **Three-**Week ~~3 Follow up~~ **Clinic V**~~v~~isit for participants, a final contact (in person or by telephone [except for HIV test results]) may be required to provide the final study test results, post-test counseling, and treatment from these visits.

44. In Section 8.2, fifth paragraph: The following reports are produced:
    - Clinical quality control
    - Safety review
    - Pre-existing conditions
    - Adverse events (AEs) requiring review
    - Adverse event/concomitant medication
    - Safety summary
    - ~~WBC/differential~~

45. In Section 8.2.2, fifth paragraph, second bulleted item: Having at least one **Grade 3 or higher** macroscopic finding or other clinical evidence of damage during follow up (judged not to be due to pathogen or iatrogenic trauma) to the vulvar and/or vaginal **deep** epithelium and/or cervical mucosa including ulceration and other lesions, severe **global** erythema, and/or severe **global** edema judged definitely, probably, or possibly related to the study gel or applicator.

46. In Section 8.2.2, sixth paragraph, fifth sentence: The quorum will consist of the DAIDS Medical Officer, a NICHD ~~representative,~~ **Medical Officer, and** one of the MTN safety physicians~~, a representative from each of the sites, a CORE FHI representative, and a SCHARP Clinical Affairs Research Nurse~~.

47. In Section 8.3.1, fourth paragraph: Participants who develop any pelvic exam abnormality will be followed until the AE resolves or stabilizes. Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product. The study clinician will suggest follow up care or a referral for such care if deemed appropriate. Study site

staff will document on study CRFs all AEs reported by or observed in enrolled study participants or their partners from the time of their first dose of study gel through the **Three-**Week ~~3~~ **Clinic** Visit or early termination, regardless of severity and presumed relationship to study gel or applicators. ~~All AEs, except vulvitis, vaginitis and cervicitis will be graded using the DAIDS AE Grading Table Version 1.0, Dec 2004, (also referred to as the "Toxicity Table").~~ **The Female Genital Toxicity Table (Appendix IX) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE, as noted above. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, Dec 2004. In cases where an AE is covered in both tables, the Female Genital Toxicity Table will be the grading scale utilized.**

48. In Section 8.3.2: The severity (intensity) grades that will be used for this study are~~:~~

- ~~Mild: the participant was aware of the AE, but was still able to perform all activities of daily life; medical therapy required was minimal or none.~~
- ~~Moderate: the participant had to discontinue some activities of daily life due to the AE; medical therapy required was minimal or none.~~
- ~~Severe: the participant was incapacitated by the AE, and was unable to perform normal activities; medical therapy required was significant.~~
- ~~Life-threatening: Any event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.~~
- ~~Death~~ **defined in the DAIDS AE Grading Table Version 1.0, Dec 2004 and the Female Genital Toxicity Table.**

49. Table 16 has been removed from the protocol.

~~**Table 16: Protocol-Specific Toxicity Table**~~

~~**CLINICAL**~~				
~~**PARAMETER**~~	~~**GRADE 1 MILD**~~	~~**GRADE 2 MODERATE**~~	~~**GRADE 3 SEVERE**~~	~~**GRADE 4 POTENTIALLY LIFE-THREATENING**~~
~~**ESTIMATING SEVERITY GRADE**~~				

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Symptom not mentioned in DAIDS Toxicity Table or Protocol-specific Toxicity Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
Vulvitis and/or vaginitis	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that require minimal medical therapy (such as a course of topical or oral antibiotics or antifungal) or cause greater than minimal interference with usual social and functional activities	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that result in inability to perform usual social and functional activities and/or require significant medical intervention such as a surgical procedure or hospitalization	Life-threatening vulvitis and/or vaginitis with perforation
Cervicitis	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require minimal medical therapy (such as a course of oral antibiotics) or that cause greater than minimal interference with usual social and functional activities	Cervicitis or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require significant medical intervention (such as intravenous antibiotics) or that cause inability to perform usual social and functional activities	Life-threatening
* Findings include erythema, edema, grossly white finding, petechiae, ecchymosis, peeling, ulceration, abrasion, laceration.				

50. In Section 10.2.2, second bullet: The proportion of participants who at their **Two-**Week ~~2~~ Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;

51. In Section 10.2.3, third bullet: Detection of SPL7013 in blood samples at Day 0 and **Two-**Week ~~2~~ Clinic Visit (Target Day 14)

52. In Section 11.3, first paragraph, first sentence: Dr. Sharon Hillier, who completed a training program in clinical and public health microbiology certified by the American Board of Medical Board of Microbiology, directs the Site Support and Diagnostic Training Core in the MTN ~~Central~~ **Network** Laboratory at Magee-Womens Research Institute.

53. In Section 11.3, second paragraph, first sentence: Dr. John Mellors directs the Virology Core in the MTN ~~Central~~ **Network** Laboratory at the University of Pittsburgh School Of Medicine.

54. In Section 11.4, first paragraph, fourth sentence: Training and written instructions outlining management and reporting, study gel dispensing, product accountability, and other study operations will be provided by Family Health International, the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), and the MTN ~~Central~~ **Network** Laboratory.

55. In Section 12, third paragraph, second sentence: Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN ~~C~~**N**L, Family Health International, Statistical Center for HIV/AIDS Research & Prevention, NIAID, NICHD, Starpharma Pty Ltd, FDA, and US regulatory authorities.

56. In Section 13.9.1, HIV pretest and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Participants must receive their HIV test results to take part in this study. The investigators do not expect a screening population at high risk for HIV infection. However, trained clinical staff will refer participants who ~~test positive or indeterminate via the HIV antibody screen test~~ **are confirmed to be HIV-infected per the HIV Antibody Testing Algorithm in Appendix III** to a physician for follow-up testing and care. Participants who have positive or indeterminate results will have standard post-test counseling as well as limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if needed or requested by the participant.

57. In Appendix I:

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Screen 1	Screen 2	Enroll	Phone Call	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit	Inter./ Safety Visit
Target Day	≤30 Days		Day 0	Day 2	Day 7	Day 14	Day 21	PRN
Window Period	≤36 Days		Day 0	Day 2-3	Day 6 – 8	Day 13 – 15	Day 20 – 24	
Study Communications								
Informed Consent	X		X					
Assign Participant ID	X							
Eligibility Assessment	X	X	▲					
Collect Demographics	X							
HIV Pre- & Post-Test Counseling	X							
Screening Results (as available)	X	X	X					
Treatment or Referral	▲	▲	▲		▲	▲	▲	▲
Record/Update Medical and Menstrual History	X	X	X		X	X	X	X
Baseline Behavioral Questionnaire			X					
Record/Update Con. Meds.			X		X	X	X	▲
Record Adverse Events					X	X	X	▲
Vaginal Product History			X					
Acceptability Assessment						X		
Adherence Assessment					X	X		
Male Condom Counseling	X		X		X	X		▲
Record/Update Contacts	X	X	X		X	X	X	X
Schedule Next Visit	X	▲	X		X	X	▲	▲
Obtain Random Assignment			X					
Phone Assessment				X				
Study Burden Questionnaire							X	
Reimbursement	X	X	X		X	X	X	
Laboratory								
Qual. Urine Pregnancy Test	X	X	▲		X	X	X	X
Urinalysis	X		▲		▲	▲	▲	▲
Urine Culture & Sensitivity	▲		▲		▲	▲	▲	▲
CBC, Liver Function Panel, Creatinine Level, Coag. Panel	X		X		X	X	▲	▲
RPR (Syphilis)	X		▲		▲	▲	▲	▲
Confirmatory Tests for Syphilis	▲		▲		▲	▲	▲	▲
HIV Antibody Screen	X							▲
HIV Confirmatory Testing	▲							▲
SPL7013 Level			X			X		
Plasma Archive			X			X		
Vaginal pH	X		X		X	X	X	▲
Quantitative Vaginal Cultures			X		X	X	X	▲
Vaginal Wet Prep Slide	X		X		X	X	X	▲
Gram-Stained Vaginal Smears	X		X		X	X	X	▲
Cervical Swabs for Cytokines and Innate Factors			X		X	X	X	▲
Urine SDA for Gonorrhea & Chlamydia	X		▲					
Genprobe Aptima					▲	▲	▲	▲
Pap Smear of Cervix	X							▲
Herpes Culture	▲				▲	▲	▲	▲
Clinical								
Colposcopy			X		▲	X	▲	▲
Vital Signs	X		X		X	X	X	▲
Abdominal/Pelvic Exam	X		X		X	X	X	▲

X=protocol-defined procedure; ▲=performed as clinically indicated; Plasma archive will only apply if participant has signed the consent for Storage of Specimens

58. In Appendix II, bullets: For trichomoniasis or symptomatic BV, treat or refer for treatment. If resolved, restart study gel use. If observed at **Two-**Week ~~2~~ **Clinic ~~V~~Visit**, treat and follow up to document resolution

- For symptomatic candida vaginitis: manage with oral medication and re-evaluate in 3 – 5 days. If resolved, restart study gel use. If observed at **Two-**Week ~~2~~ **Clinic ~~V~~Visit**, treat and follow up to document resolution
- For asymptomatic candida vaginitis:
    - If a participant has asymptomatic candida vaginitis she should continue study gel use and be re-evaluated in 7 days
    - If at the **Two-**Week ~~2~~ **Clinic** Visit there are signs and symptoms compatible with vaginitis, treat and follow up to document resolution
- For asymptomatic BV:
    - Continue study product as scheduled and reevaluate per visit schedule

59. In Appendix III: ~~MTN~~ HIV ANTIBODY TESTING ALGORITHM

60. Appendix IX has been removed from the protocol and placed in Section 13 of the MTN-004 Study-Specific Procedures Manual. A new Appendix IX has been added to the protocol: Female Genital Toxicity Table.

APPENDIX IX: FEMALE GENITAL TOXICITY TABLE

Female Genital Toxicity Table Version 1.1 1-23-07

Female Genital Toxicity Table for use in Topical Microbicide Studies					
PARAMETER	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	NORMAL	MILD	MODERATE	SEVERE	POTENTIALLY LIFE-THREATENING
General					
Odor	No complaint	Mild-moderate unpleasant odor	Severe unpleasant odor	n/a	n/a
Pain/Tenderness	Specify area: Vulvar/Perineum, Vagina, Cervix (including cervical motion tenderness), Uterus, Adnexae, Pelvic/Lower Abdominal, or Ovulatory	* Note - If both pain and tenderness are present only report the one with the most severe grade			
Pain *	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social or functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Tenderness *	None	Mild tenderness	Moderate tenderness	Severe tenderness	n/a
Dyspareunia (pain with sexual activity)	None	Pain causing no or minimal interference with sexual function	Pain causing greater than minimal interference with sexual function	n/a	n/a
Dysmenorrhea/cramping with menses	None	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social or functional activities or the need for narcotic medication	n/a

Genitourinary Signs/Symptoms by Anatomic Location					
Vulva					
Vulvar/Vaginal itching	None	Itching causing no, mild, or moderate interference with daily activities	Itching causing inability to perform usual social and functional activities; may require intervention such as antihistamine or bathing to provide relief.	n/a	n/a
Vulvar edema	None	Mild, non-pitting edema.	Moderate, 1-2+ pitting edema.	3+ pitting edema, severe enough to require urinary drainage, or weeping edema +/- skin breakdown	n/a
Vulvar erythema	None	Erythema covering < 50% of vulvar surface	Erythema covering ≥ 50% of vulvar surface.	n/a	n/a
Vulvar lesions (Findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc	Blisters, ulcerations or pustules - no treatment indicated	Blisters, ulcerations or pustules with treatment indicated	Severe epithelial disruption with hospitalization indicated	n/a
Vulvar rash	None	Rash covering <50% of vulvar surface	Rash covering ≥50% of vulvar surface	Severe epithelial disruption with hospitalization indicated	n/a
Bartholin's or Skene's gland	No findings	Cyst with no inflammation	Cyst or absoess with outpatient intervention indicated	Cyst or abscess with hospitalization indicated	Necrotizing fasciitis from Bartholin's abscess
Vagina					
Vaginal edema	None	Mild-moderate engorgement	Lost of ruggae and friability	n/a	n/a
Vaginal erythema	None	Erythema covering <50% of vaginal surface	Erythema covering ≥ 50% of vaginal surface	n/a	n/a
Vaginal dryness	No complaint	Dryness causing no or minimal interference with usual sexual, social, or functional activities	Dryness causing greater than minimal interference with usual sexual, social, & functional activities	n/a	n/a
Vaginal discharge by subject report **	Subject's usual amount of discharge, regardless of color or quantity.	Mild-moderate increase in amount above patient baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention	n/a	n/a
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination	n/a	n/a
*** Note - If vaginal discharge is present both by history and on examination only report the one with the most severe grade**					
Vaginal abrasions or lacerations (including probable applicator injuries)	None	Superficial disruptions and disruptions extending through the mucosa with minimal impact on life	Large disruptions extending through the mucosa or large superficial disruptions hospitalization not indicated	Large disruptions extending through the mucosa or large superficial disruptions hospitalization indicated	Lacerations extending into the peritoneal cavity, bladder or rectum
Vaginal lesions (Findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc	Blisters, ulcerations or pustules, no treatment indicated	Blisters, ulcerations or pustules with treatment indicated	Severe epithelial disruption requiring hospitalization	n/a
Vaginal and Cervical masses (polyps, myomas or possible malignancy)	None, or normal variants such as Nabothian cyst or Gartner duct cyst	Polyp or myoma or undiagnosed mass w/o symptoms	Polyp, myoma or undiagnosed mass causing mild symptoms e.g. bleeding/ pain not requiring more than mild analgesia	Polyp, myoma or undiagnosed mass causing severe symptoms such as bleeding/pain affecting bladder and bowel function	Visible cervical cancer
Cervix					
Cervical edema	None	Edema without friability	Friable cervix	n/a	n/a
Cervical erythema	None	Erythema covering < 50% of cervix	Erythema covering ≥50% of cervix	n/a	n/a
Cervical discharge	White or clear discharge	Small amount of purulent discharge at os	Purulent discharge extending onto cervix or vagina	n/a	n/a
Visible cervical lesions (Findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc	Blisters, ulcerations or pustules, no treatment indicated	Blisters, ulcerations or pustules with treatment indicated	n/a	n/a

Uterus					
Uterine masses/enlargement based on bimanual examination	normal to 8 week size, no palpable myomas	Enlarged uterus and mild symptoms e.g., bleeding/pain requiring mild analgesics	Enlarged uterus/myoma with moderate pain or symptoms e.g. bleeding	Mass causing severe bleeding/pain or with impact on bowel/bladder function	Uterine mass that requires transfusion or surgery
Polyp, submucosal fibroid or thickened endometrium detected by transvaginal ultrasound, new or increasing in size from prior exam	None or unchanged/reduced in size from prior exam	New myomas <6 cm diameter, one or multiple or diameter increased <6 cm since prior exam	New myomas ≥6 cm diameter, single or multiple or diameter increased ≥6 cm since prior exam	Hospitalization and/or surgery indicated	n/a
Adnexa					
Not pregnancy- or infection-related adnexal masses based on bimanual exam (Use if no ultrasound done, if U/S done use ultrasound categories below)	None, ≤ 4 cm, normal size ovary	> 4 cm with minimal or no symptoms	>4 cm with severe symptoms e.g. pain but hospitalization not indicated (see footnotes below)	>4 cm with severe symptoms e.g. pain and hospitalization indicated (see footnotes below)	n/a
Hydrosalpinx based on ultrasound	None	Asymptomatic, suspected hydrosalpinx	Hydrosalpinx with pain, but w/o evidence of infection or ectopic pregnancy	Signs/symptoms of infection with hospitalization and/or surgery indicated	n/a
Adnexal mass based on ultrasound	None	Simple cyst, asymptomatic	Simple cyst, symptomatic	Mass suspicious for malignancy	Malignant mass
Abdomen					
Abdominal mass not palpable on pelvic exam of unknown diagnosis	None or known (pre-existing) mass unchanged in size	New mass or increased size of known mass requiring mild analgesia with minimal impact	New mass or increased size of known mass with moderate symptoms	Mass causing severe bleeding/pain with impact on bladder/bowel function or with hospitalization indicated	Malignancy
Urinary Tract					
Urinary frequency	None	Up to 2 times patient's normal frequency	>2 times patient's normal frequency	n/a	n/a
Dysuria	None	Superficial only	Deep +/- superficial	Inability to void due to pain	n/a
Hematuria	None	Microscopic, no intervention indicated (beyond evaluation for infection)	Gross blood in urine or medical intervention/ evaluation indicated (beyond evaluation for infection)	Persistent bleeding with transfusion, hospitalization or intervention indicated to obtain hemostasis (endoscopy, interventional radiology or operative)	Profuse hemorrhage with shock or orthostatic dizziness

Composite Signs/Symptoms (Use instead of individual categories if 2 or more signs/symptoms are present)					
		Use Mild if all signs/symptoms would individually be grade 0 or 1	**Use Moderate if one or more signs/symptoms would individually be grade 2 and all others grade 1 or 0**	**Use severe if one or more signs/symptoms individually would be grade 3**	
No organism identified but inadequate testing performed					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness or discharge)	None	Mild signs/symptoms	Moderate signs/symptoms	Severe signs/symptoms	n/a
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness and discharge)	None	Mild signs/symptoms	Moderate signs/symptoms	Severe signs/symptoms	n/a
PID (if Gonorrhea or Chlamydia identified use that category)	None	n/a	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution.
No organism identified after appropriate testing performed					
Vulvovaginitis (combinations of pain, itching, erythema, edema, rash, tenderness or discharge)	None	Mild signs/symptoms	Moderate signs/symptoms	Severe signs/symptoms	n/a
Cervicitis (combinations of dyspareunia, erythema, edema, tenderness and discharge)	None	Mild signs/symptoms	Moderate signs/symptoms	Severe signs/symptoms	n/a
PID (if Gonorrhea or Chlamydia identified use that category)	None	n/a	Cervicitis with mild uterine tenderness, ± mild cervical motion tenderness, no signs of peritoneal irritation	More diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution.

Genitourinary Infections					
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement such as encephalitis, hepatitis.
Candida	Absence of symptoms regardless of candida test results	Positive culture, wet mount or other laboratory test for yeast, with mild symptoms	Positive culture, wet mount or other laboratory test for yeast, with moderate to severe symptoms	n/a	n/a
Trichomonas	Negative	n/a	Positive wet mount, culture, PCR or other licensed test, excluding pap smear, showing T. vaginalis, regardless of symptoms.	n/a	n/a
Bacterial Vaginosis	Negative	Asymptomatic BV diagnosed by Amsel criteria, wet mount, Gram stain or licensed diagnostic test	Symptomatic confirmed by wet mount, Gram stain or any licensed diagnostic test	n/a	n/a
Chlamydia	Negative	n/a	Positive culture or other diagnostic test for Chlamydia, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Chlamydia with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess or surgery required for resolution.
Gonorrhea	Negative	n/a	Positive culture or other diagnostic test for Gonorrhea, asymptomatic or with mild uterine or cervical motion tenderness (no signs of peritoneal irritation)	Positive test for Gonorrhea with abdominal or uterine or adnexal tenderness on examination, with or without adnexal mass, diffuse tenderness, any signs of peritoneal irritation, or indications for hospitalization	Tubo-ovarian abscess, surgery required for resolution or disseminated gonococcal infection.
Syphilis	Negative treponemal or non-treponemal test or both positive with known treatment and stable titers(< 4 fold increase)	n/a	Syphilis diagnosed by a positive treponemal test along with a positive nontreponemal test and no previous treatment or a four-fold rise in titer on the nontreponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes	Criteria for grade 2 syphilis in the presence of neurologic symptoms or a positive CSF VDRL or FTA-ABS.	n/a
Urinary Tract Infection (by urinalysis and urine culture)	Negative	5-10 WBC/hpf on urinalysis with a negative culture per protocol definition (with or without symptoms)	>10 WBC/hpf on urinalysis or a positive culture per protocol definition (with or without symptoms)	Pyelonephritis	Sepsis (septicemia) due to urinary tract infection
Genital Dysplasia					
Condyloma, specify site: cervical, vaginal, vulvar, perianal	None	Condylomata causing no or mild interference with daily function	Condylomata causing moderate interference with daily function	Condylomata causing severe interference with daily function, secondary infection or hospitalization indicated	n/a
Intraepithelial Neoplasia by biopsy: VIN, CIN, VAIN	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (Use this category only if treatment performed without diagnostic testing, otherwise use biopsy category above)	nl PAP	ASCUS or LSIL	HSIL	Carcinoma-in-situ or Carcinoma	n/a
Abnormal Uterine Bleeding Unrelated to Pregnancy					
Menorrhagia (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia (intermenstrual or frequent bleeding)	None, or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for >3 months (oligomenorrhea/amenorrhea)	n/a	n/a
Postcoital Bleeding	None	Occasional (<25% of coital acts) OR Increase from usual with no or minimal interference with usual, social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual, social functioning (including sexual	Consistent (>75% of coital acts) OR Incapacitating or severe interference with usual, social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Complications of Pregnancy					
First trimester bleeding	None	Spotting or bleeding less than menses with continuation of pregnancy	Bleeding like menses or heavier with continuation of pregnancy	Spontaneous abortion, or profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Spontaneous abortion with profuse bleeding and/or shock
Postabortal endometritis/ salpingitis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, requiring < 3 days of parenteral antibiotics	Severe symptoms requiring > 3 days of IV antibiotics or development of tubo-ovarian abscess	Ruptured TOA or diffuse peritonitis or severe uterine infection for which operative intervention indicated
Postpartum hemorrhage	EBL < 500 cc for vaginal delivery or < 1000 cc after CS or reported as normal	EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased	EBL > 1000 for vaginal delivery or > 1500 for CS, with or without mild dizziness, no transfusion required	Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products is indicated.	Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated.
Postpartum endometritis	None	Low grade fever and uterine tenderness, resolved with oral antibiotics	Moderate symptoms, treated by < 3 days of parenteral antibiotics	Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin	Severe infection or infection for which operative intervention is indicated
Chorioamnionitis	None	Fever (> 38C or 100.4F) with two or more: FHR > 160 BPM, maternal HR > 120, uterine tendemess between contractions or purulent AF or preterm labor	Same as grade 1 plus fever > 38.4C or 101F	Criteria for grade 2 plus fetal distress or fever > 40C or 104F	Criteria for grade 3 plus either fetal demise or maternal symptoms of shock
Episiotomy infection	None	Mild erythema, edema and tenderness of wound	Fever > 38C or 100.4F with erythema, edema and tenderness of wound	Fever with wound dehiscence or debridement required	Fever with signs of wound infection and shock or necrotizing fasciitis

Second/third trimester bleeding	None	Bleeding less than menses	Bleeding like menses or greater but not requiring intervention	Bleeding requiring delivery or other intervention such as transfusion	Bleeding with fetal demise or coagulopathy
Preterm rupture of membranes	None	n/a	Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 32 weeks' gestation or < 1500 grams birth weight
Preterm contractions	None	Preterm contractions which resolve without medical intervention	Preterm contractions with cervical change which result in medical intervention but not resulting in preterm delivery	Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight	Delivery < 32 weeks' gestation or < 1500 g birth weight
Poor fetal growth	Above 10th %ile	Fetal growth < 10th %ile but > 3rd %ile for gestational age by ultrasound or newborn exam	n/a	Fetal growth < 3rd %ile for gestational age by ultrasound or newborn exam	n/a

Footnotes:
1. If pain or tenderness is included in the grading of another caregory (eg. PID) it should not be graded again in the pain or tenderness category

61. In the Reference List, first listing: [1] UNAIDS. ~~Report on the global AIDS epidemic. 2006. Ref Type: Internet Communication~~ **2006 AIDS Epidemic Update: Global Summary. http://www.who.int/hiv/mediacentre/news62/en/index.html accessed May 9, 2007.**