MTN 005 Protocol Specific Training

Study Design and Procedures

Overview

- To review study objectives
- To review the study design, endpoints, and sample size
- To ensure understanding of the inclusion and exclusion criteria for study participation
- To briefly review the study visit procedures

Study Objectives and Endpoints

Primary Objectives of MTN 005

- Evaluate the safety of the study IVR in HIV-uninfected women over 12 weeks of use
- Evaluate the adherence to the study IVR in HIV-uninfected women over 12 weeks of use

Primary Endpoints of MTN 005

- Endpoints:
  - Evidence of Grade 2 or higher genitourinary events as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004 (Clarification dated August 2009), Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies)
  - For women randomized to the study IVR arm, participant report of frequency of study IVR removal (voluntary and involuntary) and duration without IVR inserted in vagina over 12 weeks of use

Secondary Objectives of MTN 005

- Describe changes in sexual behavior and changes in vaginal hygiene practices in the study IVR vs. no IVR group over 12 weeks of use/non-use
- Evaluate the acceptability of the study IVR in HIV-uninfected women over 12 weeks of use
- Measure vaginal flora characteristics, and descriptively examine changes in these characteristics over the course of study IVR use

Secondary Endpoints of MTN 005

- Endpoints:
  - Per participant report, changes in sexual behavior and vaginal hygiene practices
  - For women randomized to the study IVR arm, participant report of acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in participant and/or partner sexual feeling
  - Changes in vaginal flora from enrollment to week 12 as measured by Gram stain Nugent score and quantitative culture (note that these quantitative vaginal cultures will only be available from the US sites, therefore reducing the available sample size for this objective)

Exploratory Objectives of MTN 005

- Test candidate biomarkers in the cervicovaginal environment before and after the use of study IVR
- Evaluate the study IVR after 12 weeks of use for the presence of biofilms (US sites only)

Exploratory Endpoints of MTN 005

- Endpoints:
  - Changes in vaginal biomarkers (US Sites only)
  - Presence of biofilms on study IVR surface (US sites only)

Study Design

Study Design

- Multi-site, open-label, two-arm, randomized controlled trial comparing study IVR to no IVR with randomization of 2:1 (IVR: No IVR)

Study Design

- Study Duration:
  - 16 weeks for each participant; 14 month approximate total study duration

- Sites:
  - Bronx-Lebanon Hospital Center, Bronx, NY; USA
  - University of Alabama at Birmingham, Birmingham, AL; USA
  - National AIDS Research Institute, Pune, India

Inclusion Criteria

1) Age 18-45 years (inclusive) at Enrollment, verified per site standard operating procedures (SOP)
2) Willing and able to provide written informed consent to be screened for and to take part in the study
3) Willing and able to provide adequate locator information, as defined in site SOPs
4) HIV-uninfected at Screening based on testing performed by study staff at Screening (per algorithm in Appendix II) and willing to receive HIV counseling and test results

Inclusion Criteria

5) In general good health at Screening and Enrollment, as determined by the site Investigator of Record (IoR) or designee

6) Per participant report at Screening and Enrollment, sexually active, defined as having had penile-vaginal intercourse at least once in the past 30 days prior to Screening and Enrollment

7) Per participant report at Screening and Enrollment, expecting to continue penilevaginal intercourse at least monthly for the duration of study participation

Inclusion Criteria

8) Per participant report, using an effective method of contraception at Enrollment, and intending to use an effective method for the duration of study participation. Effective methods include hormonal methods (except contraceptive vaginal rings), IUD inserted at least 7 days prior to enrollment, study provided male condoms, and/or sterilization (of participant or her sexual partner(s) as specified in site SOPs)

Inclusion Criteria

9) Pap result in the 12 calendar months prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) or satisfactory evaluation with no treatment required of non-Grade 0 Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines or per local standard of care, in the 12 calendar months prior to the Enrollment Visit

Inclusion Criteria

10) At Screening and Enrollment, agrees not to participate in other drug or device research study for the duration of study participation

11) Able and willing to abstain from the use of non-study vaginal products and/or practices (other than tampons) including but not limited to spermicides, diaphragms, contraceptive vaginal rings, vaginal antibiotic or antifungal medication, sex toys, lubricants or condoms that contain silicone, menstrual cup and douching, within the 14 days prior to Enrollment through study termination

Exclusion Criteria

1) Participant reported history of:
   a) Adverse reaction to silicone (ever)
   b) Adverse reaction to latex (as defined per SSP)
   c) Adverse reaction to titanium dioxide
   d) Any current male sex partner with known history of adverse reaction to latex, silicone, titanium dioxide or any components of the study product (as defined per SSP)
   e) Last pregnancy outcome within 30 days or less prior to enrollment
   f) Hysterectomy

Exclusion Criteria

2) At Screening or Enrollment, has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies

Exclusion Criteria

- Note: Cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding and is not exclusionary.
- Note: Otherwise eligible participants with exclusionary pelvic examination findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 45 days of providing informed consent for Screening, the participant may be enrolled.

Exclusion Criteria

3) Pregnant at Screening or Enrollment, or per participant report intending to become pregnant during the period of study participation

Exclusion Criteria

4) At Screening or Enrollment:
   a) Unwilling to comply with study participation requirements
   b) Has a clinically apparent deep disruption of vulvar, vaginal, or cervical epithelium (colposcopic findings not visible by naked eye are not exclusionary)
   c) Is diagnosed with a symptomatic urinary tract infection (see additional information below)
   d) Is diagnosed with a reproductive tract infection (RTI) or syndrome requiring treatment per current US Centers for Disease Control (CDC) guidelines (see additional information below)
   e) Has any other abnormal physical or pelvic exam finding that, in the opinion of the investigator or designee, would contraindicate study participation

Exclusion Criteria

- Note: RTIs requiring treatment, per site specific treatment guidelines, include BV, vaginal candidiasis, other vaginitis, trichomoniasis, chlamydia (CT), gonorrhea (GC), syphilis, active HSV lesions (HSV-2 seropositive women not excluded except with active lesions), chancroid, pelvic inflammatory disease, genital sores or ulcers, or cervicitis. Otherwise eligible participants diagnosed with RTI and/or UTI during Screening will be offered treatment or a prescription for treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for Screening, the participant may be enrolled.

Exclusion Criteria

5) At Screening or Enrollment, has condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives
6) Severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver
7) Participant report of 3 or more sexual partners in the month prior to Screening

Visit Schedule

Participant Visits

Screening	Enrollment	4-Week	8-Week	12-Week	16-Week
Group	↓	↓	↓	↓	↓
A	[	Study IVR Use Period		]	Termination
B	[	No IVR (Same visits as A)		]	

Questions???