MTN-005

Expanded Safety and Acceptability Study of a Non-medicated Intravaginal Ring

A Study of the Microbicide Trials Network

Sponsored by:

International Partnership for Microbicides

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Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institutes of Health

A Non-IND Study

Protocol Chair:
Craig Hoesley, MD

Version 1.0
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MTN-005

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TABLE OF CONTENTS

TABLES

MTN-005

Expanded Safety and Acceptability Study of a Non-medicated Intravaginal Ring

LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	audio computer-assisted self interviewing
AE	adverse event
AIIMS	All India Institute of Medical Sciences
BV	bacterial vaginosis
CAB	community advisory board
CDC	(US) Centers for Disease Control
CFR	code of federal regulations
CONRAD	Contraceptive Research and Development Organization
CRPMC	Clinical Research Products Management Center
CRF	case report form
CTA	Clinical Trial Agreement
DAIDS	Division of AIDS
EAE	expedited adverse event
EC	Ethics Committee
EIA	enzyme immunoassay
FHI	Family Health International
GCP	Good Clinical Practices
hCG	human chorionic gonadotropin
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus-Type 1
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
HSV-2	herpes simplex virus-type 2
IATA	International Air Transport Association
IFA	immunofluorescence assay
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IVR	intravaginal ring
ISO	International Organization for Standardization
LDMS	Laboratory Data Management System
mg	milligram
mL	milliliter
mm	millimeter
MTN	Microbicide Trials Network
NAAT	nucleic acid amplification test
NIAID	National Institute of Allergy and Infectious Diseases

LIST OF ABBREVIATIONS AND ACRONYMS (Continued)

NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPOS	normal propylorthosilicate
OHRP	Office for Human Research Protections
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development Inc.
PSRT	Protocol Safety Review Team
PTID	Participant Identification
RCC	Regulatory Compliance Center
RPR	rapid plasma reagin
RTI	reproductive tract infection
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDA	strand displacement assay
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure (s)
SSP	study specific procedure (s)
STI	sexually transmitted infection
UA	urinalysis
UADE	unanticipated adverse device effect
US FDA	United States Food and Drug Administration
UTI	urinary tract infection
WB	Western Blot
WHO	World Health Organization

MTN-005

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INVESTIGATOR SIGNATURE FORM

Version 1.0 / 03 April 2008

A Study of the Microbicide Trials Network (MTN)

Sponsored by:
International Partnership for Microbicides

Co-sponsored by:
US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Coordinating and Operations Center. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to the MTN Manuscript Review Committee, DAIDS, and IPM for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Site Investigator

_____ _____
Signature of Site Investigator Date

MTN-005

Expanded Safety and Acceptability Study of a Non-medicated Intravaginal Ring

PROTOCOL SUMMARY

Short Title: Safety and Acceptability of a Non-medicated Intravaginal Ring (IVR)

Protocol Chair: Craig Hoesley, MD

Sample Size: Total: 252 (168 and 84 in the IVR and No IVR arms, respectively)
India: 150 (100 and 50 in the IVR and No IVR arms, respectively)
US with competitive enrollment for two US sites
102 (68 and 34 in the IVR and No IVR arms, respectively)

Study Population: Sexually active, HIV-uninfected women between the ages of 18 and 45 years

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

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

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

Study Regimen: Participants will be randomized to study IVR or no IVR. The study IVR will be used for a 12 week period. Participants will be followed every 4 weeks until the study termination visit.

Table 1: Study Regimen

	Screening	Enrollment	4-Week	8-Week	12-Week	16-Week
GROUP	↓	↓	↓	↓	↓	↓
A		**[**	**STUDY IVR USE PERIOD**		**]**	**TERMINATION**
B		**NO IVR (SAME STUDY VISITS AS GROUP A)**				

Study Objectives

Primary Objectives

- Evaluate the acceptability of the study IVR in HIV-uninfected women over 12 weeks of use

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

Primary Endpoints:

- For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function.

- 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, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies).

Secondary Objectives

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

- Measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of study IVR use

Secondary Endpoints

- For women randomized to the study IVR arm, participant report of frequency of study IVR removal and duration of time without IVR inserted in vagina over 12 weeks of use

- Changes from enrollment to week 12 in vaginal flora as measured by Nugent score

- Changes from enrollment to week 12 in quantitative vaginal culture[1] as measured by count of *Lactobacillus* (H_2O_2 positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis, Escherichia coli, Staphylococcus aureus, Candida* species, Group B *Streptococcus,* and *Enterococcus* species. (Note that these quantitative vaginal cultures will only be available from the two US sites, therefore reducing the available sample size for this objective).

- Assessment of vaginal symptoms and signs suggestive of bacterial vaginosis (BV) or vulvovaginal candidiasis

- Changes in vaginal pH and vaginal wet mount microscopy

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Expanded Safety and Acceptability Study of a Non-medicated Intravaginal Ring
MTN Protocol Number:	MTN-005
Date:	03 April 2008

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 New Proposed Modalities in HIV Prevention

That half of all HIV infections worldwide are among women indicates the pressing need for alternative prevention methods to stem the spread of heterosexual HIV infection. Research continues on many different strategies targeted at the prevention of HIV transmission, including topical microbicides, oral pre-exposure prophylaxis, prevention case management, vaccines, treatment of sexually transmitted infection, and others[2, 3]. Recent studies have provided strong evidence that male circumcision can prevent female to male transmission of HIV[3] but there remains a critical need for female controlled methods of prevention. Use of an intravaginal ring (IVR) to deliver microbicide products is a novel investigational method for prevention of heterosexual transmission of HIV, and one that may circumvent potential difficulties related to adherence to daily or coitally dependent regimens of microbicide use. Evaluating the acceptability and safety of this delivery method are therefore necessary first steps before evaluating the efficacy of vaginal rings for the prevention of HIV.

2.2 Intravaginal Rings

There are currently three IVRs that have received US Food and Drug Administration (US FDA) approval[4-6]. NuvaRing® (Organon) is approved for use as a vaginal contraceptive, releases etonogestrel and ethinyl estradiol and must be replaced every month. Estring® (Pfizer) is a hormone replacement therapy that releases a low dose of estradiol and must be replaced every three months. Femring® (Warner Chilcott) is another hormone replacement therapy that releases estradiol (available in two different dosing options) and must be replaced every three months.

Several different rings have been investigated for contraceptive effectiveness. The Population Council has developed and carried out numerous safety and effectiveness studies on a progesterone ring for lactating women[7, 8] While not an effective contraceptive method for cycling women, it can be used by nursing women to extend the contraceptive effectiveness of lactation. The method was well accepted and effectively protected women from pregnancy. A Chilean company is currently manufacturing and distributing this ring in Chile and Peru. This ring may also be used for hormone therapy in women who require a progestin. Phase III studies are currently in progress for a 1-year contraceptive ring developed by the Population Council that releases Nestorone, a synthetic progestin and a low dose of ethinyl estradiol[9].

Safety studies have been conducted for all three rings currently approved by the US FDA. Published safety data from these studies include results from physical, pelvic, and colposcopic exams. In general, the adverse events (AE) reported in these studies were mild in nature and only a small percentage was related to the device. No clinically relevant changes or abnormalities were found upon examination in study participants[10-13]. Nonetheless, as with any vaginal device, there is consensus that such products are not appropriate for women who are prone to vaginal irritation or ulceration[4, 5].

Limited studies have also been conducted to determine the effect of IVR use on vaginal microflora. A study evaluating changes in the quantities of vaginal cells, aerobic and anaerobic bacteria, *Chlamydia trachomatis*, *Gardnerella vaginalis*, yeast, and *Trichomonas vaginalis* was conducted in 59 women using a combined contraceptive vaginal ring for either a 21, 28, 42, or 56 day cycle[14]. No increases in pathogenic bacteria were found upon examination of vaginal cultures. Another study conducted with a Silastic® ring containing a combined hormonal contraceptive evaluated the effect of the ring on bacterial flora over 20 cycles of use among 76 women[15]. The investigators found no significant changes in bacterial flora over the course of the study. Two studies conducted among 92 women with NuvaRing® showed no adverse effects on vaginal flora as measured by Nugent score[16, 17]. Interestingly, a NuvaRing® study conducted by Veres et al. found an increase in H_2O_2-producing *Lactobacillus* colonies as measured by Nugent score and colony morphology. Presence of H_2O_2-producing lactobacilli is beneficial to vaginal health and it has been suggested that further studies be conducted to confirm these findings.

Acceptability is one of the key drivers of product uptake. Acceptability of NuvaRing®, Estring®, and Femring® has been measured through patient reporting; often through questionnaires, diary cards, and interviews[18]. In general, participants are asked about the ease of ring insertion and removal, whether or not she or her partner felt the ring during intercourse, if the partner objects to the ring, whether or not the ring is comfortable, if they are satisfied with the ring, and whether or not the ring is deemed to be effective as either a contraceptive method or hormone replacement therapy.

The success of IVRs in delivering effective contraceptive and hormone- replacement methods has spurred an interest in developing IVRs expressly for the prevention of HIV. Phase I/II safety studies have been conducted for the IVR containing TMC120, a non-nucleoside reverse transcriptase inhibitor (NNRTI)[19-22]. The IVRs used in these studies (both active and placebo) are silicone elastomer rings with the same design as the Femring®, and have been well tolerated by most study participants. The non-medicated version of the Femring® will be the study product investigated in MTN-005.

2.3 Silicone Elastomer

Silicone has long been one of the materials of choice for medical applications. Common silicone medical components include catheters, feeding and drainage tubes, infusion sleeves, shunts and electrosurgical hand pieces. Silicones do not stain or corrode other materials, and can be formulated to comply with US FDA, International Organization for Standardization (ISO), and Tripartite biocompatibility guidelines for medical products[23].

2.4 Preclinical Studies

When a single dose of the NuSil silicone material extracted in 0.9% sodium chloride solution was injected intravenously in mice, there was no evidence of significant systemic toxicity for up to 72 hours after dosing[24]. Intracutaneous injection of the NuSil silicone material extracted in 0.9% sodium chloride solution and cottonseed oil (0.2 mL dose) in rabbits did not result in significant irritation or toxicity at up to 72 hours after dosing. Following intramuscular implantation of the NuSil silicone material in rabbits and examination of the implantation sites 90 days later, the material was classified as slightly irritant[24].

In an in vitro biocompatibility study in which an extract of the NuSil silicone material in Minimal Essential Medium was incubated with L-929 mouse fibroblast cells for up to 72 hours, there was no evidence of cell lysis or cytotoxicity[24]. In an in vitro hemolysis test, in which whole rabbit blood was added to the NuSil silicone material in 0.9% sodium chloride solution and incubated for 1 hour to determine the effect due to direct contact with the material or the presence of leachables, the material was considered not to be hemolytic. In an Ames test, a saline extract of the NuSil silicone material was considered to not be mutagenic[24].

2.5 Clinical Studies

In 2002, Warner Chilcott conducted an acceptability study of same the non-medicated IVR that will be used in this study in nearly 6000 women throughout the United States[24]. Overall, the non-medicated IVR was well tolerated by subjects. The most frequently reported AE was vaginal discharge (1.4%) and no other AEs were reported with a frequency of >1%. In a 13-week long, phase III double-blind, randomized, controlled clinical trial of the estrogen-containing Femring® conducted with postmenopausal women subjects, the non-medicated IVR was the same non-medicated IVR comparator that is the IVR proposed for use in MTN-005[25]. Of the 333 women in the study, 108 were randomized to the placebo ring group, 113 to the Estradiol 0.05mg/day group, and 112 to the Estradiol 0.10mg/day group. The non-medicated ring treatment group showed a higher incidence of vaginal discharge (8.3% vs. 1.8% and 2.7%), genital disorders (8.3% vs. 2.7%), vulvovaginitis (6.5% vs. 5.3% and, 0.9%) and vaginal irritation (3.7% vs. 0.9% and 1.8%)[5]. Medical assessment was that these findings were not unexpected because they demonstrated the effect of the non-medicated IVR in an estrogen-deprived atrophic vagina. Furthermore, the medical opinion was that it is not uncommon to find vaginal mucosa defects or lacerations in the postmenopausal vagina.

The safety of the non-medicated IVR that will be used in this study was recently evaluated in IPM 008, a pharmacokinetics and safety study of the TMC120 ring[19-22]. IPM 008 was a randomized, double-blinded, placebo controlled trial in thirteen sexually abstinent healthy women. Ten women were randomized to the treatment group and three women to the placebo group. The women in both the treatment and placebo groups wore the study rings for 7 days. The study results showed that there were no clinically relevant changes over time with regards to physical examinations, vital signs, vaginal pH, Nugent scores, laboratory parameters, and urinalysis. Furthermore, no serious adverse events (SAE) were reported during this study, and of the AEs that were reported, none appeared to be related to the study products.

IPM 011 is a safety and acceptability study of the same non-medicated silicone elastomer vaginal ring that will be used in MTN-005. This study is a randomized, open-label crossover study currently enrolling participants at four sites in Kenya, South Africa and Tanzania in 200 healthy sexually active women. The participants are either in the Vaginal Ring group or Observational Study (no ring) group for the first twelve weeks, and if asymptomatic for genital infections and negative for findings on the pelvic examination after the first twelve week period is completed, participants then crossover into the opposite group for an additional twelve weeks. In addition to the enrollment visit, the participants have follow-up visits at 2, 4, 8, and 12 weeks prior to the crossover, and again are scheduled for 2, 4, 8, and 12 week post-crossover visits. Participants undergo a colposcopy examination at enrollment, crossover, and at the last study visit. Participants also undergo pelvic examinations at the screening, enrollment, 2 and 8 weeks, crossover, 2 and 8 weeks post-crossover, and at the last study visit. Study staff will conduct assessments for AEs, including vaginal complaints, at all of the follow-up visits.

2.6 Marketing Experience

Warner Chilcott's IVR has been approved as the delivery method for a hormone replacement drug Menoring® in the United Kingdom (2001) and Femring® in the United States (2003). Organon's IVR has been approved as the delivery method for the combined contraceptive, NuvaRing® (2001).

The US FDA recently placed a black box warning on Femring®; however, this warning is a result of data associating oral conjugated estrogens with an increased risk of certain serious medical complications in postmenopausal women. The additional warning stems from The Women's Health Initiative study that reported an increased risk of cardiovascular events in postmenopausal women during five years of treatment with oral conjugated estrogens combined with medroxyprogesterone acetate and the Women's Health Initiative Memory Study, that reported an increased risk of developing probable dementia in postmenopausal women over four years of treatment with oral conjugated estrogens combined with medroxyprogesterone acetate[5]. Thus, this black box warning does not apply to the study IVR.

2.7 Study Hypothesis and Rationale

2.7.1 Study Hypothesis

MTN-005 hypothesizes that the study IVR will be safe and acceptable for a three month period of use.

2.7.2 Rationale

IVRs have the potential to significantly reduce the heterosexual transmission of HIV if found to be safe, acceptable, and effective against HIV infection. This study will provide data to support the safety and investigate the acceptability of a three month period of IVR use in US and Indian populations. Safety of the silicone elastomer ring has primarily been studied in postmenopausal women. While safety and tolerability of NuvaRing® has been studied in thousands of sexually active younger women, its ethylene-vinyl-acetate copolymer (EVA) composition and smaller diameter may preclude results from these studies from being extrapolated to the safety and tolerability of the silicone elastomer ring in pre-menopausal women. MTN-005 will investigate the safety and tolerability of the silicone elastomer study IVR in sexually active younger women, contributing to the body of data regarding IVR use in this population.

Product acceptability is a critical factor in determining whether an IVR should be introduced in a particular setting. This study will investigate acceptability and adherence parameters in both Indian and US populations. Currently there are very limited published acceptability data specifically reporting findings among Indian women for any IVR. The All India Institute of Medical Sciences (AIIMS) served as a study site for two WHO multi-center studies to assess the acceptability, side-effects, and

contraceptive efficacy of a contraceptive vaginal ring releasing 20 micrograms of levonorgestrel per day[26]. Women who regularly attended the outpatient gynecology clinic at AIIMS were recruited for this study. Fifty women participated in the 12-month study and 46 women participated in the 24-month study. Among participants, 38% in the 12-month study and 35% in the 24-month study discontinued ring use as a result of menstrual irregularities and vaginal irritation. A total of 16% of the participants in the 12-month study and 17% of the participants in the 24-month study reported menstrual irregularities, whereas as 12% of the participants in the 12-month study and 11% of the participants in the 24-month study reported vaginal irritation. While these data give some idea of tolerability to IVR among Indian women, they are specific to a hormone-containing device, and not necessarily applicable for a non-medicated ring of different design.

While data exist on tolerability parameters for the study IVR among perimenopausal women in the US[18, 27, 28], acceptability data in pre-menopausal women for this particular ring design are currently limited. As the thickness of the proposed study IVR is nearly twice that of the commonly used NuvaRing®, it will be important to evaluate whether reproductive age women find this alternate ring design to be acceptable. Furthermore, there are currently no published data on contraceptive or hormonal vaginal ring use among Indian women even though discussions of vaginal rings have been published in a limited number of Indian medical journals[29, 30]. Articles published in Indian medical journals tend to focus on vaginal rings as novel contraceptives and do not specifically address IVR acceptability among Indian women.

The availability of acceptability data in areas where there is a high risk of HIV acquisition is crucial. UNAIDS recently reported that among young people in India, ages 15-24, only 51% of the women as compared to 59% of the men surveyed, reported condom use during their last casual sexual encounter[31]. These data highlight an urgent need for acceptable methods of HIV prevention. Since the study IVR is a new platform for microbicide delivery it is imperative to assess its acceptability prior to proceeding with further studies. Even if a ring were developed that was effective in reducing HIV transmission, if the product has physical or clinical attributes that women and their partners dislike or find distasteful, it is less likely that women will initiate use or use it consistently. Therefore, a primary objective of this study is to assess the acceptability of the study IVR in study participants.

Assessments of IVR acceptability will include audio computer-assisted self-interviewing (ACASI) questionnaire instruments that participants will complete in a private setting. The advantage of ACASI over face-to-face interviews is that neither the investigator nor anyone else in the interview area hears the question or response, thus reducing social desirability bias. In addition, the researcher does not have to be concerned with differences in the characteristics or interviewing styles of the interviewers[32]. Recent studies in developing countries have increasingly implemented ACASI in Kenya[33-35], Malawi[36]; Zimbabwe[37]; Thailand[38, 39], India[40], Vietnam[41] and Mexico[42] among very diverse populations, including some in remote rural areas, with varying degrees of literacy and computer exposure. Findings from these studies suggest that

even in countries with low literacy or among populations unfamiliar with computers, ACASI is a useful, and often superior, technique for collecting data on sensitive behaviors.

MTN-005 will also examine the impact of study IVR use on vaginal flora. Studies have shown that the presence of H_2O_2 producing lactobacilli in the vagina offer a protective effect against sexually transmitted infections[43-48]. For example, a study conducted in female sexual contacts of infected men, demonstrated correlation between reduced prevalence of *Chlamydia trachomatis*, *Trichomonas vaginalis*, and symptomatic *Candida* and presence of H_2O_2 producing lactobacilli[49]. Another study highlighted a lower prevalence of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* in women with lactobacilli compared to women with little to no lactobacilli present in the vagina[50]. Furthermore, longitudinal studies conducted in Kenya[48] and Malawi[44], have clearly demonstrated a link between HIV acquisition and changes in vaginal flora. A third study conducted in South Africa showed a correlation between elevated vaginal pH levels and an increased risk of HIV acquisition[45]. These studies demonstrate a clear link between vaginal flora and susceptibility to sexually transmitted infections. There are currently no published data on the impact of three-month use of this type of IVR on quantitative measures of vaginal flora. MTN-005 also seeks to assess whether or not the study IVR can harbor organisms that are associated with biofilm formation. Studies have shown that the presence of biofilms can result in the expression of drug resistant genes as well as acute disseminated infection[51, 52]. Study site staff will perform a biofilm assessment via culture and/or other techniques depending on site capacity, of the study IVRs when they are collected at the 12-Week Visit or when the IVRs are returned to the study site. The specimens will then be shipped to the Network Laboratory as appropriate.

Currently, there are limited published data on the impact of contraceptive or hormonal vaginal rings on vaginal flora or the potential for biofilm formation[15-17]. Furthermore, the degree of microbiologic testing generally accepted for safety assessment of a hormone replacement or contraceptive vaginal ring may not be as extensive as what may be expected for safety assessment of a potential platform for HIV prevention. A drug delivery vehicle expressly designed to prevent male-to-female transmission of HIV must not enhance the risk of HIV acquisition. As such, documentation of flora changes noted with use of this IVR is an important part of confirming the study IVR's overall safety. Due to site laboratory capacity and the rapid shipping required for quantitative vaginal culture, only sites with capacity will contribute specimens for this study objective.

The inclusion of a no ring group in MTN-005 will permit the collection of data on AEs (including colposcopic findings) and vaginal flora changes that are likely to be present in the study population in the absence of vaginal ring use. The inclusion of this group will also provide data on changes in sexual behavior without ring use during the study period.

3 OBJECTIVES

3.1 Primary Objectives

- Evaluate the acceptability of the study IVR in HIV-uninfected women over 12 weeks of use

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

3.2 Secondary Objectives

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

- Measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of study IVR use

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-005 will be a three-site, open label, two-arm, randomized controlled trial of a non-medicated IVR.

4.2 Summary of Major Endpoints

- For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function

- Evidence of Grade 2 or higher genitourinary events as defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies).

4.3 Description of Study Population

The study population will include 252 evaluable generally healthy 18-45 year-old women who are HIV-uninfected, non-pregnant, sexually active and using adequate contraception, as described in Sections 5.2.

4.4 Time to Complete Enrollment

The approximate time to complete study enrollment is expected to be six months for the US sites and ten months for the India site. The time of total study duration is expected to be a minimum of approximately fourteen months, including the study follow-up period.

4.5 Study Groups

Two study groups are planned (IVR and no IVR). Both study groups will be assigned to complete four follow-up visits (4-Week, 8-Week, 12-Week, and 16-Week/Study Termination).

Table 2: Study Groups

Group	N	Description
A	168	IVR
B	84	No IVR

4.6 Sequence and Duration of Trial Periods

The total duration of participation from the Enrollment Visit to the Termination Visit is 16 weeks. Visits may be completed within specified ± 7 day windows around target dates. Detailed information regarding visit windows will be thoroughly described in the MTN-005 Study-Specific Procedures (SSP) Manual.

4.7 Expected Duration of Participation

The expected duration of participation for an individual participant is 16 weeks.

4.8 Sites

Three study sites are planned:

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

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria outlined below will be utilized to ensure the appropriate selection of study participants for MTN-005.

5.2 Inclusion Criteria

Women must meet all of the following criteria to be eligible for inclusion in the study:

1. Age 18-45 years (inclusive) at screening, verified per site standard operating procedures (SOP)

2. Willing and able to provide written informed consent for screening and enrollment

3. Willing and able to provide adequate locator information, as defined in site SOPs

4. HIV-uninfected at screening (per algorithm in Appendix II)

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, usual menstrual cycle with at least 21 days between menses and no history of intermenstrual bleeding in the past three months (does *not* apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera®, or any type of IUD)

7. Per participant report at screening, sexually active, defined as having had penile-vaginal intercourse at least once in the past 30 days prior to screening

8. Per participant report at screening, expecting to continue penile-vaginal intercourse at least monthly for the duration of study participation

9. Per participant report, use of an effective method of contraception at enrollment, and intending to use same method for the duration of study participation and one month thereafter; effective methods include hormonal methods (except IVR); IUD inserted at least 30 days prior to enrollment; study provided male condoms, and sterilization (of participant or her sexual partner or partners as specified in the SSP)

10. Normal Pap smear result at screening or adequately documented normal Pap smear result per SSP within the 12 calendar months prior to screening (ASCUS with no evidence of high risk HPV included)

11. At screening and enrollment, agrees not to participate in other drug or device research study for the duration of study participation

12. Willing to agree not to use any intravaginal product, including douches, creams, lubricants etc. during the course of study participation

5.3 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

1. Participant reported history of:
    a. Adverse reaction to silicone (ever)
    b. Adverse reaction to latex (defined per SSP)
    c. Any current male sex partner with known history of adverse reaction to latex or silicone (defined per SSP)
    d. Gynecologic procedure (e.g., biopsy, tubal ligation, dilation and curettage, cosmetic genital) within 90 days prior to enrollment

2. Pregnant at screening or enrollment, or per participant report intending to become pregnant during the period of study participation

3. 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. Has any vaginal or cervical warts and external genital warts requiring treatment
    d. Is diagnosed with a urinary tract infection (see additional information below)
    e. 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)
    f. Has any other abnormal physical or pelvic exam finding that, in the opinion of the investigator or designee, would contraindicate study participation

RTIs requiring treatment include symptomatic BV, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, chlamydia, gonorrhea, syphilis, active HSV lesions (HSV-2 seropositive 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 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.

4. Per participant report, use of the following at enrollment, and/or anticipated use during the period of study participation: diaphragm, sex toys, douching and other intravaginal cleansing practices, female condom, IVR, spermicide, and/or menstrual cup. Tampon use will be permitted.

5. At screening or enrollment, has any social or medical 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. Participation in other drug or device research study at enrollment and/or during the period of this study participation

7. Severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver in either the standing or supine position.

6 STUDY PRODUCT

6.1 Regimen

Study participants will be randomized to either Group A to receive the study IVR or Group B to receive no study IVR (see Table 3). Participants in Group A will receive instructions on study IVR insertion and use and will then self insert (or by clinician if necessary), the study IVR at the Enrollment Visit. The study IVR should remain in place for 12 consecutive weeks. The study IVR will be removed by the physician at the 12-Week Visit. Follow-up will continue for an additional 4 weeks after the final removal of the study IVR.

Table 3: Study Regimen

Group	N	Group Description
A	168	IVR for 12 consecutive weeks
B	84	No IVR

6.2 Administration

The study IVR will be inserted into the vagina, by the participant (or clinician if necessary), at the Enrollment visit.

Study participants will be given detailed instructions, in the clinic, on proper study IVR insertion and removal. Hands should be thoroughly washed before and after study IVR insertion and/or removal. Additional detail on administration (IVR insertion, removal, procedures in the event of expulsion or loss) will be provided in the SSP Manual.

6.3 Study Product Formulation

6.3.1 Study IVR

The study IVR is made of cured silicone elastomer composed of an elastomer base, normal propylorthosilicate (NPOS), and stannous octoate but will contain no active pharmaceutical ingredient. The ring dimensions are as follows: outer diameter 56 mm, cross-sectional diameter 7.6 mm, core diameter 2 mm.

6.4 Study Product Supply and Accountability

6.4.1 Study Product Supply

The study IVRs will be manufactured by Warner Chilcott (Lame, Northern Ireland) and supplied by the International Partnership for Microbicides (IPM), Inc. (Silver Spring, MD).

The Pharmacist of Record (PoR) can obtain the study IVR for this protocol by following the instructions provided by the MTN CORE.

6.4.2 Storage and Dispensing

The study IVRs must be stored between 15°C to 30°C (59°F to 86°F). Study IVRs (including replacement IVRs) are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber.

6.4.3 Accountability

Each site PoR is required to maintain complete records of all study IVRs. The procedures to be followed will be provided by the MTN CORE.

6.5 Participant Counseling

Participants will receive study IVR adherence counseling at the Enrollment, 4-Week, and 8-Week Visits. Site staff will counsel participants to refrain from removing the ring (except as directed) and from using concomitant vaginal products and/or devices as described in Section 6.7.1. Site staff will also provide counseling for re-insertion in case of accidental ring expulsion.

The site staff will counsel participants to remove the IVR immediately and contact study site staff if they experience a rash or other skin trouble, itching, joint pain, or difficulty breathing as these may be signs of allergy.

6.6 Assessment of Participant Adherence

Participant behaviors regarding condom and study IVR use will be collected via standardized questions developed by the protocol team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data. Assessment of participant adherence will be addressed using a quantitative instrument.

6.7 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation. All concomitant medications as well as illicit substances reported throughout the course of the study will be recorded on case report forms designated for that purpose. All prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications.

6.7.1 Prohibited Products and Devices

Concomitant use of non-study vaginal products or other devices including menstrual cups, sex toys, douching and intravaginal cleansing, female condoms, diaphragms, vaginal ring, cervical caps, and/or spermicides are prohibited for the duration of the study except for tampons. Participants who report such use will be counseled regarding the use of alternative methods and provided or referred to family planning services for provision of alternative methods as applicable.

6.7.2 Recommended Practices

Study sites will distribute a single brand of latex male condoms to study participants for use during study participation. Instructions and counseling on use of male condoms will be provided throughout study participation. Study provided male condoms will not be impregnated or coated with spermicide. In the event that a participant needs additional male condoms between visits, she may request these from clinic staff at any time.

7 STUDY PROCEDURES

The following visits should take place for study participants:

7.1 Screening Visit

Screening Visit (up to and including 45 days prior to Enrollment Visit)

Administrative

- Assign participant ID (PTID)
- Obtain written informed consent for screening
- Collect demographic information
- Collect locator information
- Assess behavioral eligibility
- Provide reimbursement for study visit
- Schedule next study visit

Clinical

- Collect medical/menstrual history
- Collect concomitant medications
- Perform complete physical exam (see Appendix III)
- Provide counseling
    - Contraceptive
    - HIV testing process and results
    - HIV/STI (Sexually Transmitted Infection) risk reduction/Male condom
- If clinically indicated, treat for UTI (Urinary Tract Infection)/RTIs/STIs, treat or refer for other findings

Urine

- Collect urine sample
    - Qualitative hCG (human chorionic gonadotropin)
    - Dipstick urinalysis (UA) (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)
    - Nucleic Acid Amplification Test (NAAT) for chlamydia and gonorrhea (US FDA approved for female urine)

Blood

- Collect blood samples
    - Syphilis serology (with confirmatory tests as needed)
    - HIV-1 test (with confirmatory tests as needed (US FDA approved HIV test))

Pelvic

- Perform pelvic exam (see Appendix III)
- Collect pelvic samples
    - Vaginal pH
    - Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis)
    - If clinically indicated, herpes culture (at sites where standard of care for diagnosis)
    - Gram stained smear of vaginal fluid, obtained from lateral vaginal wall
    - Pap smear, if no documented result of normal Pap smear in the past twelve months

Study Supply

- Provide study specified male condoms

7.2 Enrollment Visit

Administrative

- Review/update locator information
- Confirm behavioral eligibility
- Obtain written informed consent for enrollment
- Administer comprehension checklist
- Provide results from screening tests (if not previously provided)
- Schedule next study visit
- Provide reimbursement for visit
- Follow procedures for randomization assignment

Clinical

- Obtain obstetric history
- Update medical/menstrual history
- Update concomitant medications
- Document pre-existing conditions
- Perform complete physical exam (see Appendix III)
- If clinically indicated, treat for UTI/RTIs/STIs, treat or refer for other findings
- Administer baseline behavioral assessment
- Administer baseline acceptability assessment
- Provide counseling
    - Contraceptive
    - HIV testing process and results from previous visit (if indicated)
    - HIV/STI risk reduction/Male condom
    - Protocol adherence
    - For Group A, product use/adherence

Urine

- Collect urine sample
    - Qualitative hCG
    - If clinically indicated, dipstick UA (and culture if positive for leukocyte esterase or nitrites; may omit culture if not standard of care for UTI diagnosis)
    - If clinically indicated, NAAT for chlamydia and gonorrhea (US FDA approved for female urine)

Blood

- Collect blood sample
    - If clinically indicated, syphilis serology (with confirmatory tests as needed)

- If clinically indicated, HIV-1 test (with confirmatory tests as needed (US FDA approved HIV test))

Pelvic Exam and Pelvic Samples

- Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess condition of vaginal and/or cervical epithelium or blood vessels
  - Digital images may be recorded

- Collect pelvic samples
  - Vaginal pH
  - Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis)
  - If clinically indicated, herpes culture (at sites where standard of care for diagnosis)
  - Gram stained smear of vaginal fluid, obtained from lateral vaginal wall
  - Quantitative vaginal cultures (at US sites only)
- Perform pelvic exam (see Appendix III)

Study Supply

- Provide study specified male condoms
- For Group A, participants will receive instructions on study IVR insertion, self-insert one study IVR followed by digital exam by clinician to check placement. Participants will also be instructed to rinse ring in warm water and re-insert in event of ring expulsion, unless ring falls into toilet or other unsanitary surface in which case participant will be instructed to return used ring to clinic. Due to variations in water quality, participants may also receive a bottle of water with which to rinse the study ring in case of expulsion.

7.3 Follow-up Visits

Note for all follow-up visits: all follow-up visits should be scheduled, ideally, on dates (within the ± 7 day visit window) when the participant is not on her menses. If a study visit does occur during the participant's menses, all visit procedures (except pelvic exam/colposcopy and associated pelvic lab specimens) should be performed at that time. If indicated, the pelvic exam, colposcopy, and associated specimen collections required for the given visit will be rescheduled for a date as soon as practical (preferably within the 7 day visit window) after the end of participant's menses.

4-Week, 8-Week, and 12-Week Visits

Administrative

- Review/update locator information
- Provide results from prior visits (if not previously provided)
- Schedule next study visit
- Provide reimbursement for visit

Clinical

- Update medical/menstrual history
- Review/update concomitant medications
- Perform targeted physical exam (see Appendix III)
- If clinically indicated, treat for UTI/RTIs/STIs, treat or refer for other findings
- Administer follow-up behavioral assessment
- Administer follow-up adherence assessment
- Administer final acceptability assessment (for Group A participants at 12-Week Visit or in the event that use of the study IVR is permanently discontinued)
- Provide counseling
    - Contraceptive
    - HIV testing process and results from previous visits (if indicated)
    - HIV/STI risk reduction/Male condom
    - Protocol adherence
    - For Group A, product use/adherence (omit at 12-Week Visit)

Blood

- Collect blood sample
    - If clinically indicated, collect syphilis serology (with confirmatory tests as needed)
    - If clinically indicated, HIV-1 test (with confirmatory tests as needed (US FDA approved HIV test))

Urine

- Collect urine sample
    - If clinically indicated, qualitative hCG
    - If clinically indicated, dipstick UA (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)
    - If clinically indicated, Nucleic Acid Amplification Test (NAAT) for chlamydia and gonorrhea (US FDA approved for female urine)

Pelvic Exam and Specimens

- Perform naked eye examination (all study visits) and colposcopic examination (12-Week Visit only, and if indicated) as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge
    - Digital images of abnormal findings may be recorded
- Collect pelvic samples
    - Vaginal pH
    - Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis)
    - If clinically indicated, herpes culture (at sites where standard of care for diagnosis)
    - Gram stained smear of vaginal fluid, obtained from lateral vaginal wall
    - Quantitative vaginal cultures (at US sites only)
- Perform pelvic exam (see Appendix III)
- Physician to remove study IVR from Group A participants at 12-Week Visit, or at visit in which study IVR use is permanently discontinued.
- For US sites only: a biofilm assessment will be performed on the used ring that is removed at the 12-Week Visit if the ring is removed by a study clinician.
    - In the event that an IVR is removed at an earlier visit, the used ring will have a biofilm assessment if assessment criteria are met, including removal by a study clinician.

Study Supply

- Provide study specified male condoms
- Collect used study IVR (in case of ring expulsion)
- In case of ring expulsion, participants may also receive a bottle of water with which to rinse the study ring

7.4 16-Week/Study Termination Visit

Administrative

- Review/update locator information
- Provide results from prior visits (if not previously provided)
- Provide reimbursement for visit
- If indicated, schedule next study visit

Clinical

- Update medical/menstrual history
- Review/update concomitant medications
- Perform complete physical exam (see Appendix III)

- If clinically indicated, treat for UTI/RTIs/STIs, treat or refer for other findings
- Provide counseling
    - Contraceptive
    - HIV testing process and results from previous visits (if indicated)
    - HIV/STI risk reduction/Male condom
    - Protocol adherence
- Administer final behavioral assessment (in the event that a participant drops out of the study prior to the 16-Week Visit, the final behavioral assessment will not be administered)

Blood

- Collect blood sample
    - HIV-1 test (with confirmatory tests as needed (US FDA approved HIV test))
    - If clinically indicated, collect syphilis serology (with confirmatory tests as needed)

Urine

- Collect urine sample
    - Qualitative hCG
    - If clinically indicated, dipstick UA (and culture if positive for leukocyte esterase or nitrites; may omit if culture not standard of care for UTI diagnosis)
    - NAAT for chlamydia and gonorrhea (US FDA approved for female urine)

Pelvic Exam and Specimens

- Perform naked eye examination and colposcopic examination as described by the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products (Update 2004) to assess (1) condition of vaginal and/or cervical epithelium or blood vessels and (2) quantity and quality of vaginal discharge
    - Digital images of abnormal findings may be recorded
- Collect pelvic samples
    - Vaginal pH
    - Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis)
    - If clinically indicated, herpes culture (at sites where standard of care for diagnosis)
    - Gram stained smear of vaginal fluid, obtained from lateral vaginal wall
    - Quantitative vaginal cultures (at US sites only)
- Perform pelvic exam (see Appendix III)
- Biofilm Assessment (for Group A if indicated, for participants at US sites only)

- Collection of used IVR (for Group A if indicated)

Study Supply

- Provide study specified male condoms

7.5 Follow up Procedures for Participants who Discontinue Study Product

Participants who discontinue study product will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule with the exceptions described below.

7.5.1 Participants Who Seroconvert to HIV

Study staff will record information regarding seroconversions that occur during study participation on study case report forms (CRF). Participants in Group A will be advised to discontinue study IVR use. Protocol-specified procedures will continue except:

- HIV serology
- Further provision of study IVR (for Group A)
- Counseling for HIV/STI risk reduction. Counseling will be modified to address primary and secondary HIV/STI prevention for infected women and prevention for transmission to sex partners.

7.5.2 Participants Who Become Pregnant

Participants in Group A who become pregnant during study participation will discontinue study IVR use. All protocol-specified procedures will continue except:

- Pelvic exam (unless clinically indicated)

7.5.3 Participants Who Voluntarily Discontinue Study IVR

All protocol-specified study procedures will continue except counseling related to study IVR use and adherence.

7.5.4 Participants Who Discontinue Study IVR Use Permanently (Advised by Study Staff)

All protocol-specified study procedures will continue except counseling related to study IVR use and adherence.

7.6 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. Participants will be encouraged to seek care for any vulvovaginal or other related complaints with the study staff. Laboratory analyses may be conducted according to the clinical judgment of the site investigator or designee. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care.

7.7 Clinical Evaluations and Procedures

See Appendix III for an outline of physical exam and pelvic exam components.

7.8 Acceptability Measures

All participants will be asked questions about sexual behavior and hypothetical study IVR use. For participants in Group A, acceptability of the study ring will be measured by 1) study continuation rates over the 12-week period 2) participants' answers to questions regarding adherence to the prescribed ring schedule, ease of insertion, ease of removal, comfort with touching oneself, tolerance of foreign body, physical discomfort, partner perceptions especially awareness during and interference with sex, changes in sexual activity, and expulsion during urination and bowel movements, and 3) participants' perceptions of changes in the quantity, color and/or odor of vaginal discharge associated with use of the study ring as well as any resulting changes in vaginal hygiene practices. Background factors that will be considered in addition to demographic characteristics are type of toilet (applicable to India site only), marital status/partner change, experience with tampons and other vaginal products, current vaginal hygiene practices, prior clinical trial experience and usage of and knowledge about the contraceptive vaginal ring (NuvaRing®) as well as other contraceptive methods.

7.9 Laboratory Evaluations

7.9.1 Local Laboratory Testing

<u>Blood</u>

- HIV-1 test (enzyme immunoassay (EIA), western blot (WB) if indicated; see Appendix II. US FDA approved HIV test)

- Syphilis serology (with confirmatory tests as needed)

Urine
- Qualitative hCG
- Urinalysis
- Urine culture (if clinically indicated)
- NAAT for chlamydia and gonorrhea (US FDA approved for female urine)

Pelvic Specimens
- Pap smear
- Vaginal pH
- Vaginal fluid for wet mount microscopy (saline for BV, Trichomoniasis; KOH for vulvovaginal candidiasis)
- Herpes culture (if clinically indicated and if local standard of care)

7.9.2 Network Laboratory Testing

Blood
- HIV-1 confirmatory testing as needed (see Appendix II)

Urine
  - NAAT for chlamydia and gonorrhea (for US sites not currently able to perform this test on site(US FDA approved for female urine))

Genital
- Quantitative vaginal cultures (at sites with capacity)
  These organisms will include *Lactobacillus* species, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, anaerobic gram-negative rods (Bacteroides, Prevotella, Porphyromonas), Enterococcus species, Group B Streptococcus, and Candida species.
    - Gram stained vaginal smear with leukocyte quantification
- Biofilm Assessment of used study IVRs (US sites only)
  May include culture and/or other techniques

7.10 Specimen Collection and Processing

Each study site will adhere to the standards of Good Clinical Laboratory Practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements(http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/labs/LabPolicy.pdf),MTN-005 SSP manual (www.mtnstopshiv.org), and site SOPs for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-collect specimens.

7.11 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/).

7.12 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. This applies to both US and international sites. Biohazardous waste (including used IVRs returned to the study site) will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7.13 Final Contact

The 16-Week/Study Termination Visit ± 7 days for all participants will include laboratory testing. As results are not expected to be available on the same day for participants, a final contact may be required to provide the final study test results, post-test counseling, and treatment from these visits. For participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. The sites may also use a final contact visit to follow up on unresolved AEs at the 16-Week/Study Termination Visit. Study sites may complete the final contact visit(s) at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

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, DAIDS Medical Officer, MTN CORE Protocol Safety Physician, Statistical Data Management Center (SDMC) Clinical Affairs Nurse, and Protocol Statistician, will serve as the PSRT; the PSRT will be chaired by the MTN CORE Protocol Safety Physician. The MTN SDMC will prepare routine safety data reports for review by the PSRT, which will meet via conference call approximately once per month or as needed throughout the period of study

implementation to review safety data, discuss product use management and address any potential safety concerns. The content, format and frequency of safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

The MTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification.

In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

Decisions regarding permanent discontinuation of study product in individual participants will be made by the PSRT based on careful review of all relevant data.

In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study product for all participants and stop accrual into the study, the protocol team will request a review of the data by the Study Monitoring Committee (SMC) before recommending that the study be stopped. Members of the SMC will be independent investigators with no financial interest in the outcomes of this study. If at any time, a decision is made to discontinue study product in all participants, the site investigators of record will notify the responsible Institutional Review Boards/Ethics Committees (IRB/EC) expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant enrolled in a clinical trial and which does not necessarily have a causal relationship with an investigational product or study participation. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or

disease temporally associated with the use of an investigational product or study participation, whether or not considered related to the product or study participation. This definition will be applied beginning from the time of random assignment. The term "investigational product" for this study refers to the study IVR.

Study participants will be instructed to contact the study site staff to report any AEs they may experience. In the case of a life-threatening event, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE (including pelvic exam abnormalities, excluding colposcopic findings) will be followed clinically until the AE resolves (returns to baseline) or stabilizes.

Study site staff will report on study case report forms all AEs, excluding findings observed by colposcopy only, reported by or observed in enrolled study participants from the time of enrollment (random assignment) until study termination, regardless of severity and presumed relationship to study product. The DAIDS AE Grading Table Version 1.0, Dec 2004, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies), will be the primary tool for grading AEs for this protocol, with the exception of asymptomatic BV which will not be a reportable AE. AEs not included in that addendum will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where an AE is covered in both tables, the DAIDS AE Grading Table, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies) will be the grading scale utilized. These tables are available at http://rcc.tech-res.com/eae.htm.

Participants also will be encouraged to report to the study clinician any problems experienced by their male sex partners that might be potentially related to study product. AEs of male partners will be documented in the participant chart, but will not be reported on study case report forms. If any such problems are reported, study staff should evaluate and document the occurrence and the IoR (or designee) should inform the PSRT, so that this information can be considered during routine PSRT safety data reviews. Should any concerns arise with regard to partner safety the PSRT will advise all study sites on appropriate action.

8.3.2 Serious Adverse Event

SAEs will be defined per 21 CFR 312.32 guidelines as AEs occurring at any dose that:

- Result in death
- Are life-threatening AEs
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity, or
- Are congenital anomalies/birth defects.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 Adverse Event Relationship to Study Product

The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (dated 6 May 2004) and clinical judgment. The relationship categories that will be used for this study are:

- *Definitely related*: AE and administration of study agent are related in time, and a direct association can be demonstrated with the study agent.

- *Probably related*: AE and administration of study agent are reasonably related in time, and the AE is more likely explained by the study agent than by other causes.

- *Possibly related*: AE and administration of study agent are reasonably related in time, and the AE can be explained equally well by causes other than the study agent.

- *Probably not related*: a potential relationship between administration of study agent and AE could exist, but is unlikely, and the AE is most likely explained by causes other than the study agent.

- *Not related*: the AE is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of "not related".

8.4 Unanticipated Adverse Device Effect Reporting Requirements

Unanticipated Adverse Device Effects (UADE)
An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UADEs must be documented on the DAIDS EAE Reporting Form available on the RCC website (http://rcc.tech-res-intl.com) and submitted by study sites to the DAIDS Medical Officer and IPM. .

8.5 Local Regulatory Requirements

Site investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. This reporting will include site IRB/EC-mandated reporting of AEs, SAEs, and other relevant safety information.

IRB/EC Notification by Investigator
Reports of all UADE (including follow-up information) must be submitted to the IRB/EC as soon as possible and in no event later than 10 working days after the investigator first learns of the event. Copies of each report and documentation of IRB/EC notification and receipt will be kept in the Clinical Investigator's binder.

FDA Notification by Sponsor
The study sponsor shall evaluate any UADE and submit a report of the evaluation to FDA as soon as possible but no later than 10 working days after the sponsor is notified. If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the AE in a written report to the FDA as soon as possible, but no later than 10 working days from the time the determination is made.

8.6 Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Social harms that are judged by the IoR to be serious or unexpected will be reported to responsible site IRB/ECs at least annually, or according to their individual requirements and should also be reported to the DAIDS Medical Officer and IPM on DAIDS EAE Reporting Forms. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

9.1 Toxicity Management

Toxicity is not expected in this study of a non-medicated IVR. Silicone allergy, while reported in the literature, has been described as extremely rare[53]. Participants exhibiting signs or symptoms of product toxicity, as determined by the clinical opinion of the site investigator or designee, may have the study IVR discontinued according to guidelines in Section 9.4.

9.2 Other Clinical Events

Management of sexually transmitted infections commonly referred to as STIs and other forms of vaginitis and cervicitis will be in accordance with current CDC guidelines (http://www.cdc.gov/std/treatment/) and in accordance with other country-specific guidelines. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible to avoid intravaginal medication use.

In the absence of clinical evidence of cervicitis (as described below) and/or pelvic inflammatory disease, participants with gonorrhea and/or chlamydia detected during follow-up may be treated with the study IVR in place.

If suspected finding is reported by participant between scheduled visits, an interim visit may be scheduled at the discretion of the site investigator. Management of genital events observed at scheduled or interim visits will be in accordance with the following:

Deep epithelial disruption (ulceration) excluding findings observed by colposcopy only

- Hold study IVR for deep epithelial disruption confirmed by site investigator
- Swab for herpes simplex culture (per clinical judgment of site investigator) (herpes serology optional)
- Suspected syphilis chancre should be managed in accordance with current CDC guidelines.
- Re-evaluate in 48-72 hours and reinstate study IVR use if resolved
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time may reinstate study IVR use. If unresolved at this second reevaluation, need to discontinue product permanently and provide care per local standard.
- If there is reoccurrence with no identified etiology, then consider permanent discontinuation.

Superficial epithelial disruption (abrasion/peeling) excluding findings observed by colposcopy only

- Continue study IVR use.
- Perform naked eye evaluation with or without colposcopy.
- Re-evaluate by speculum examination in 48-72 hours.
- If condition worsens, hold study IVR use. Otherwise continue study IVR use.

Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface excluding findings observed by colposcopy only

- Continue study IVR use.
- Perform naked eye evaluation with or without colposcopy.

- If asymptomatic, re-evaluate at next regularly scheduled visit.
- If symptomatic, re-evaluate by speculum examination in 48-72 hours.
- If worsened significantly, hold study IVR use, until further evaluation is scheduled. Otherwise, continue study IVR use.

Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema excluding findings observed by colposcopy only

- Hold study IVR.
- Perform naked eye evaluation with or without colposcopy.
- Re-evaluate in 48-72 hours and reinstate study IVR use if resolved.
- If unresolved at 48-72 hours, re-evaluate in another 48-72 hours. If resolved at that time may reinstate use. If unresolved at this second reevaluation, need to discontinue product permanently and provide care per local standard.

Abnormal vaginal discharge excluding findings observed by colposcopy only

- Perform vaginitis evaluation, including assessment of signs, symptoms, vaginal pH and wet mount microscopy for Candida vaginitis, trichomoniasis, and BV.
- Provide treatment and continue study IVR use for all cases of trichomoniasis, symptomatic Candida vaginitis, and symptomatic BV.
- Study IVR use may be continued without treatment in the presence of asymptomatic Candida vaginitis and/or asymptomatic BV.

Unexpected genital bleeding excluding findings observed by colposcopy only

- Continue study IVR use (at clinician's discretion).
- Perform naked eye evaluation with or without colposcopy.
- If determined to be due to deep epithelial disruption, refer to guidelines above, otherwise continue study IVR use.

Cervicitis (including findings on exam such as inflammation and/or friability) excluding findings observed by colposcopy only

- Remove study IVR.
- Evaluate for *N. gonorrhoeae* and *C. trachomatis.*
- If *N. gonorrhoeae* and *C. trachomatis* detected, provide treatment and reevaluate in 72 hours. If all symptoms and signs are resolved at that time, may reinstate use with replacement study IVR.

Genital petechia(e) excluding findings observed by colposcopy only

- Continue study IVR use.
- Perform naked eye evaluation with or without colposcopy.
- No further evaluation or treatment is required.

Genital ecchymosis excluding findings observed by colposcopy only

- Continue study IVR use.
- Perform naked eye evaluation with or without colposcopy.
- No further evaluation or treatment is required.

UADE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study IVR

- For Grades <4, hold study IVR.
- Evaluate according to current clinical practice at the site.
- Provide treatment as clinically indicated, when resolved reinstate study IVR use at clinician's discretion.
- For Grade 4, permanently discontinue study IVR.

9.3 Pregnancy

All study participants are required to be using an effective method of contraception at enrollment, and intending to use same method for the duration of study participation. Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers. Study staff also will provide participants with male condoms and counseling on use of these condoms ideally during every sex act during study participation.

Pregnancy testing will be performed at the Screening, Enrollment, and 16-Week/Early Termination study visits, and when clinically indicated during study follow-up. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff during the course of the study. The site IoR or designee will counsel any participants who become pregnant regarding possible risks if the pregnancy is continued according to site-specific SOPs. The IoR or designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Study staff will be responsible for follow-up with the participant until the pregnancy outcome is determined. Pregnancy outcomes will be reported on relevant case report forms.

Participants who become pregnant during the course of the study will permanently discontinue study product use but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete all study visits. All protocol-specified procedures will continue except:

- Provision of study IVR (for participants randomized to the IVR arm)
- Pelvic exam (unless clinically indicated)

9.4 Criteria for Temporary or Permanent Discontinuation of Study Product

Participants may voluntarily discontinue product use for any reason at any time. Site IoRs will temporarily or permanently discontinue participants from product use per the specifications below, which may be further clarified in the SSP. Site IoRs also may, with the approval of the PSRT, temporarily or permanently discontinue participants from study IVR use for reasons not shown here or in the SSP, e.g., to protect their safety.

The criteria for temporary discontinuation of study IVR use for an individual participant are outlined in Section 9.2.

The criteria for permanent discontinuation of further study IVR use for an individual participant are outlined in Section 9.2, but also include:

- Pregnancy
- HIV-1 seroconversion
- Completion of regimen as defined in the protocol
- Request by participant to terminate treatment
- Clinical reasons determined by the physician

Participants who discontinue product use will continue to complete study visits and procedures as originally scheduled, except that study IVRs will no longer be provided for participants randomized to the study IVR arm.

9.5 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the PSRT, withdraw participants before their scheduled termination visit to protect their safety. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office for Human Research Protections (OHRP)), or site IRBs/ECs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the site-initiated withdrawal of any study participant. 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 study procedures and follow-up, provided the participant is still within her original 16-week follow-up period.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a three-site, open label, two-arm, 2:1 randomized, controlled trial comparing acceptability and expanded safety of a study IVR for 12 weeks of use to no IVR use among sexually active, HIV-uninfected women. A total of 252 women (168 and 84 in

the IVR and no IVR arms, respectively) will be randomized, 150 in Pune, India (100 and 50 in the IVR and no IVR arms, respectively) and 102 (68 and 34 in the IVR and no IVR arms, respectively) for the two combined US sites (with competitive enrollment for the two US sites).

10.2 Study Primary and Secondary Endpoints

10.2.1 Study Primary Endpoints

Consistent with the primary study objectives to assess the acceptability and safety of the study IVR when used for 12 consecutive weeks, the following primary endpoints will be assessed:

10.2.1.1 Acceptability

- For women randomized to the study IVR arm, participant report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions (including context of expulsion), and changes in sexual function

10.2.1.2 Safety

- Evidence of Grade 2 or higher genitourinary events as defined by the DAIDS AE Grading Table, Version 1.0, Dec 2004, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies)

10.2.2 Study Secondary Endpoints

Consistent with the secondary study objectives to measure vaginal flora characteristics and changes of these over the course of study IVR use, the following endpoints will be assessed:

- For women randomized to the study IVR arm, participant report of frequency of study IVR removal and duration of time without IVR inserted in vagina over 12 weeks of use

- Changes from enrollment to week 12 in vaginal flora as measured by Nugent score

- Changes from enrollment to week 12 in quantitative vaginal culture[1] as measured by count of *Lactobacillus* (H_2O_2 positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis, Escherichia coli, Staphylococcus aureus, Candida* species, Group B *Streptococcus,* and *Enterococcus* species. (Note that these quantitative vaginal cultures will only be available from the two US sites, therefore reducing the available sample size for this objective).

- Assessment of vaginal symptoms and signs suggestive of BV or vulvovaginal candidiasis

- Changes in vaginal pH and vaginal wet mount microscopy

10.3 Study Hypotheses

MTN-005 hypothesizes that 12 weeks of study IVR use will be safe and well-tolerated. In addition, we anticipate that the study IVR will be acceptable to US and non-US women.

10.4 Sample Size

10.4.1 Safety Endpoints

The proposed total sample size is N=252 randomized into 2 arms: 168 and 84 women in the study IVR and no IVR arms, respectively. Given that assessing acceptability of and adherence to the study IVR are primary objectives, and that acceptability and adherence can only be assessed in the study IVR arm, a 2:1 randomization was selected to increase the precision on estimates of acceptability and adherence. A 2:1 randomization will slightly decrease the power for the comparison of safety profiles between the study IVR and no IVR arms, but the decrease in power is not substantial. Participants who are non-adherent to the study product and/or the study visit schedule will not be replaced.

For the study IVR arm, if the true rate of a given toxicity endpoint is 5%, 168 women provide 80% power to exclude safety and toxicity endpoint rates greater than 10.0%, where the safety and toxicity endpoints for a woman are defined as the occurrence of the safety endpoint during follow-up, that is the occurrence during follow-up of:

Evidence of Grade 2 or higher genitourinary events as defined by the DAIDS AE Grading Table, Version 1.0, Dec 2004,.Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies).

For the no IVR arm, if the true rate of a given safety and toxicity endpoint is 5%, 84 women provide 80% power to exclude safety and toxicity endpoint rates greater than 13.3%.

The safety and toxicity rates of women using the study IVR and the rates for those not using the study IVR will be formally compared. A sample size of 252 women with a 2:1 randomization (i.e. 2 IVR : 1 no IVR) will assure with 80% power that a 95% confidence interval for the difference between the study IVR and no IVR safety and toxicity rates has an upper limit no more than 6.9% when the true toxicity rates for study IVR and no IVR are both 5%. The above calculations have been performed assuming true rates of toxicity of 5%. However, it is anticipated that the true rates are smaller than 5%. If this

is the case, the above power computations are conservative and the actual power will be slightly higher. Table 4 displays 95% confidence interval upper bounds for different assumptions on the safety and toxicity rates in the IVR and no IVR arms. These bounds correspond to non-inferiority bounds computed using an exact one-sided 95% confidence interval for the difference in rates between the two arms as described in Section 10.8.2.1.

Table 4: 95% confidence interval upper bound for the difference between IVR and no IVR safety and toxicity rates

		Assumed rate in IVR arm					
Assumed rate in no IVR arm		**1%**	**5%**	**7.5%**	**10.0%**	**12.5%**	**15.0%**
1%		3.6%	9.8%	13.0%	-	-	-
5%		-	6.9%	10.1%	13.1%	-	-
7.5%		-	-	8.1%	11.3%	14.2%	-
10.0%		-	-	-	9.4%	12.3%	15.2%
12.5%		-	-	-	-	10.4%	13.2%
15.0%		-	-	-	-	-	11.2%

10.4.2 Acceptability Endpoints

Several components of acceptability (e.g., report of discomfort, removal and insertion difficulties, episode of expulsions, bowel, urinary and sexual difficulties (see Section 7.8)) will be used to assess overall acceptability. Each component will be assessed by a dichotomous measure where women will be categorized into (1) those reporting no acceptability issues during the 12 weeks of study IVR use (e.g., those reporting no discomfort) and (2) those reporting at least one issue during the 12 weeks of study IVR use (e.g., those reporting some discomfort). Acceptability can only be assessed among the 168 women randomized to the study IVR arm. An acceptability endpoint is defined as a negative report by a participant, on any of the above components of acceptability. A sample size of 168 women will provide a precision of 6.4% (i.e. half-width of the 95% exact confidence interval) assuming an observed acceptability of 80%. Substantial heterogeneities in acceptability between the Indian and the US sites might be observed in which case acceptability will be estimated separately for Indian and US women. For the Indian site, a sample size of 100 women using the study IVR will provide a precision of 8.3% assuming an observed acceptability of 80% while this precision would be 10.2% with a sample size of 68 US women using the study IVR. Due to the smaller sample size within each site, no formal comparison will be performed for comparing acceptability between sites.

10.4.3 Secondary Endpoints: Changes in Vaginal Flora

Changes in Nugent scores will be assessed by comparing the Nugent score at enrollment with the one observed at 12 weeks. An abnormal Nugent score is defined as a Nugent score higher than 3 while a normal Nugent score is defined as a score of 3 or

less. The proportion of changes between enrollment and week 12 from normal to abnormal will be compared as well as the one from abnormal to normal.

Changes in Nugent score over time are naturally occurring. Based on a sample of 1016 women (Hillier, SL. Unpublished data), 28.4% of women with a normal Nugent score at enrollment had an abnormal Nugent score 4 months later while 32.8% of women with an abnormal Nugent score at enrollment had a normal Nugent score 4 months later. Therefore, for the purpose of power calculations, we are estimating the proportion of changes in Nugent scores from enrollment to week 12 at 30% in the no IVR arm and this for both from normal to abnormal and from abnormal to normal. Furthermore, we are estimating that 55% and 45% of women will be normal and abnormal, respectively, at enrollment.

The proportion of women with a change in Nugent score from normal to abnormal, at enrollment and 12 weeks, respectively, will be compared between the study IVR and no IVR arms. Assuming that the true proportion of changes in the no IVR arm is 30%, a sample size of 252 women (138 normal women at enrollment and available for the analysis) with a 2:1 randomization will allow detection of an absolute difference of 25% with 80% power (i.e. 30% of women in the no IVR arm and 55% of women in the study IVR arm).

Similarly, the proportion of women with a change in Nugent score from abnormal to normal, at enrollment and 12 weeks, respectively, will be compared between the study IVR and no IVR arms. Assuming that the true proportion of changes in the no IVR arm is 30%, a sample size of 252 women (114 abnormal women at enrollment and available for the analysis) with a 2:1 randomization will allow detection of an absolute difference of 28% with 80% power (i.e. 30% of women in the no IVR arm and 58% of women in the study IVR arm).

In addition to looking at shifts in the Nugent score, within arm descriptions, and between arm comparisons, will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than ≥1 log change in dominant members of the microflora, including *Lactobacillus* (H2O2 positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species) and to assess differences in the quantitative levels of these flora between arms during follow-up. Quantitative vaginal culture will be assessed only at the US sites and therefore the available sample size for these analyses will be 102 women (68 in the study IVR arm and 34 in the no IVR arm). A sample size of 102 women with a 2:1 randomization will detection of a medium effect size of 0.59 with 80% power in comparing quantitative levels between arms.

10.5 Randomization Procedures

Women will be randomized using a 2:1 ratio to one of the two arms, i.e. two women will be randomized to the study IVR arm for each woman randomized to the no IVR arm.

Randomization will be stratified by site to ensure a 2:1 balance within each site. The randomization scheme will be generated and maintained by the SDMC. The SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Additional envelopes will be provided to each site for the purpose of enrolling a greater number of participants per site if enrollment "slots" need to be shifted from one site to another during the course of the study. If for some reason a site experiences difficulty reaching its accrual target, consideration will be given to shifting enrollment "slots" to the other site, with prior approval of the Protocol Chair.

Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. The randomization document contained within the envelope indicates the study arm (study IVR or no IVR) to which the participant is assigned. For participants assigned to the study IVR arm, this randomization document is the study prescription. Clinic staff will store assigned randomization envelopes and copies of the randomization document in the participants' study charts.

10.6 Justification for the No IVR arm

Inclusion of a no IVR arm in this safety, acceptability, and adherence study will enable investigators to compare the incidence of AEs as well as changes in vaginal flora among women using the study IVR to that of women using no IVR.

10.7 Participant Accrual and Retention

Based on previous studies of vaginal products with similar eligibility requirements conducted at these 3 sites (i.e. HPTN 059), the accrual of 252 eligible participants with normal reproductive tracts is expected to require the screening of approximately 380 volunteers. The target for retention will be 95% of enrolled participants over the 16 weeks follow-up period. Therefore, it is anticipated that approximately 252 women will be enrolled in the study. Accrual is anticipated to take approximately 6 months and 10 months at the US and non-US sites, respectively. Monthly accrual targets by site are given in the table below.

Table 5: Monthly Accrual Target for MTN-005

Monthly Accrual Target for MTN-005

Study Month	Monthly Accrual Target both US Sites	Monthly Accrual Target Non-US Site	Monthly Cumulative Accrual Target
1	12 (6 per site)	6	18
2	18 (9 per site)	16	34
3	18 (9 per site)	16	34
4	18 (9 per site)	16	34
5	18 (9 per site)	16	34
6	18 (9 per site)	16	34
7	0	16	16
8	0	16	16
9	0	16	16
10	0	16	16
Total	102 (51 per site)	150	252

10.8 Data Monitoring and Analysis

10.8.1 Study Monitoring Committee (SMC)

In addition to the safety monitoring done by the PSRT (described in Section 8.2, the MTN SDMC will prepare study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment when feasible) for review by the MTN SMC. The SMC will conduct interim reviews of study progress (blinded to treatment assignment when feasible), including rates of participant accrual, retention, rates of adherence to study IVR use, and product safety. These reviews will take place approximately every 90 days, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.8.2 Primary Analysis

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-arm assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between the study IVR arm and the no IVR arm is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression nonparametric methods if data are non-Normal. To assess the adequacy of the randomization, study IVR and no IVR participants will be compared for baseline characteristics including

demographics, pelvic examination, and laboratory measurements using descriptive statistics. Due to the small sample size, formal baseline comparisons will not be done.

10.8.2.1 Primary Safety Analysis

The primary aim of the study is to assess the safety and toxicity of the study IVR. First, an intent-to-treat (ITT) analysis will be performed where data from all visits are included. To assess safety, the number and the percentages of participants experiencing the safety or toxicity endpoint described in Section 10.2.1.2, will be presented by arm. For each arm, binomial rates will be presented along with their corresponding exact 95% confidence interval estimates. For assessing the difference between the arms, a non-inferiority bound will be computed using an exact one-sided 95% confidence interval for the difference in rates between the two arms (see Section II in *Therapeutic Equivalence* in Encyclopedia of Biopharmaceutical Statistics) [54]. Second, a per-protocol analysis will also be performed since non-adherent women in the IVR arm that are included in the ITT analysis might potentially lower the rate of safety endpoints in the IVR arm. Therefore a per-protocol analysis, where visits of non-adherent women will be excluded from the analysis, will be used to explore the sensitivity of the conclusions obtained via the primary safety analyses based on the ITT dataset. For this analysis, all visits of adherent women (defined as using the product 50% of the time or more) will be included where comparison of safety rates between arms will be performed using generalized estimating equation methods to take into account that the 4-week visits are not independent within a participant.

The above primary safety analysis will be supplemented by the following additional analyses. Adverse experiences will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific adverse experience will be tabulated by severity and by relationship to study product (for the study IVR arm only). For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Finally, a listing of UADE reported to the DAIDS Medical Officer and IPM will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

10.8.2.2 Primary Acceptability Analysis

To assess acceptability of women randomized to the study IVR arm, the number and the percentage of participants experiencing during follow-up at least one negative report on acceptability including genitourinary discomfort, ring insertion/removal issues, expulsions, and/or changes in sexual function will be presented. This binomial

proportion will be used to assess the acceptability of the study IVR along with its corresponding 95% confidence interval.

The above primary acceptability analysis will be supplemented by presenting the above proportion by site along with its corresponding 95% confidence interval.

10.8.3 Secondary Analyses

10.8.3.1 Adherence

To assess adherence of women randomized to the study IVR arm, the proportion of participants who kept the study IVR inserted at all times during the first 12 weeks of follow-up will be calculated along with its 95% confidence interval. For the not completely adherent women, the average period of time during follow-up when the study IVR was outside the vagina as well as the average number of removals of the study IVR from the vagina will be computed. All enrolled women in the study IVR arm will be included in this analysis.

10.8.3.2 Vaginal Flora

In order to assess the effect of the study IVR on the vaginal flora of sexually active, HIV-uninfected women, clinically significant changes in vaginal flora will be evaluated by the Nugent score with shift tables from baseline (Enrollment) to follow-up visits at week 4, 8, 12, and 16 to assess the effect on vaginal flora.

The Nugent score is graded 1 to 10 as follows:

1. Normal, 0 to 3
2. Intermediate, 4 to 6
3. BV, 7 to 10

Any shift from normal at baseline to intermediate or BV at a follow-up visit, or intermediate or BV at baseline to normal at a follow-up visit, will be considered a clinically meaningful change in vaginal flora. The proportion of changes within each arm will be reported and will be formally compared using the Fisher exact test (from the derivation of the two-sample case of the McNemar's test of change). Please refer to Levin and Serlin [55] for more details. In addition, this analysis will be supplemented by an analysis using the change from baseline in Nugent score for each woman. Comparison for differences in change from baseline between arms will be assessed by using an unpaired t-test or a Mann-Whitney test (if distribution of change scores does not allow the use of the unpaired t-test).

In addition to looking at shifts in the Nugent score, within arm descriptions, and between arm comparisons will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than ≥1 log change in dominant members of

the microflora, including *Lactobacillus* (H2O2 positive and negative strains)), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species) and to assess differences in the quantitative levels of these flora between arms during follow-up. Note that this analysis can only be performed using women from the US sites since quantitative cultures will not be conducted for women at the India site.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the SDMC. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution.

11.2 Source Documents and Access to Source Data/Documents

Source documents and access to source data/documents will be maintained in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with US regulations, the investigator will retain all study records on site for at least two years after study closure. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

11.3 Quality Control and Quality Assurance

Quality control and quality assurance procedures for MTN-005 will be performed in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites.

11.4 Study Coordination

Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by NIAID and IPM. Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents, the DAIDS AE Grading Table, and the DAIDS AE Grading Table, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies). Training and written instructions outlining management and reporting, study IVR dispensing to participants, product accountability, and other study operations will be provided by FHI, SCHARP, and the MTN Network Laboratory.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC). On-site study monitoring will be performed in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 Code of Federal Regulations (CFR) Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation

- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices

- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms

- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

Site investigators will allow study monitors and MTN CORE staff to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN Network Laboratory, FHI, SCHARP, NIAID, local regulatory authorities, and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks to human participants. Volunteers will take part in a thorough informed consent process. Before beginning the study, the investigators will have obtained IRB/EC approval. The investigators will permit audits by the NIH, IPM, the US FDA, or any of their appointed agents.

13.1 Institutional Review Boards

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an IRB/EC prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study- related documents must be approved by the EC/IRB and DAIDS prior to implementation.

13.2 Protocol Registration

Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office. For additional information, refer to the protocol registration documents located at http://rcc.tech-res.com/forms.htm. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. Protocol registration material can be sent electronically to epr@tech-res.com. For questions regarding protocol registration, please call 1-301-897-1707. MTN CORE (FHI) staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB/EC(s) and the RCC prior to implementing the amendment.

13.3 Risk Benefit Statement

13.3.1 Risks

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination, including colposcopy, may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of STI status may cause sadness or depression in volunteers. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions. Use of the study IVR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse).

13.3.2 Benefits

Participation in this study likely will have no direct benefit to volunteers other than access to screening for RTIs/STIs and appropriate referral if RTIs/STIs are diagnosed. Participants will also have access to screening for HIV and appropriate referral if HIV is diagnosed. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of syphilis. Pregnancy testing may offer the opportunity for early detection of pregnancy with expedient referral for pregnancy management. Pap smear may offer the opportunity for early detection of a cervical and/or vaginal abnormality with expedient referral if an abnormality is detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. Study staff will administer a comprehension checklist to potential participants prior to obtaining written informed consent to ensure that participants fully comprehend the nature of the study. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable country-specific regulatory requirements and will adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Participants are provided with copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices VI, VII and VIII 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. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Prior to the beginning of the trial, site investigators will have IRB/EC written approval of the protocol, informed consent forms, and any other study-related information to be provided to participants.

The informed consent process will give individuals all of the relevant information they need to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Listed study investigators or their designees will obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

Community input will have been sought for the development of the sample informed consent forms. The informed consent process covers all elements of informed consent required by research regulations. In addition, the process specifically addresses the following topics of importance to this study:

- The importance of adherence to the study visit and procedures schedule.
- The potential risks of study participation (and what do if such risks are experienced).
- The potential social harms associated with study participation (and what do if such harms are experienced).
- The real yet limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan (e.g., whether community-based visits will be conducted) and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12).

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that will be applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants. Since the Certificate cannot be enforced outside of the US, however, it will apply only to US site staff and participants.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Participants who test positive for pregnancy at screening or enrollment visits will not be eligible to participate in this study. During the informed consent process, women will be informed that the silicone elastomer IVR is not a method of contraception.

All potential participants will be required by the Eligibility Criteria for Screening and Enrollment to be currently using a reliable method of contraception, such as hormonal contraception (except IVR), intrauterine device, male condoms, or sterilization. Women who become pregnant during the study period following randomization and exposure to study product will discontinue product use but not be excluded from analysis.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children under 18 years old.

13.7 Compensation

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits, childcare, and time away from work. Participants are reimbursed at each visit.

13.8 Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases including HIV identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

13.9 Access to HIV-related Care

13.9.1 HIV Counseling and Testing

HIV pre-test 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. 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 necessary.

13.9.2 Care for Participants Identified as HIV-Infected

Study staff will provide participants with their HIV test results in the context of post-test counseling. According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women. Participants at sites which have completed protocol registration for the MTN-015 seroconverter protocol may be offered participation in that study.

13.10 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, IPM, the OHRP, site IRBs/ECs, or other country-specific government or regulatory authorities.

14 PUBLICATION POLICY

DAIDS and MTN policies and a Clinical Trial Agreement (CTA) between IPM and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN Manuscript Review Committee, DAIDS, and IPM for review prior to submission.

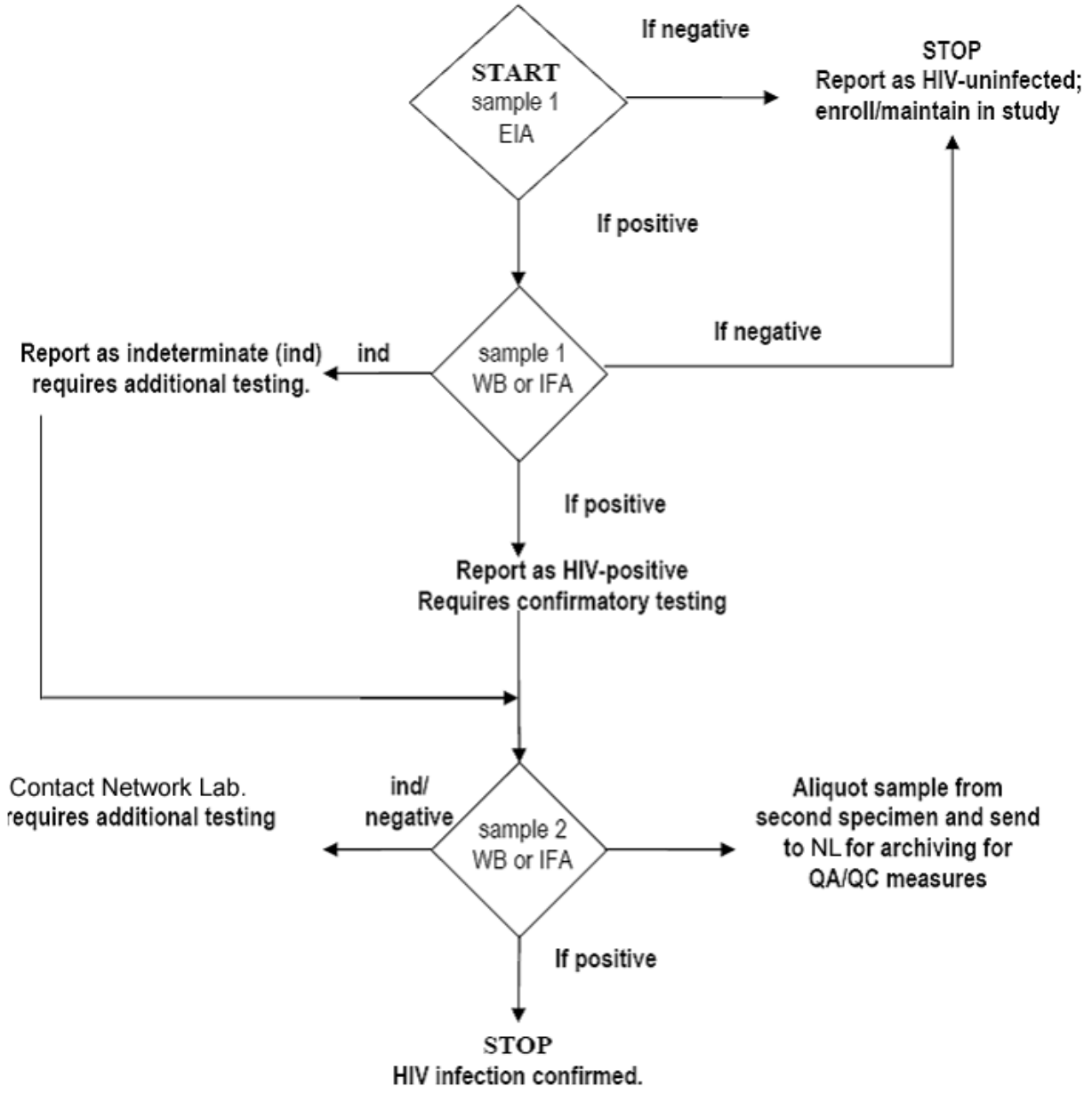
15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	ENR	4W	8W	12W	16W	Interim
	Up to and incl. 45 days prior to ENR	Day 0	Must occur within ±7 days of scheduled visit				
Informed Consent	x	x					
PTID	x						
Compr. Checklist		x					
Demographics	x						
Locator Information	x	x	x	x	x	x	x
Behavioral Eligibility	x	x					
Reimbursement	x	x	x	x	x	x	
Provide Results		▲	▲	▲	▲	▲	▲
Randomization		x					
Schedule Next Visit	x	x	x	x	x	▲	▲
Med./Mens. History	x	x	x	x	x	x	x
Obstetric History		x					
Pre-existing Cond.		x					
Behav. Assessment.		x	x	x	x	x	
Adher. Assessment			•	•	•	•▲	
Accept. Assessment		x	•▲	•▲	•	•▲	
Concomitant Meds	x	x	x	x	x	x	x
Compl. Phys. Exam	x	x				x	▲
Targ. Phys. Exam			x	x	x		▲
Contraceptive Coun.	x	x	x	x	x	x	▲
HIV Test Related	x	▲	▲	▲	▲	x	▲
HIV/STI/Male Condom Counseling	x	x	x	x	x	x	▲
Protocol Adherence Counseling		x	x	x	x	x	▲
Product Use/Adher. Counseling		•	•	•			▲
Treat UTI/RTI/STI	▲	▲	▲	▲	▲	▲	▲
Qualitative hCG	x	x	▲	▲	▲	x	▲
Dipstick Urinalysis	x	▲	▲	▲	▲	▲	▲
Urine Culture	▲	▲	▲	▲	▲	▲	▲
NAAT for GC/CT	x	▲	▲	▲	▲	x	▲
Syphilis Serology	x	▲	▲	▲	▲	▲	▲
Confirm. Syphilis	▲	▲	▲	▲	▲	▲	▲
HIV-1 Test	x	▲	▲	▲	▲	x	▲
Confirm. HIV-1	▲	▲	▲	▲	▲	▲	▲
Pelvic Exam	x	x	x	x	x	x	▲
Vaginal pH	x	x	x	x	x	x	▲
Vaginal Wet Mount	x	x	x	x	x	x	▲
Gram Stain	x	x	x	x	x	x	
Pap Smear	▲						▲
Colposcopy		x			x	x	▲
Vaginal Cultures (US sites only)		x	x	x	x	x	
Biofilm Assessment (at US sites only)			•▲	•▲	•▲	•▲	•▲
Herpes Culture	▲	▲	▲	▲	▲	▲	▲
Study IVR		•	•▲	•▲			•▲
Male Condoms	x	x	x	x	x	x	▲
Collect Used IVR			•▲	•▲	•	•▲	•▲

▲ *if indicated* ●*For group A (group randomized to Study IVR)*

APPENDIX II: HIV ANTIBODY TESTING ALGORITHM



Note: HIV positive results will only be reported to participants once the result is confirmed by Western Blot Testing. Once a participant's HIV status is confirmed, sites will follow site specific SOPs for notification to local agencies.

APPENDIX III: COMPONENTS OF EXAMINATIONS

Complete Physical Exam

- Height (may be omitted after the Enrollment Visit)
- Weight (may be omitted after the Enrollment Visit)
- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- General appearance
- Abdomen
- Other components as indicated by participant symptoms

Targeted Physical Exam

- Components as indicated by participant symptoms

Pelvic Exam

- Vulva
- Perianal area
- Speculum exam
    - Vagina (including vaginal discharge)
    - Cervix (including cervical discharge)
- Bimanual exam, if clinically indicated
    - Cervix
    - Uterus
    - Adnexae

APPENDIX IV: SAMPLE INFORMED CONSENT FORM (SCREENING)

MTN-005

Expanded Safety and Acceptability Study of a Non-medicated Intravaginal Ring

Version 1.0
03 April 2008

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Safety and Acceptability of a Non-medicated Intravaginal Ring (IVR)**

Introduction

You are being asked to take part in this screening process because you are a woman between the ages of 18 and 45 years and you may be able to join the research study named above. This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH). The International Partnership for Microbicides (IPM) is supplying the study product for MTN-005. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening process includes interview questions, urine and blood tests, a physical exam, including a pelvic (female genital) exam.

This is a screening consent form. It gives you information about the screening process. The study staff will explain this to you and what is expected of you. You are free to ask questions at any time. If you agree to take part in screening, you will be asked to sign this consent form or make your mark in front of a witness. You will be given a copy of this form to keep.

Why Are These Screening Exams and Tests Being Done?

These exams and tests are being done to see if you can be in this study. The research study will try to find out more about whether using vaginal rings for twelve weeks is safe and acceptable for women. A vaginal ring is a ring that is placed in the vagina and can release certain medicines to prevent pregnancy or can release hormones to lessen the symptoms of menopause. A member of the study staff will show you a vaginal ring. For example, Femring® is a vaginal ring that postmenopausal women use to lessen the symptoms of menopause such as hot flashes and night sweats. Women in the United States have been using Femring® ever since it was approved by the United States Food and Drug Administration in 2003. The type of ring that will be used in this study is made from the same materials as Femring® except that **the rings that will be used in this study contain no medicine at all. The rings used in this study will not protect you from pregnancy, HIV or any infection passed through sex**. About two thirds of the women in this study will be asked to use the ring for twelve weeks and some women will not use anything at all. The other purpose of this study is to find out what women think about using a vaginal ring.

Although vaginal rings have been approved by the United States Food and Drug Administration, this particular research study would like to find out more information about how the rings affect the vagina. For example, if you can join the study, some of the tests that will be done will look for changes in the bacteria that are normally found in the vagina.

The United States National Institutes of Health is providing funds for this study to take place. A total of 252 women from Pune, India, Alabama, USA, and New York, USA, will join this study (150 in India and 102 in the US). Each woman will be in the study for a total of 16 weeks. If you can join the study, you will have a study visit every 4 weeks.

Some women may not be able to join the study because of information found during the screening exams and tests.

What Do I Have To Do If I Take Part in the Screening Exams and Tests?

If you agree to have the screening exams and tests, you will have one to two screening visits here at the study site. Depending on what your screening exams and tests show more screening visits will be needed. Your first visit will continue today, after you read, discuss, and sign or make your mark on this form. No study exams or tests will be started before the screening exams and tests have been fully explained to you, you have let us know that you understand the screening process, and you have signed or made your mark on this form.

This visit will take about one to two hours. You will be asked to do these things if you decide you want to be in the study:

- Sign this form or make your mark after you have read it, understand it, and had the chance to ask questions about the study.

- To find out if you can join the study you will be asked some questions. The questions will be about you, how we can contact you and where you live. You will be asked questions about your health, the medicine you take, your periods, and how often you have vaginal sex.

- If your answers to those questions show that you may join the study, you will have to give urine for a pregnancy test. You will receive the result of your pregnancy test today. If you are pregnant, you will not be able to join the study. However, site staff will talk to you about options available to you. They will refer you to available sources of medical care and other services you may need.

- If you are not pregnant, study staff will talk to you about HIV and other infections passed through sex. You will have tests for HIV, gonorrhea, chlamydia, syphilis, bacterial vaginosis, candidiasis, trichomoniasis, and herpes simplex virus (you will be tested for herpes only if the study nurse or doctor thinks you have signs of herpes, like a blister or ulcer on the genitals). You will talk about HIV/AIDS and

other infections passed through sex. You will also talk about ways that HIV and other infections passed through sex are passed from one person to another, and things you can do to protect yourself from them. You will talk about what it may mean to know the results of these tests. You can talk about whether or not you are prepared to know these test results. If you are having health problems that may be a result of infections passed through sex, the study staff will refer you for treatment or give you medicine to treat them.

- The vaginal ring used in this study will not stop you from becoming pregnant; therefore you should not use this as a birth control method. You must agree to use effective method of birth control such as birth control pills or another hormonal based method (except vaginal rings), an intrauterine device (IUD), study provided male condoms, be sterilized, or have sex with a partner who is sterilized. You may not use diaphragms, spermicides, or spermicidal male condoms. If you are using male condoms, you must only use the ones provided in this study. Study staff will talk to you about the different ways to avoid becoming pregnant. The study staff will provide male condoms to you free of charge.

- If you are willing to have HIV testing and testing for infections passed through sex, you will be asked to give blood (about a tablespoon) [SITES TO INSERT LOCAL EQUIVALENT] and urine for the tests. You must hear your HIV test results to join the study.

- Your urine will also be checked for gonorrhea, chlamydia, and to see if you are pregnant. Your blood will be tested for HIV and syphilis. It will take about [INSERT LENGTH OF TIME] to get the results of your tests. We will give you your results as soon as they are ready.

- You will have a physical exam and a pelvic exam. If you do not know what will be done during a pelvic exam, the study staff will show you pictures of what happens. The study doctor or nurse will check for discharge, or other signs of infection, and other possible problems. They will also take some fluids to check for bacterial vaginosis, vaginal yeast infection, or trichomoniasis.

- If a sore (or other problem) is seen during the exam of your vagina, you may need medicine to treat it. You will be asked to see your regular clinic for medicine or be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

- If you do not have results with you today of a Pap smear (a test to check for cervical cancer) that was done in the past 12 months the study doctor will also collect samples from your cervix to check for anything that is not normal. If the test is not normal, you may be asked to see your regular clinic for more tests. It takes about [SITES TO INSERT AMOUNT OF TIME] before Pap test results are ready.

We will give you the results as soon as they are ready. The results of your Pap test may affect whether you can use the vaginal ring being tested in this study.

It takes about [SITES TO INSERT AMOUNT OF TIME] before results for HIV and infections passed through sex are ready. You will talk to with the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies you may be able to join.

If your exams and tests show that you have an infection passed through sex, you may need medicine to treat it. The study staff will refer you to your regular clinic for medicine or give you medicine here to treat the infection. You will be asked to come back here after taking all the medicine. At that time, you may be able to enter the research study.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed through sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners since they should also be tested. If you do not want to inform your partners yourself, the outreach workers will contact them according to the confidentiality guidelines of the [HEALTH AUTHORITY].

If your exams and tests show no problems, you will be able to enter the research study. You will receive a different informed consent form if you return for the Enrollment Visit.

If at any time during the screening it is found that you cannot join the study, the screening process and your visit will end.

Why Would The Doctor Stop the Screening Procedures Early?

The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the US National Institutes of Health (NIH), the MTN, the International Partnership for Microbicides, the Ethics Committees, the Office for Human Research Protections, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- Your exams, tests and answers to the questions show you cannot join the study.
- The study staff feels that having the screening exams and tests would be harmful to you.
- You do not want to find out your HIV test result.
- You are not able to come to the visits or complete the screening exams and tests.
- Other reasons that may prevent you from completing the study.

What Are The Risks Of The Screening Visit Tests?

Risk of Blood Draws:
You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:
You may feel discomfort or pressure during the pelvic exam. You may have mild vaginal bleeding (spotting). The mild bleeding will stop shortly after the exam.

Other Possible Risks:
You may become embarrassed, worried, or nervous when discussing sex; ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your test results. If you have HIV or other infections, knowing this could make you worried, nervous, or sad. You may be referred to a trained counselor who can help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly.

Are There Benefits To Taking Part In This Study?
You may get no direct benefit from the screening exams and tests. However, you will have a physical exam and a pelvic exam, and counseling and testing for HIV and infections passed through sex. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, 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 male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your regular clinic or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for infections passed through sex and other infections. If you have any of these infections, you will be referred for treatment if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential infections passed through sex.

What Other Choices Do I Have Besides This Study?
You do not have to participate in this study, if you choose not to do so.

The only known way to protect against HIV during sex is to use a condom every time you have sex.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your healthcare provider about these and other choices that may be available to you.

What About Confidentiality?
Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified. To make sure that the study is being done the right way, we may ask you if you will allow a staff member working for the study sponsor to observe your study exams or questions. You can say no to this and still be in the study. You are encouraged but not required to tell sexual partners about your being in this study.

Your records may be reviewed by:
- The US Food and Drug Administration (US FDA)
- US National Institutes of Health (NIH)
- Office for Human Research Protections (OHRP)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Organization supporting this study (International Partnership for Microbicides)

[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

What Are The Costs To Me?
There is no cost to you for the screening exams and tests.

Will I Receive Any Payment?

You will be paid for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of having the screening exams and tests. If you are injured as a result of having the screening exams and tests, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company if you have one. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form. [SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant?

Taking part in the screening exams and tests is completely up to you. You may choose to not have the screening exams and tests any time. You will be treated the same no matter what you choose. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

What Do I Do If I have Problems or Questions?

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered, you have let us know that you understand, and you agree to take part in this study, please sign your name or make your mark below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

MTN-005

Version 1.0
03 April 2008

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Safety and Acceptability of a Non-medicated Intravaginal Ring (IVR)**

Introduction

You are being asked to take part in this study because you are a woman between the ages of 18 and 45 years and you have passed the screening questions and tests for the research study named above. This Microbicide Trials Network (MTN) study is funded by the US National Institutes of Health (NIH). The International Partnership for Microbicides (IPM) is supplying the study product for MTN-005. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The enrollment process includes interview questions, urine and blood tests, a physical exam, including a pelvic (female genital) exam.

This is an enrollment consent form. It gives you information about the study product, study questions and exams, and what you have to do to be in the study. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the study at any time. If you agree to take part in this study, you will be asked to sign this consent form or make your mark in front of a witness. You will be given a copy of this form to keep.

Why is this Study Being Done?

This study is being done to see if a kind of vaginal ring is safe and acceptable to women. A vaginal ring is a ring that is placed in the vagina and can release certain medicines to prevent pregnancy or hormones to lessen the symptoms of menopause. For example, Femring® is a vaginal ring that postmenopausal women use to lessen the symptoms of menopause such as hot flashes and night sweats. Women in the United States have been using Femring® ever since it was approved by the United States Food and Drug Administration in 2003. The type of ring that will be used in this study is made from the same materials as Femring®, except that **the rings that will be used in this study contain no medicine at all. The rings used in this study will not protect you from pregnancy, HIV or any infection passed through sex**. About two thirds of the women in this study will be asked to use the ring for 12 weeks and about one third will not use the ring. As this is a randomized trial, women who join this study will not be

able to choose their group assignment. The other purpose of this study is to find out what women think about using a vaginal ring.

Vaginal rings have been developed to prevent pregnancy and to provide hormones to older women, and have been tested in many thousands of women since 1970. Although these vaginal rings have been approved by the United States Food and Drug Administration, this particular research study would like to find out more information about how rings without medication might affect the vagina. For example, if you can join the study, some of the tests that will be done will look for changes in the bacteria that are normally found in the vagina.

The United States National Institutes of Health is providing funds for this study to take place. A total of 252 women from Pune, India, Alabama, USA, and New York, USA, will join this study (150 in India and 102 in the US). Each woman will be in the study for a total of 16 weeks. If you are in the study, you will have a study visit every 4 weeks.

What Do I Have To Do If I Take Part in the Study?

If you agree to be in the study, you must not use or plan to use the following at enrollment, during the period of study participation, and for an extra month after the study ends: non-study vaginal products or other devices including diaphragm, sex toys, douching and other intravaginal cleansing practices, female condom, intravaginal ring (except for the one provided in this study if you are in the group that will use the ring), spermicide, and/or menstrual cup. You will be allowed to use tampons.

You will also have these study visits here at the study site:

- Enrollment Visit
- 4-Week Visit
- 8-Week Visit
- 12-Week Visit
- 16-Week Visit

Enrollment Visit

Your Enrollment Visit will continue today, after you read, discuss, and sign or make your mark on this form. No study activities will be started before they have been fully explained to you, you have let us know that you understand the enrollment process and you have signed or made your mark on this form.

The Enrollment visit will take about one to two hours. You will be asked to do these things for the Enrollment Visit if you decide you want to be in the study:

- Sign this form or make your mark on it after you have read it, understand it, and had the chance to ask questions about the study
- Tell the study staff how they can stay in contact with you
- Answer questions about your sexual behavior and what vaginal products you have used before
- Tell the study staff about previous pregnancies and how many children you have

- Tell the study staff about any medical problems, changes in your health or menstrual periods
- Tell the study staff about any medicines you are taking now
- Have a physical exam
- Hear about
    - how to avoid pregnancy and infections passed during sex while you are in the study
    - how to use the study provided male condoms
    - how to follow the rules of the study
    - how to use the vaginal ring, if you are in the group that uses the vaginal ring
- Provide a urine sample for a pregnancy test, and to test for urine infection
- Provide a urine sample to test for gonorrhea and chlamydia
- Provide a blood sample for syphilis testing (if you have signs of syphilis)
- Provide a blood sample for HIV testing (if the study doctor thinks you need an HIV test)
- Have a pelvic exam and colposcopy. During the colposcopy, the study doctor or nurse will look at your genital area and into your vagina through a lens called a colposcope. The lens works like a magnifying glass to help the nurse or doctor see anything that may not be normal. The lens will not be inside your body. They may take digital video pictures of the colposcopy with a camera. You may tell the study staff not to record these images. These images will be kept strictly confidential and used only by study physicians to decide upon the significance of possible changes in the vagina or cervix.
- Provide samples of vaginal discharge that will be collected with a swab to check for vaginal infections and vaginal cultures (types and amounts of bacteria in the vagina)
- Have a test for herpes infection if you have signs of herpes infection (like a sore or blister on the genitals)
- Receive male condoms
- If you are in the group that uses the vaginal ring, the study staff will also discuss with you these things:
    - The study staff will tell you how to insert the ring, and then give you privacy so that you can put the ring in yourself. A study doctor or nurse will then check to see that you have put the ring in the right way. If you are having difficulty putting in the ring, you can ask questions and receive more advice. Please let the doctor or nurse know if you do not think that you will be able to put the ring in by yourself.
    - If your ring falls out before your next visit and you do not feel comfortable rinsing the ring in clean, warm water and putting it back in your vagina, you will need to save this ring in a special bag that we will give you and bring it back to your next visit.
    - If you need to remove your ring before your next scheduled visit, please go to the clinic as soon as you are able to so that a study clinician can remove the ring. If you are not able to wait until you go to the clinic to

have your ring removed, please save this ring in a special bag that we will give you and bring it back to your next visit.

Scheduled Monthly Visits (4-Week, 8-Week, 12-Week and 16-Week/Study Termination Visits)

These procedures will take about an hour. You will have the following routine procedures at your 4 scheduled visits:

- Tell the study staff how they can stay in contact with you (let us know about any changes to your address, phone number or other ways to contact you)
- Tell the study staff about any medical problems, changes in your health or menstrual periods
- Tell the study staff about any medicines you are taking now
- Answer questions about your sexual behavior
- Have a physical exam
- Hear about
    - how to avoid pregnancy and infections passed during sex while you are in the study
    - how to use the study provided male condoms
    - how to follow the rules of the study
- Provide a urine sample to test for urine infection (if you have signs of urine infection)
- Provide a blood sample for syphilis testing (if you have signs of syphilis)
- Have a pelvic exam
- Provide samples of vaginal discharge that will be collected with a swab to check for vaginal infections and vaginal cultures (types and amounts of bacteria in the vagina)
- Have a test for herpes infection if you have signs of herpes infection (like a sore or blister on the genitals)
- Receive male condoms
- Receive test results

Additional Procedures

You will complete all of the regular monthly procedures plus:

- Learn how to use the vaginal ring, if you are in the group that uses the vaginal ring (4-Week and 8-Week Visits)
- Answer questions about the vaginal ring it (if you are in the group that uses the ring) (4-Week, 8-Week, and 12-Week Visits)
- Provide a urine sample for a pregnancy test (if the study doctor thinks you need a pregnancy test) (4-Week, 8-Week, and 12-Week Visits)
- Provide a urine sample for gonorrhea and chlamydia (if you have signs of gonorrhea or chlamydia) (4-Week, 8-Week, and 12-Week Visits)
- Provide a blood sample for an HIV test (if the study doctor thinks you need an HIV test) (4-Week, 8-Week, and 12-Week Visits)

- Have a colposcopy (12-Week and 16-Week/Study Termination Visits)
- Have the study ring removed by the physician. The study staff will then take a sample of the fluid that is on the ring for testing. You will not get the results of this test because the test is for research purposes only and will not result in information that could be used for your health. (12-Week Visit)
- Answer questions about what you thought about the ring (if you are in the group that uses the ring) (12-Week Visit)
- Provide a urine sample for a pregnancy test (16-Week/Study Termination Visit)
- Provide a urine sample for gonorrhea and chlamydia (16-Week/Study Termination Visit)
- Provide a blood sample for an HIV test (16-Week/Study Termination Visit)

It takes about [SITES TO INSERT AMOUNT OF TIME] before results for colposcopy, HIV and infections passed through sex are ready. You will not receive the results of the vaginal cultures, because these types of tests do not give information that can be used for medical care. You will talk to the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have an infection passed through sex, you may need medicine to treat it. You will be asked to see your regular clinic for medicine or be given medicine here. The study staff will ask you to stop using the vaginal ring, if you are in the group that uses the ring. You will be asked to come back here after taking all the medicine.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE]

[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed through sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [HEALTH AUTHORITY] may then contact you about informing your partners since they should also be tested. If you do not want to inform your partners yourself, the outreach workers will contact them according to the confidentiality guidelines of the [HEALTH AUTHORITY].

Why Would The Doctor Take Me Off This Study Early?

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the US National Institutes of Health (NIH), the International Partnership for Microbicides, the Ethics Committee, the Office for Human Research Protections (OHRP), the MTN, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study).
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the ring (if you are in the group that uses the ring) but continue to come in for your follow up visits and procedures if:

- You are pregnant
- You become infected with HIV.
- The study doctor decides that using the ring would be harmful to you or your partner.
- You require a treatment that you may not take while using the ring.
- You have a bad reaction to the ring.

If the study doctor asks you to stop using the ring, you will still be advised to come in for all of the scheduled follow-up visits that are described above, including things like the physical exam, vital signs, pelvic exam (except if you are pregnant), blood tests, and questionnaires. You will stop using the ring until the study doctor decides it is safe for you to start using the ring again, if possible.

What Are the Risks of Being in the Study?

Risk of Pregnancy:

The rings that will be used in this study contain no medicine at all and will not protect you from pregnancy; therefore you should not use this as a birth control method. You must agree to use effective method of birth control such as birth control pills or another hormonal based method (except vaginal rings), an intrauterine device (IUD), study provided male condoms, be sterilized, or have sex with a partner who is sterilized while you are participating in the study and for an extra month after the study has ended. Study staff will talk to you about the different ways to avoid becoming pregnant. The study staff will provide male condoms to you free of charge.

If you think you may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your choices. If you have a positive pregnancy test and if you are in the group that is using the study ring, we will ask you to stop using the ring right away and return it to the clinic, but will ask you to continue to be in the study and to come in for your follow-up visits. You will continue to have all of the scheduled procedures except for the pelvic exam.

If you are pregnant at the 16-Week/Study Termination visit, you will continue to be followed by the study clinician until you are no longer pregnant. The study staff will contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. This study cannot provide care related to termination of pregnancy, though study staff can provide you with information about your access to termination of pregnancy as part of counseling you about your pregnancy test results.

Risks of Vaginal Ring
If you are in the group that uses the vaginal ring, you might have the following side effects that have been seen in women who have used a vaginal ring: more discharge from the vagina, irritation in the vagina, discomfort with sex, or pressure in the vagina. These effects, if you have them, would not be expected to be serious or permanent. There is also a chance that your partner may feel the vaginal ring.

Risk of Blood Draws:
You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams and Colposcopy:
You may feel discomfort or pressure during the pelvic exam. You may have mild vaginal bleeding (spotting). The mild bleeding will stop shortly after the exam.

Other Possible Risks:
You may become embarrassed, worried, or nervous when discussing how you have sex; ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your test results. If you have HIV or other infections, knowing this could make you worried or nervous. You may be referred to a trained counselor who can help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are in the study. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly.

Are There Benefits To Taking Part In This Study?
You may get no direct benefit from being in this study. However, you will have physical exams and pelvic exams, and counseling and testing for HIV and infections passed through sex. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, 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 male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your regular clinic or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for infections passed through sex and other infections. If you have any of these infections, you will be referred for treatment if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential infections passed through sex.

What Other Choices Do I Have Besides This Study?
You do not have to be in this study, if you choose not to do so.

The only known way to protect against HIV during sex is to use a condom every time you have sex.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your regular doctor about these and other choices that may be available to you.

What About Confidentiality?
Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified.

Your records may be reviewed by:

- The US Food and Drug Administration (US FDA)
- US National Institutes of Health (NIH)
- Office for Human Research Protections (OHRP)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Organization supporting this study (International Partnership for Microbicides)

[For US sites only:] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the US Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. You are encouraged but not required to tell sexual partners about your being in this study.

What Are The Costs To Me?
There is no cost to you for the study visits, study provided male condoms, or treatment for treatable infections passed by sex.

Will I Receive Any Payment?
You will be paid for your time and effort for each study visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to

you for coming to the study visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE].

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of being in this study. If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company if you have one. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form. [SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant?

Taking part in the study is completely up to you. You will be treated the same no matter what you decide. If you choose to not to be in the study, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know that you would like them.

What Do I Do If I have Problems or Questions?

For questions about this study or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered, you have let us know that you understand, and you agree to take part in this study, please sign your name or make your mark below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX VI: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

MTN-005

Phase 2 Expanded Safety and Acceptability Study of a Silicone Elastomer Intravaginal Ring

Version 1.0
03 April 2008

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: **Vaginal Ring Study**

INTRODUCTION

You have decided to take part in a US National Institutes of Health research study. While you are in this research study there may be some samples of blood and/or fluid from your vagina taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask any questions, if you have some. If you agree to the storage of your samples, you will be asked to sign this consent form. You will be given a copy of this form to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

The research doctors want to save any extra blood and vaginal fluid leftover from your tests during the study. This leftover blood and vaginal fluid will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples will be used to look for evidence of your body's response to infection (such as examining cells, proteins, and other chemicals in your body) while you were in the study. Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less likely to become infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission. The researchers do not plan to contact you or your regular clinic with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. If a rare situation came up where the researchers decided that one of the test results would provide important information for your health, the researchers would notify your study doctor

and your study doctor would try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the National Institutes of Health, an Ethics Committee, and a special committee at the researcher's institution (an Institutional Review Board) whose purpose is to protect you as a research participant.

HOW LONG WILL YOU KEEP MY SAMPLES?
There is no time limit on how long your samples will be stored.

HOW WILL MY SAMPLES BE STORED?
Your samples may be sent to the United States for storage and testing. Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples to store them and to keep track of where they are, but these people will not have information that directly identifies you (a code number will be on these samples, but not your name). An Institutional Review Board/Ethics Committee will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY SAMPLES BENEFIT ME?
There are no direct benefits to you.

WHAT ARE THE RISKS?
There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the biological parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?
To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

[For US sites only:] We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not

connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, National Institutes of Health (NIH), Office for Human Research Protections, study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your samples, contact (*insert the name of the investigator*) at *(insert telephone number)*.

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board) at (insert telephone number)*.

SIGNATURE PAGE
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), understand it, and all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

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