

HIVNET/HPTN Protocol 016A

Condom Promotion and Counseling
Version 6.0

A study of the HIV Prevention Trials Network

Sponsored by:
The National Institutes of Allergy and Infectious Diseases

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I, the Principal Investigator, 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 five years, or until FHI (the International Master Contractor) advises that it is no longer necessary, whichever comes first.

Publication of the result of this trial will be governed by DAIDS policies. Any presentation, abstract, or manuscript will be made available by the investigators to DAIDS and FHI.

Signature of Principal Investigator

Date

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SCHEMA

Condom Promotion and Counseling

- Design:** Participants will be counseled in HIV prevention, condom use and negotiation skills during 5 visits over 2 months. Completers of this program who are HIV-negative will be asked to return for four quarterly follow-up visits to provide information on continued condom use and sexual behavior, in order to generate knowledge and prepare the study cohort for a Phase III microbicide effectiveness trial.
- Population:** Women (regardless of HIV serostatus) attending postnatal and family planning clinics at 3 sites in Malawi (Blantyre and Lilongwe) and Zimbabwe.
- Sample Size :** 1000 women per site.
- Intervention:** Behavioral counseling messages for 5 visits over 2 months; subsequent quarterly visits with no drug intervention provided.
- Study Duration:** 14 months for each participant. The Condom Promotion and Counseling Study will continue until a Phase III microbicide protocol is approved and ready for implementation.

Primary Objectives:

- Evaluate the effectiveness of condom promotion and counseling messages on uptake of condoms as a means to prevent HIV transmission by comparing the prevalence of consistent condom use (defined as using condoms in more than 75% of coital acts) at enrollment versus the end of an 8 week intensive condom promotion counseling program;
- Evaluate the overall effectiveness of condom promotion and counseling messages on continued use of condoms as a means to prevent HIV transmission by comparing the prevalence of consistent condom use at the condom promotion exit visit with the prevalence of consistent condom use during quarterly visits following the condom promotion counseling program.

2.2 Secondary Objectives

Among women attending postnatal and family planning clinics in Malawi and Zimbabwe:

- Determine the incidence of HIV-1;
- Determine the incidence of other STDs (GC, CT, TV, HIV, syphilis), yeast, bacterial vaginosis and genital lesions (in HIV-1 uninfected women)
- Determine the prevalence of HIV-1
- Determine the prevalence of other STDs (GC, CT, TV, HIV, syphilis), yeast, bacterial vaginosis and genital lesions (in HIV-1 uninfected and infected women)
- Determine feasibility of recruiting a large study cohort (1000 participants per site) with high retention rates (> 90% over one year).

LIST OF ACRONYMS

AE	Adverse experience (also adverse event)
BV	Bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
CT	<i>Chlamydia trachomatis</i>
DAIDS	Division of AIDS
DSMB	Data and Safety Monitoring Board
EIA	Enzyme Immuno Assay (same meaning as ELISA)
ELISA	Enzyme-linked Immunosorbent Assay (same meaning as EIA)
FHI	Family Health International
GC	Gonococci (neisseria gonorrhoea)
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HIVNET	HIV Network for Prevention Trials
ID	Identification number
IMC	HIVNET International Master Contractor
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
KOH	Potassium hydroxide
LCR	Ligase chain reaction
N-9	Nonoxynol-9
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office of Human Research Protection
OTC	Over-the-counter
PI	Principal Investigator
PCR	Polymerase Chain Reaction
RPR	Rapid Plasma Reagin
SAE	Serious adverse experience
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SMC	Study Monitoring Committee
SPA	Single Project Assurance
SSP	Study Specific Procedures Manual
STD	Sexually transmitted disease
TPHA	<i>Treponema Pallidum</i> Hemagglutination Assay
TV	<i>Trichomonas Vaginalis</i>
UNAIDS	Joint United Nations Programme on HIV/AIDS
USFDA	U.S. Food and Drug Administration
WHO	World Health Organization

1. Introduction

1.1 Background and Rationale

This study is intended to prepare women to participate in a Phase III clinical trial of vaginal microbicides. During this preparatory period, condom promotion and counseling will be carried out. The effectiveness of this educational activity on uptake and consistent use of male condoms will be determined. The study sites involved in this protocol were prepared to initiate a Phase III effectiveness trial of the vaginal microbicide Conceptrol gel (100 mg nonoxynol-9 (N-9) gel per application), the HIVNET 016 trial. Recently, however, the results of a Phase III trial of a 52 mg N-9 gel (Advantage-S) conducted by UNAIDS were presented at the XIII International AIDS Conference in Durban, South Africa. These preliminary results suggested that N-9 users had a higher rate of HIV incidence than placebo users. This information combined with the results of other clinical trials of N-9, which showed that N-9 was either not effective or marginally beneficial, led the protocol team to reconsider this product. Therefore, the Phase III portion of the HIVNET 016 trial was canceled prior to enrollment and randomization of women into the appropriate study arms. Currently, these women are participating in an extensive Condom Promotion and Counseling study that was originally designed to precede the main Phase III study.

Vaginal microbicides to prevent transmission of HIV and STDs remain a high priority for these research sites. The HPTN investigators and the protocol team are actively involved in the selection of alternative products, which could potentially be safe and effective. During this transitional period, and to maintain the research infrastructure which has been established, it was decided to continue the Condom Promotion and Counseling study. This allows collection of data on condom use, incidence and prevalence of STDs, and additional information that will improve the quality of future Phase III vaginal microbicide trials.

Unlike previous studies that targeted commercial sex workers, the current studies of condom promotion, and ultimately the Phase III study, enroll women of reproductive age who are attending postnatal or family planning clinics in Malawi and Zimbabwe. Sexually active women in these countries represent large populations suitable for recruitment at sites with established infrastructure. In addition, these populations satisfy several desirable criteria for studies of vaginal microbicides. For example, the HIV incidence is high (4.2% in Malawi and 5.5% in Zimbabwe), use of condoms is low (approximately 15% life-time use in Malawi), the loss to follow-up rates from previous cohort studies have been low (10-25% per year), and levels of rectal sex and intravenous drug use are low. It is anticipated that a study of women who are not commercial sex workers could provide a more stable study population and therefore better retention and follow-up, as well as more broadly generalizable results than previous microbicide studies in commercial sex workers.

We originally selected a dose of 100 mg N-9 gel (Conceptrol® gel) for the 016 study, based on experience with other N-9 products that have been tested for HIV/STD control. For example, in the study in Cameroon that showed no effect on HIV acquisition by Roddy et al. (1998)¹ the low dose of

N-9 found in the 70 mg film studied might have been responsible for the result. On the other hand, in the study by Kreiss et al. (1992)² among commercial sex workers in Nairobi, Kenya, there was a concern that a 1000 mg N-9 sponge might have increased the frequency of genital lesions. Besides dose of the vaginal microbicide, other factors were taken into account. These included a) future availability of the product, b) stability of the product in different ambient conditions, c) volume, distribution and bioavailability of the product within the vagina, and d) acceptability of the product. The choice of the placebo was linked to that of the active product and was intended to be an "inert" product with no potential activity. It is likely, however, that some characteristics of the placebo (e.g., lubricating effect) cannot be completely avoided. In a Phase III vaginal microbicide study, the design, selection of study populations, type and dose of the product, and type of placebo are influenced by numerous factors. The Protocol Team has been guided by results of prior studies and by expert opinion. The protocol team members have benefited from the discussions and suggestions made at ad-hoc expert meetings held by HIVNET/HPTN and others.

In addition to evaluating effectiveness in reducing HIV/STD acquisition, vaginal microbicide studies need to address two important factors. These are safety and acceptability. A potential adverse effect that has also been discussed is the effect of application of vaginal products on the vaginal ecosystem.³ Ideally, long term use of vaginal products should not decrease the concentration of lactobacilli (the predominant normal flora), increase the frequency of vaginal *E. coli* (and other organisms), or increase yeast infections. Depletion of lactobacilli may limit production of hydrogen peroxide and other antibacterial activities that are protective against pathogenic organisms such as STDs and possibly HIV.^{4,5} Low vaginal pH has been postulated to inhibit CD4 lymphocyte activation and reduce HIV target cells in the vagina.⁶ Therefore, lack of lactic acid production by lactobacilli could lead to an elevated pH, which may be more conducive to growth and survival of the virus.⁷

Since the need for a vaginal microbicide to prevent heterosexual spread of HIV is a major priority, evaluation of these products should continue, but cautiously, with full understanding of the concerns and limitations that have been raised in previous studies. To evaluate effectiveness and safety of vaginal microbicides, a large cohort of women will need to be followed over time.

Two vaginal microbicide products, BufferGel and PRO2000, have been tested in Phase I clinical trials among African women and have been shown to be safe. Both products are considered for the Phase III study. A study design of four arms including BufferGel, PRO2000, a placebo, and a condoms-only arm is now being developed. We anticipate about nine months to develop the protocol and to obtain the necessary regulatory approvals. During this period, we will implement the current protocol of extended condom promotion and microbicide-preparedness. The condom promotion and intensive counseling study will provide an opportunity to educate women on condom use before being screened for the Phase III trial. Evaluation of acceptability and compliance is critical in vaginal microbicide studies. To accurately estimate effectiveness of the product during a typical use, both clinical and acceptability data should jointly be evaluated. To achieve these objectives, adequate information will be collected during this preparatory study on sexual activity, use of traditional vaginal agents, use of condoms, partner characteristics, and rates of STDs in these populations. Different techniques, including recall interviews

and questionnaires on most recent events, will be used to collect the desired data. Counseling sessions will be structured and documented to minimize variations between clients and sites. Study workers who are not the primary counselors will conduct evaluation of the participant responses.

In summary efforts should continue to find preventive interventions to slow the rapid spread of heterosexual HIV infection. UNAIDS estimates that approximately 21 million individuals infected with HIV are in sub-Saharan Africa. These infections constitute 68% of all HIV infections and 80% of all female HIV infections in the world⁸. Although the male condom has been vigorously advocated in Africa, its rate of consistent use has not substantially increased as in regions of Asia (e.g., Thailand). Unfortunately, women are not able to negotiate consistent condom use due to cultural and social barriers deeply rooted in African societies. Methods women can control, such as vaginal microbicides, are urgently needed.

2.0 Study Objectives and Design

2.1 Primary Objectives

- Evaluate the effectiveness of condom promotion and counseling messages on uptake of condoms as a means to prevent HIV transmission by comparing the prevalence of consistent condom use (defined as using condoms in more than 75% of coital acts) at enrollment versus the end of an 8 week intensive condom promotion counseling program;
- Evaluate the overall effectiveness of condom promotion and counseling messages on continued use of condoms as a means to prevent HIV transmission by comparing the prevalence of consistent condom use at the condom promotion exit visit with the prevalence of consistent condom use during quarterly visits following the condom promotion counseling program.

2.2 Secondary Objectives

Among women attending postnatal and family planning clinics in Malawi and Zimbabwe:

- Determine the incidence of HIV-1;
- Determine the incidence of other STDs (GC, CT, TV, HIV, syphilis), yeast, bacterial vaginosis and genital lesions (in HIV-1 uninfected women)
- Determine the prevalence of HIV-1
- Determine the prevalence of other STDs (GC, CT, TV, HIV, syphilis), yeast, bacterial vaginosis and genital lesions (in HIV-1 uninfected and infected women)
- Determine feasibility of recruiting a large study cohort (1000 participants per site) with high retention rates (> 90% over one year).

2.3 Study Design

This is a multi-center, prospective observational study of approximately 3000 women attending postnatal and family planning clinics in Malawi and Zimbabwe with the purpose of assessing 1) the effects of intensive 8 week condom promotion counseling on uptake and continued use of condoms, 2) prevalent and incident HIV-1 and STDs, and 3) the feasibility of recruiting a large study cohort with high retention rates in preparation for a Phase III microbicide effectiveness study. An overview of the study design is presented in Table 2 of the Appendix, and details regarding study visits and procedures are presented in Section 4. Briefly, informed consent will be obtained at the enrollment visit (visit #1) where HIV pre-test counseling will be done along with HIV and STD testing (outlined in Table 1 of the Appendix). In addition, a baseline questionnaire including information regarding sexual behavior and current condom usage will be filled out. Lab results on HIV and STDs from this visit will be used to calculate the prevalence of HIV and other STDs in this cohort.

The first follow-up visit (visit #2) will take place 2 weeks after enrollment. At this visit, HIV post-test counseling, STD treatment and additional STD testing (if necessary), and a counseling session on condoms (scripts are provided in the study procedures manual) will occur. A sexual behavior questionnaire will be filled out at this visit. Additional condom promotion counseling sessions will take place at the second and third follow-up visits (visits #3 and #4) which are scheduled at 4 and 6 weeks post enrollment. The 3 condom promotion counseling sessions have been structured to teach women methods for preventing sexual transmission of HIV and other STDs, with an emphasis on effectively using condoms. STD and HIV testing and treatment will be done at the second and third follow-up visits if necessary, and a condom use log form and sexual behavior log form filled out. At the fourth follow-up visit (visit #5), a condom use log form and sexual behavior log form will be filled out. To determine the effectiveness of the condom promotion counseling on uptake of condom use, the data on condom use collected at this visit will be compared with the data on condom use collected at the enrollment visit as outlined in section 8.

Women who were HIV uninfected at their enrollment visit will then be invited to return every three months, for a period of one year, for follow-up visits. At these visits, participants will be tested for HIV and STDs (outlined in Table 1 of the Appendix), and information regarding ongoing condom use and sexual behavior will be collected. Data from these visits will be used to calculate HIV incidence and STD incidence as outlined in Section 8. In addition, data collected regarding condom use at these visits will be used to evaluate how effective condom promotion counseling is on continued use of condoms as outlined in Section 8.

3. Study Population

3.1 Inclusion Criteria

To be eligible for inclusion in this study, a woman *must be*:

- willing and able to give informed consent
- at least 18 years old
- willing to undergo clinical evaluations, including speculum examination and HIV testing
- sexually active
- willing to adhere to follow-up schedule.

3.2 Exclusion Criteria

To be eligible for inclusion in this study, a woman *must not*:

- have a history of adverse reaction to products containing latex *unless* the site is able to substitute polyurethane male or female condoms for her use.

4. Schedule of Visits and Procedures

All efforts to evaluate HIV preventive methods must be structured so that participants completely understand the nature of HIV transmission and how best to prevent transmission. Not all women will be able to negotiate condom use with their partners, nor will all women want to use condoms, even after intervention counseling. We need to ascertain the prevalence of condom use in the populations that will ultimately host a Phase III microbicide trial, and to determine to what degree intensive counseling results in both short-term and sustained condom use.

A two month intensive condom promotion and counseling study with subsequent quarterly follow-up visits will be used to provide potential Phase III participants with behavioral intervention counseling, and to assess willingness and ability to use condoms consistently, in both short and long-term use.

A schedule of events and study timeline are attached as Tables 2 and 3 respectively.

Ancillary study for validation of self-reported condom use through biological markers:

To test the use of biological markers as a means to validate self-reported condom use by participants, the sites will collect data on incident trichomoniasis infection on participants enrolled in the two-month condom promotion program. Trichomoniasis diagnosed at the first visit will be treated, and a test of cure evaluated at the second visit (scheduled to be two weeks after the first visit). Trichomoniasis diagnosed at the final visit will be counted as an incident infection if a negative finding was noted at any of the earlier visits.

During the quarterly follow-up visits, participants will be tested for additional STDs including HIV (see Appendix B) and treated as needed, but no test of cure visit will be scheduled in addition to the next regularly scheduled visit three months later. Treatment will result in a presumption of cure.

4.1 Schedule Overview for the Two Month Intensive Counseling Program:

- Recruitment and enrollment: All women seeking services at the study clinics will be informed about the study. The intervention program will be explained to the participants, informed consent procedures will take place, and the participants will be asked to undergo HIV testing, with appropriate pre- and post-test counseling. Identification numbers will be assigned to track HIV and STD results. All women meeting the inclusion/exclusion criteria will be asked to participate in the condom promotion program independent of their HIV test results.
- There will be 5 scheduled visits over the 8 week intensive counseling period:
 - Visit #1: Consenting, baseline questionnaires (to include demographics and contraceptive use); screening STD tests
 - Visit #2: 2 weeks after Visit #1; first counseling session; STD test results, treatment if needed; sexual behavior assessment

- Visit #3: 2 weeks after Visit #2; second counseling session; STD test if needed; treatment if needed; sexual behavior and condom use assessments
- Visit #4: 2 weeks after Visit #3; third counseling session; STD test if needed; treatment if needed; sexual behavior and condom use assessments
- Visit #5: 2 weeks after Visit #4; STD tests to detect incident infections; treat if needed; sexual behavior and condom use assessments

- To be eligible to return for quarterly follow-up visits participants must be HIV-negative. HIV-positive participants, at the discretion of the clinic site, may continue with quarterly visits to protect their confidentiality, but no further data will be collected from them.
- Eligible participants will return every 3 months for the following:
 - behavioral interview to assess ongoing condom use and sexual behaviors
 - pelvic exam to detect STDs (GC, CT, TV), BV and genital lesions
 - blood draw for HIV and syphilis
- Participants who seroconvert to HIV+ during the quarterly follow-up visits will be discontinued from the cohort. Although no further data will be collected from them, they may be offered the option of returning for scheduled follow-up visits in the interest of protecting their confidentiality.
- Each site will continue with this study until a protocol for a Phase III effectiveness trial is ready for implementation at the clinic sites. Each individual volunteer will participate for a maximum of 14 months.

4.2 Visit 1: Enrollment visit

The study will be described to each participant. When clinic staff are satisfied the participant understands the study and agrees to enroll, the participant will be asked to sign (or provide other mark, if illiterate) a consent form for the screening procedures, and will be given a copy of the consent form to take home (see Appendix A for sample consent forms).

All participants will be assigned a participant ID number and evaluated to determine their eligibility according to the participation inclusion/exclusion criteria.

The following screening procedures will be done:

- an interview with the woman to make sure she understands the purpose and nature of the study, the visit schedule, and is willing to comply with study requirements,
- pre-test HIV counseling,
- blood draw for HIV and syphilis serology (following pre-test counseling, 7 ml of blood is removed by venipuncture for HIV testing by ELISA and for syphilis serology by RPR and TPHA)

- pelvic exam for STD test specimen collection (all sites will record, at a minimum, data on TV; sites may also conduct the entire specimen collection sequence as shown in Appendix B).

Contact information

For each participant, clinic staff will obtain contact information. Each study site will develop its own participant locator form and determine the best way to collect this information for its own study population. In the event that a participant misses a scheduled appointment, the clinic staff will try to establish communication with the participant through all possible means (e.g., telephoning if this is possible, writing to the participant and contacts, and/or visiting the participant's home or workplace). The confidentiality of the participant will be protected during any attempts to make contact. The need to attend all scheduled follow-up visits will be emphasized to all study participants at every visit.

The participants will be scheduled to return in 2 weeks for the next visit, Visit 2, when they will receive post-test counseling, their HIV and syphilis test results, and the first messages of the condom promotion program.

4.3 Visits for Intensive Condom Promotion and Counseling Study

Each participant will receive condom counseling messages at Visits 2, 3 and 4. After Visit 4, no intensive messages will be provided, although counselors will continue to answer questions and remind participants of the need to use condoms to prevent STD transmission.

Activities at Visits 2, 3, and 4:

- A questionnaire to collect information on frequency of intercourse and condom use
- A counseling session on condoms (scripts are provided in the Study Specific Procedures Manual)
- STD test results from prior visit, if needed
- STD treatment, if needed
- Pelvic exam for STD test of cure specimen collection, if needed
- Schedule next visit

Activities at Visit 5:

- Questionnaire to collect information on frequency of intercourse and condom use
- STD test results from prior visit, if needed
- STD treatment, if needed
- Pelvic exam for STD tests, all participants
- Schedule first quarterly visit

4.4 Microbicide Preparedness Follow-up Visits

Participants will return at three-month intervals (every 13 weeks – Visits 6, 7, 8 and 9) for the duration of the study. Those who tested positive for HIV at enrollment into the Condom Promotion Study will

not be part of the active cohort that contributes data to the study database. The purpose of this cohort is to develop a study population that can participate in a Phase III microbicide effectiveness trial, which will enroll only HIV negative women. However, women who test HIV positive may return to the clinic for follow-up visits at the discretion of the site. No data will be collected from these participants.

Activities at the quarterly follow-up visits:

- Interview to collect information on sexual behavior, vaginal hygiene practices and condom use
- HIV prevention education
- Pelvic exam for STD tests (see Appendix B)
- STD treatment, if needed
- Pre-test counseling for HIV test
- Blood draw for HIV and syphilis serology
- Schedule next visit

Participants will return in one to two weeks for test results following each visit, and will receive appropriate post-test counseling and STD treatment if required.

STDs

Whenever an STD is diagnosed, treatment will be given to the participant at no cost. If one of the laboratory tests is positive without clinical evidence of an STD and/or if a prescribed treatment has to be adjusted after laboratory results become available, the participant will be traced and treated. Where possible, the infected participant's partner will be referred for treatment.

4.5 Strategies to Maximize Follow-Up

High rates of loss to follow-up introduce bias and reduce the validity of the study findings. Every effort will be made to minimize losses in each site. Specifically, the following procedures will be implemented:

- Study workers will be trained to fully explain the study protocol and the need for attending scheduled visits.
- Adequate counseling and explanation of the study procedures will be repeated at each visit.
- A locator form (to include place of residence and important landmarks) will be completed at enrollment and updated at each follow-up visit.
- Home tracing of clients, who are late for their scheduled visits, will be carried out by trained tracers. Tracers are designated study workers who are specifically trained to conduct home tracing. Tracing visits have been utilized in previous cohort studies at these sites and were effective in maximizing retention.
- Each site will map the townships and the suburban areas of the city to facilitate tracing of clients and to identify areas of high mobility.
- Adequate infrastructure, e.g., vehicles and study personnel, will be available to conduct the research activities.

- A computer-generated list of participant IDs who are late for scheduled visits will be made available every week. This will provide an immediate management tool to monitor follow-up activities.
- Community contacts, through a Community Action Board and other groups, will be established to increase awareness about HIV/AIDS and potential intervention studies to reduce the spread of the disease. For example, in Blantyre, Malawi, a group of women volunteers (former participants of earlier studies) have helped to explain the purpose of ongoing studies at the community level, to dispel rumors, and to encourage women to attend their visits.

4.6 Interim Visits (ad hoc)

Interim visits are unscheduled “walk-in” visits, distinguished from adverse experience visits in that no health related reaction, effect, or abnormality is reported. Some examples of reasons for an interim visit are:

- to get more condoms
- to ask questions of study staff
- to discuss problems with study compliance

No data will be collected from these visits other than notes in the participant’s clinic notes.

4.7 Withdrawal Criteria for Study Participants

A participant may be discontinued early from the study for any of the following reasons:

- the study doctor decides that continuing the sessions would be harmful to the participant;
- the participant considers it to be in her best interest;
- the study is canceled by the local clinic or the National Institutes of Health (NIH);
- other administrative reasons.

Reasons for discontinuation from the study will be recorded on the appropriate data collection form. When early discontinuation from the study occurs, every reasonable effort will be made to assess information relevant to primary and secondary endpoints at the time of discontinuation.

4.8 Treatment of Participants Who Develop Study Outcomes

HIV infection

Participants acquiring HIV infection will be counseled and referred for medical and social care in accordance with country specific guidelines. The clinical care provided will vary by site and will depend on both the local standard of care and any guidelines provided by NIH or the network. The participant may continue to return for follow-up visits if she chooses, but no study data will be collected after her seroconversion had been verified.

STDs and genital ulcers

Participants with STDs will be treated according to the study site's normal standard of care. Where possible, partners will be referred for treatment. The guidelines for each site will be described in the site specific procedures. When such guidelines are not available, STD treatment will be according to WHO guidelines. Whenever possible, a directly observed single oral dose treatment will be given.

4.9 Determining Loss to Follow-up

A participant will be considered lost to follow-up if, at the time of study closeout at the site, she has not returned for a final follow-up visit, and attempts to contact her to obtain necessary information were unsuccessful. No participant will be considered lost to follow-up before the study is closed at the study site. For interim monitoring of the study, Kaplan-Meier plots of the time since the last visit will be used to assess follow-up.

The need to attend all scheduled follow-up visits must be emphasized to all study participants. If a participant fails to appear for a scheduled visit, attempts to contact her should be made. All attempts to contact the participant should be documented in the participant's study file. If the participant chooses to discontinue from the study after an absence, this information, and as much information as possible relevant to study endpoints will be recorded on the appropriate data collection form.

5. Adverse Experience Reporting and Handling

Each participant will be advised to contact the clinician or clinic staff immediately if she has any medical problem or complaints during the course of this study. The investigator will evaluate all complaints and assure that appropriate health care or referral is provided to all study participants.

Study participants may experience adverse events that may be related to their condom use. The condoms provided to the women at each site, are approved, widely used and marketed, and have well-established safety profiles. Expected and mild side effects of condom use will not be collected as adverse events in this study although they will be noted on the patient's record.

Any serious and/or unexpected fatal or life-threatening adverse events (SAE), regardless of cause, should be reported to the Principal Investigator, who will report them immediately to FHI as described in the Study Manual of Operations. A log of these events will be maintained and will be reported to the appropriate IRB(s) according to their reporting requirements. IF an SAE is judged to be definitely related to any study product it will be reported to the manufacturer on a MedWatch form.

6. Evaluation of Outcomes

6.1 Prevalence and Incidence of Infection

- To assess the prevalence and incidence of HIV, chlamydia, gonorrhea, trichomonas, syphilis, clinical genital ulcer disease, and monitor the occurrences of monilia and bacterial vaginosis in this population.

6.1.1 HIV

An incident HIV infection will be defined as follows:

- a single positive (or indeterminate) ELISA test followed by a confirmatory positive Western Blot at a follow-up visit, and
- negative ELISA tests at the preceding visit

At screening or enrollment visits, HIV infections will be determined by two positive ELISA tests, or if either ELISA test is indeterminate, by a confirmatory Western Blot test. At subsequent follow-up visits, HIV infections will be determined by one positive (or indeterminate) ELISA test followed by a confirmatory Western Blot.

6.1.2 Chlamydial Infection

An incident chlamydial infection will be defined as follows:

- a positive EIA confirmed by a blocking assay on a cervical sample collected at a follow-up visit, and
- a negative EIA on the cervical sample collected at the preceding visit

6.1.3 Gonococcal Infection

An incident gonococcal infection will be defined as follows:

- a cervical culture positive for *N. gonorrhoeae* at a follow-up visit, and
- a cervical culture negative for *N. gonorrhoeae* at the preceding visit

6.1.4 Trichomonas Infection

An incident trichomonas infection will be defined as follows:

- the presence of *T. vaginalis* in the wet mount of material recovered from anterior or posterior fornices at a follow-up visit, and

- the absence of *T. vaginalis* in the wet mount of material recovered from the posterior fornix at the preceding visit.

6.1.5 Genital Ulceration

An incident case of genital ulceration will be defined as follows:

- the presence of genital ulceration at a follow-up visit, and
- the absence of genital ulceration at the preceding visit.
- Genital ulceration will be further defined by a positive laboratory diagnosis of chancroid (*H. ducreyi*), syphilis (*T. pallidum*), or genital herpes (HSV).

6.1.6 Syphilis

An incident case of a syphilis will be defined as a:

- Negative RPR at baseline followed by any subsequent RPR/MHA-TP positive.

No one with a positive RPR/MHA-T at baseline will be considered in the analysis as an incident case.

- Due to the lack of standardization in the RPR response to treatment, no woman will be considered in the syphilis incident analysis after she has been treated.

6.1.7 Bacterial vaginosis

Bacterial vaginosis will be diagnosed by the use of a combination of clinical and vaginal wet mount criteria. Three of the 4 criteria are necessary for a diagnosis of BV:

1. A homogenous, white, non-inflammatory discharge that smoothly coats the vaginal walls;
2. The presence of clue cells on vaginal wet mount examination;
3. A pH of vaginal fluid > 4.5;
4. A fishy odor of vaginal discharge (ie., the whiff test).

6.2 Determine Feasibility of Cohort Recruitment and Retention

In order to generate meaningful data from a large effectiveness trial, it is essential that participating research sites have systems in place to recruit a large number of participants (in excess of 1000 women) and to ensure high rates of retention. Sites will attempt to recruit 1000 participants over 12 months, with retention rates of at least 90% at the end of 12 months. This level of retention is considered the minimal desirable level for a Phase III microbicide trial.

7. Data Collection

7.1 Forms Used

All data collection forms, and forms instructions, will be included in the Study Specific Procedures Manual.

7.2 Forms Completion and Submission

At each visit, forms will be completed by study team members as outlined in the Study Specific Procedures Manual. Data forms will be checked immediately for completeness and consistency by designated study team staff.

Data will be provided to SCHARP on a regular basis, on a schedule and by means determined to be appropriate for each site. Additional data quality testing will be performed by SCHARP. This will include range and consistency checks and assessment of completeness of data. SCHARP will provide periodic data quality control (QC) reports to each site.

To monitor the rate of enrollment and follow-up, each site will, once a week, e-mail enrollment and follow-up information to the FHI Protocol Specialist for dissemination to the protocol team. At the end of the study, this report will be corroborated with the SCHARP database to insure comparability.

7.3 Record Storage and Archive

The study site principal investigator will maintain all source documents used to complete study forms. Source documents may include laboratory requisitions and reports, documentation of referrals, and progress notes. All data collection forms and source documents must be kept in locked files in a secure area. Source documents should be kept together with the data collection forms in locked participant files unless standard clinic procedures prevent this. If source documents are stored separately from participant files, their location must be known and they must be readily accessible to any authorized representative of the study sponsor and/or regulatory agencies. All locator information must be kept in locked files in a secure area. All records must be available at all times for inspection by NIAID, FHI and SCHARP staff.

The investigator will retain study records for at least 5 years after the end of the study or until advised by FHI, or the study sponsor, that record retention is no longer necessary.

8. Statistical Considerations

8.1 Sample Size and Accrual

The sample size of 1000 women per site to be enrolled over 12 months was chosen based on the secondary objective of this study to determine the feasibility of enrolling and retaining a large number of

women. In addition to evaluating the effectiveness of condom promotion, this study will evaluate the capabilities of each site to participate in a proposed Phase III microbicide study. We estimate that in this proposed Phase III microbicide study, each of these three sites will need to enroll between 80 and 100 HIV-1 negative women per month for up to 15 months with an approximate sample size per site of 1000 to 1500. Hence, to determine the feasibility of enrolling and retaining this large number of women, each of the three study sites is expected to enroll 1000 women over a period of 12 months for a total sample size of 3000 for the condom promotion phase of the study (visits #1 through #5). Only women who were HIV negative at their enrollment women will participate in the quarterly visits portion of the study (visits #6 through #9). Assuming an HIV-1 seroprevalence of 20%, we expect approximately 2400 women in this portion of the study.

In addition, we anticipate that many of the HIV-1 seronegative women that exit the condom promotion study will be eligible to enroll into the proposed Phase III study once it begins. Hence, the condom promotion study may allow a “jump start” to the proposed Phase III study, and potentially decrease the overall follow-up time necessary in that study, due to a large proportion of women being enrolled in the first months of the proposed Phase III study.

8.2 Analysis Plan

8.2.1 Primary objectives and power

One primary objective of this study is to evaluate the effectiveness of condom promotion counseling messages on uptake of condoms as a means to prevent HIV transmission. This will be assessed by using McNemar’s test to determine if there is a significant difference between the prevalence of consistent condom use (defined as using condoms in more than 75% of coital acts) before (i.e., at the enrollment visit) versus after condom promotion counseling (i.e., at visit #5).

Assuming a 2-sided test, and zero correlation within women (which should be conservative unless the correlation is truly negative (which is unlikely)), and 3000 women enrolled, the table below outlines the differences we will be able to detect with 90% power for differing baseline prevalence of consistent condom use.

Prevalence of Consistent Condom Use at Baseline	90% Power to Detect a Difference of:
5%	± 3%
10%	± 3%
20%	± 4%
30%	± 4%
40%	± 5%
50%	± 5%

The other primary objective in this study is to determine how effective the condom promotion program is on continued use of condoms as a means to prevent HIV transmission. This will be assessed by McNemar's test to compare the prevalence of consistent condom use at the condom promotion exit visit (visit #5) with the prevalence at the quarterly visits (visits #6 through through #9) including in each comparison only women with the relevant follow-up visit. Since only women who were HIV negative at enrollment will participate in this portion of the study, and assuming 10% loss to follow-up over this time period, we expect approximately 2160 women for this analysis.

Assuming a 2-sided test, and zero correlation within women (which should be conservative unless the correlation is truly negative (which is unlikely)), and 2160 women, the table below outlines the power the differences we will be able to detect with 90% power for different prevalence of consistent condom use at the condom promotion exit visit (visit #5).

Prevalence of Consistent Condom Use at Visit #5	90% Power to Detect a Difference of:
10%	± 4%
20%	± 5%
30%	± 5%
40%	± 5%
50%	± 5%
75%	± 5%

8.2.2 Secondary Objectives

Secondary objectives of this study include determination of the prevalence and incidence of background STDs (GC, CT, TV, HIV-1, syphilis) yeast, bacterial vaginosis and genital lesions. The prevalence of STDs (other than HIV-1) will be determined using data from the first quarterly follow-up visit (which is the first visit where a full STD screen is performed). Using binomial proportions will give us estimates of STD prevalence among HIV-1 uninfected women. The prevalence of HIV-1 will be determined using binomial proportions on data from visit #1 of the condom promotion intensive counseling program. Since the first quarterly follow-up visit is the first visit where a full STD screen will be performed, the incidence of STDs (other than HIV-1) will be calculated using the first quarterly visit as the baseline visit and calculating person years of follow-up and incident cases from that visit. HIV-1 incidence will be calculated using visit #1 of the condom promotion counseling as the baseline visit and calculating person years of follow-up and incident cases from that visit forward. Kaplan-Meier analysis will be used to estimate incidence rates.

The final objective of this study is to determine the feasibility of recruiting a large study cohort with high retention rates. Enrollment numbers will be reviewed throughout the study to determine the maximum enrollment rates possible at each site. Follow-up rates will be calculated using Kaplan Meier analysis using follow-up definitions as outlined in section 4.10. To determine if compliance with the visit schedule for the condom promotion phase of the study predicts for better quarterly follow-up rates, the

log-rank test will be used to compare the follow-up rates during the quarterly follow-up portion of the study for women who attended condom promotion counseling sessions and women who missed visits.

8.2.3 Ancillary Study for Validation of Self-Reported Condom Use Through Biological Markers

To test the use of biological markers as a means to validate self-reported condom use by participants, we will use a chi-square test to compare the prevalence of incident TV at visit #5 (as defined in section 4 above) in women who reported 100% condom use, versus those who reported <100% condom use throughout the condom promotion counseling phase of the study.

9. Human Subjects

9.1 IRB Review and Reports

Prior to implementation the protocol and informed consent forms must be approved by the institutional review board (IRB) of each participating institution and by host country scientific/Ethical Committees. The study site principal investigator is responsible for preparation of all submission documents and periodic reports required by the IRB.

This protocol and the informed consent documents (Appendix A) and any subsequent modifications will be reviewed and approved by the IRB and Ethics Committees responsible for the oversight of the study.

A Single Project Assurance (SPA) or Community Project Assurance (CPA) form (as required by the Department of Health and Human Services) must be filed for each research site prior to study implementation.

Each principal investigator will report to FHI all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

Each principal investigator will make safety and progress reports to the IRB at least annually and within 3 months of study termination or completion. These reports will include the total number of subjects enrolled, the number of subjects completing the study, and all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

9.2 Informed Consent

Before participants are enrolled, the purpose and nature of the study as well as possible adverse experiences will be explained. Each statement of informed consent will comply with U.S. Regulations and guidelines from host countries. The participant must agree that she understands the investigational nature of the study, its inherent risks and benefits, other treatment alternatives, her rights to terminate participation in the study without affecting her health care at the clinic, a person to contact with questions regarding the study, and that she freely has given informed consent to participate in the study. Sample

copies of informed consent documents are contained in Appendix A. The consent form will be administered in the participant's native language, using a translation that has been approved by the applicable local IRB.

The signed informed consent forms will become a permanent part of the participant's clinic records. While the informed consents will be audited in the same manner as other records, copies will not be transferred to any agency outside of the clinic.

9.3 Confidentiality

The confidentiality of all participants enrolled in this study will be protected to the fullest extent possible. Participants' study site records may be audited by the sponsor's representatives, and/or other sponsoring organizations, or other individuals authorized to audit the study. Study participants should not be identified by name on any case report form or on any other documentation sent from the study site to SCHARP, FHI, or other sponsoring organization. All study records will be kept in a locked file cabinet. All computer entry and networking programs will identify participants with coded identification numbers only. The list linking participant ID numbers to other identifying information will be stored in a locked file in a room with limited access. Participants will not be reported by name in any report or publication resulting from data collected in this study.

10. Laboratory Specimens and 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 currently recommended by the Centers for Disease Control and Prevention (CDC).

11. Administrative Procedures

11.1 Study Coordination

The study site investigator (or designee) will participate in regularly scheduled telephone conference calls with the Protocol Chairs, NIAID Medical Officer, SCHARP Protocol Operations Coordinator, Biostatistician, and Protocol Specialist and/or Monitor in which general site operations, participant accrual, and data collection issues will be discussed.

11.2 Study Site Monitoring

Site visits by the FHI or designated DAIDS study monitor(s) will be made in accordance with HPTN policy to monitor the quality of data collected in the research records, the accuracy of the data entered in the database, and to determine that all regulatory requirements surrounding clinical trials are met.

The investigator will allow the sponsor representatives and other regulatory agencies to inspect study documents (e.g., consent forms, source documents, case report forms) and pertinent clinic records for confirmation of the study data.

Various authorized individuals may visit the study site to audit the progress of this study (e.g., HPTN personnel, sponsor personnel, regulatory personnel). A site visit log will be maintained at the study site in which all site visits made by authorized individuals are recorded. All clinical records and the data collection forms for the participants enrolled in this study will be made available for review by these authorized individuals.

11.3 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and the HPTN site principal investigator. Protocol amendments requiring IRB approval must be submitted to the IRB by the study site investigator and approval obtained prior to implementing the amendment.

In the event that a site investigator seeks an exemption or exception from the protocol for an individual participant, he or she will contact the FHI Protocol Specialist and the SCHARP Protocol Operations Coordinator with the request. The Protocol Specialist and Protocol Operations Coordinator will seek approval from the core Protocol Team: the Protocol Co-chairs, Statistician, and DAIDS Medical Officer.

11.4 Investigator Records

The study site investigator will maintain complete, accurate and current study records for a period of five years after the completion of the study or until notified by FHI, or the study sponsor, that retention of records is no longer required. Study records include the following:

- Administrative and regulatory files, including initiation documents and all reports and correspondence relating to the study
- Records for each participant, including informed consent forms, locator forms, data collection forms, and source documents.

11.5 Use of Information and Publications

Publication of the results of this study will be governed by DAIDS and HPTN policies. Any presentation, abstract or manuscript will be made available by the investigators to DAIDS for review prior to submission.

12. References

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2. Kreiss J, Ngugi E, Holmes K, Ndinya-Achola J, Waiyaki P, Roberts PL, Ruminjo I, Sajabi R, Kimata J, Fleming TR et al. *JAMA* 1992 Jul 22-29; 268(4):477-82.
3. Stone AB, Hitchcock PJ. Vaginal microbicides for preventing the sexual transmission of HIV. *AIDS* 1994; 8(Suppl 1):S285-S293).
4. Hillier SL, Krohn MA, Klebanoff SJ, Eschenbach DA. The relationship of hydrogen peroxide-producing lactobacilli to bacterial vaginosis and genital microflora in pregnant women. *Obstet Gynecol* 1992; 79:369-73.
5. Klebanoff SJ, Coobs RW. Viricidal effect of lactobacillus acidophilus on human immunodeficiency virus type 1: possible role in heterosexual transmission. *J Exp Med* 1991; 174:289-92.
6. Hill JA, Anderson DJ. Human vaginal leukocytes and the effects of vaginal fluid on lymphocyte and macrophage defense functions. *Am J Obstet Gynecol* 1992; 166:720-6.
7. Voller B, Anderson DJ. Heterosexual transmission of HIV (Letter to the Editor). *JAMA* 1992; 267:1917-8.
8. The United Nations Programme on HIV/AIDS (UNAIDS). The status and trends of HIV/AIDS epidemics in sub-Saharan Africa. Abidjan, Cote D'Ivoire: 3-4 December, 1997.

Table 1. Laboratory Tests

Specimens	Comments
Urine hCG	Urine is tested for the presence of hCG for pregnancy diagnosis by rapid dipstick analysis according to manufacturer specifications
Vaginal pH	A pH strip is held face-down against the lateral side of the vagina and allowed to become moistened with vaginal fluid. The pH is read by comparing the color on the applied pH strip to the reference colors provided by the manufacturer.
Vaginal wet mount	A cotton swab used to swab the lateral vaginal wall is placed in a test tube containing 1 ml sterile saline. A first slide is examined in the lab for the presence of clue cells, monilia, and motile trichomonads. A “Whiff” test will also be done. If trichomonas is not detected on the first slide a second slide will be prepared and examined, looking for trichomonas.
Cervical gonorrhea culture	Cotton swabs are used to inoculate a plate for GC isolation. The plates are incubated in a candle jar for 24-48 hours at 37° C.
<i>N. gonorrhoeae</i> confirmation	<i>Neisseria gonorrhoeae</i> will be identified by typical gram stain appearance, positive oxidase reaction, and the carbohydrate degradation pattern and DNase reaction observed through sugar fermentation (quadFERM+, BioMerieux Vitek, Inc., Hazelwood, MO).
Cervical chlamydia antigen	Dacron swabs provided in the manufacturer’s EIA collection kit are placed in the endocervical canal and allowed to sit for at least 10 seconds. They are placed in the vial provided, the handle of the swab is snapped off, and the vials are capped for transport to the laboratory. In the laboratory, the antigen is extracted from the swabs and ELISA is performed on the extract according to manufacturer instructions. The swabs are discarded.
RPR	At screening, enrollment, every subsequent 3 months, or if ulcer present. Blood is collected and blood serum is tested by RPR testing according to manufacturer specifications.
TPHA	Only if RPR becomes positive. Serum testing newly positive by RPR that was previously negative by TPHA will have TPHA testing performed according to manufacturer specifications.
HIV ELISA	Blood is collected and blood serum is tested by ELISA kit #1 for antibodies according to manufacturer specifications. Any participant who tests positive by ELISA kit #1 will have a confirmatory ELISA kit #2. After a woman has enrolled, if the second ELISA is borderline or positive a confirmatory western blot assay will be done. A western blot will not be performed on ELISA positive during screening.
HIV Western Blot	If the 1st ELISA is borderline or positive on subsequent visits after the subject has tested negative during screening, serum will be tested by immunoblot assay according to manufacturer specifications.

Specimens	Comments
Genital ulcer PCR	A swab from an amplicor collection kit (Roche) will be rolled over the base of all genital ulcers and placed in amplicor transport media per manufacturers instructions. The inoculated transport media will be stored at -70C, then shipped to the University of North Carolina (UNC) for analysis. By the PCR multiplex technique, HSV, Treponema pallidum and Haemophilus ducreyi will be identified.

Table 2. Schedule of Events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6+
	<i>Day 0</i>	<i>+2 weeks</i>	<i>+2 weeks from Visit 2</i>	<i>+2 weeks from Visit 3</i>	<i>+2 weeks from Visit 4</i>	<i>13 week intervals</i>
Informed consent	✓					
HIV test counseling (pre/post)	✓	✓				✓
HIV test	✓					✓
STD tests	✓	<i>(if needed)</i>	<i>(if needed)</i>	<i>(if needed)</i>		✓
HIV/STD test results		✓	<i>(if needed)</i>	<i>(if needed)</i>	<i>(if needed)</i>	<i>*see note</i>
STD treatment	<i>(if needed)</i>	<i>(if needed)</i>	<i>(if needed)</i>	<i>(if needed)</i>	<i>(if needed)</i>	<i>*see note</i>
Baseline questionnaires	✓					
Sexual Behavior Log form		✓	✓	✓	✓	
Condom Use Log form			✓	✓	✓	
Condom promotion session		✓	✓	✓		
Microbicide Preparedness Follow-up Questionnaire						✓

* Participants will return in 1 to 2 weeks to receive HIV/STD test results. If treatment for STDs is provided no follow-up test of cure will be done until next scheduled quarterly visit.

Table 3: Study Timeline

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Quarterly F/U	Proposed Phase III
X-----	X-----	X-----	X-----	X-----	X----X----X----X	
-	-		-			
2 wks	2 wks	2 wks	2 wks		13 wks intervals	

Appendix A: Sample Informed Consent Document

Sample Informed Consent Document

**Sample Informed Consent Template
for trials sponsored by the
Division of AIDS, NIAID, NIH**

REMINDER TO RESEARCH SITES: DO NOT USE PREAMBLE IN LOCAL CONSENTS

NOTE FROM OHRP (OFFICE OF HUMAN RESEARCH PROTECTION) TO SITES
ENROLLING SUBJECTS IN THIS STUDY:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB WITH A COPY OF THIS SAMPLE CONSENT ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OF SUBSTANTIVE CHANGE OR INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENTS MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB AND NOTED IN THE IRB MINUTES. JUSTIFICATION AND IRB APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO FHI FOR ANY HPTN-SPONSORED TRIAL. SPONSOR-APPROVED CHANGES IN AN HPTN-PROTOCOL MUST BE APPROVED BY THE LOCAL IRB BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB MAY OTHERWISE ADDITIONALLY REQUIRE.

TITLE OF THE RESEARCH:

Condom Promotion and Counseling, HPTN 016A, Version 6.0

PRINCIPAL INVESTIGATOR:

[Name of Investigator and contact information here]

INTRODUCTION:

You are being asked to take part in the research study named above. In this research study you are being asked to take part in condom promotion counseling sessions for the purpose of teaching you ways to prevent transmission of human immunodeficiency virus (HIV, which leads to Acquired Immunodeficiency Syndrome (AIDS)), and other sexually transmitted diseases (STDs). The best way known to prevent getting HIV is to use condoms every time you have sex, and this program will give you information about this.

This informed consent document gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent or make your mark in front of someone. You will be given a copy to keep.

Please note that:

- Your participation in this research is entirely voluntary;

- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care.

PURPOSE OF THE STUDY:

The purpose of these counseling sessions is to teach women ways to prevent getting HIV from sex. The counseling sessions will stress the use of condoms, which is the only proven way to prevent sexual transmission of HIV, other than not having sex. You will be asked to attend three counseling sessions over two months. After two months you will be asked to return to the clinic every three months for a check up visit, for one year.

After the counseling sessions, you will be asked questions about whether you think you will use condoms in the future.

This study will also find out how many people who come to this clinic are likely to have infections that are passed by having sex.

PROCEDURES:

After you sign this consent form, but before you enter the study, you will be given information about HIV testing, and will give a blood sample of about one and a half small spoonfuls [teaspoons] to test for HIV.

You will be asked to return to the clinic in one to two weeks to get your test results and have them explained to you. If you are HIV-infected, the nurse will tell you ways to prevent giving HIV to others and will refer you for additional care, if you wish. You may participate in the counseling sessions whether or not you have HIV.

You will be asked to attend three counseling sessions. After the third session you will be asked questions about your willingness and ability to consistently use condoms.

You will be asked to have a pelvic exam at some of the visits to be tested for STDs. During a pelvic exam the doctor will check the inside of your vagina.

After completing the counseling sessions, you will return to the clinic every 3 months for one year. At these visits you will have a test for HIV and a pelvic exam to test for other infections.

RISKS and/or DISCOMFORTS:

Having a pelvic examination may cause some discomfort. Some people may feel faint or dizzy when blood is drawn. You may be sore or have a bruise or swelling at the site where blood is drawn.

Knowing your HIV status may cause you anxiety. If others find out your HIV status, you may have trouble finding or keeping a job and have problems being accepted in your family and community.

POTENTIAL BENEFITS:

You may receive no benefit from these counseling sessions. Taking part in these counseling sessions may help you to use condoms more often during sex. If you use condoms every time you have sex, you will be much less likely to get HIV and other sexually transmitted diseases.

If the nurse finds that you have an STD, you will receive medicine at no cost to you.

NEW FINDINGS:

You will be told of any new information learned during the course of the counseling sessions that might cause you to change your mind about returning for more counseling.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SESSIONS WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- the study doctor decides that continuing the sessions would be harmful to you;
- you are unable to keep appointments;
- the study is canceled by the local clinic or the National Institutes of Health (NIH);
- other administrative reasons.

COSTS TO YOU:

There is no cost to you for any lab tests, or for attending the counseling sessions, or for returning for the clinic visits.

CONFIDENTIALITY:

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study.

Your records may be reviewed by the U.S. agency that reviews research, the agency that sponsors this research, and the study monitors.

RESEARCH-RELATED INJURY:

If you are injured as a result of participation in this study, the study clinic will give you immediate necessary treatment for your injuries. The cost of this treatment will not be charged to you. You will then be told where you may receive additional treatment for injuries. There is no compensation provided for research-related injuries.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

If you ever have questions about this study or in case you are injured as a result of participation in this research study, you should contact (*name of local investigator or study clinician*) at (*telephone number or address*). If you ever have questions about your rights as a research subject you may *call* (*name and title of IRB member*) at (*telephone number or address*).

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

TITLE OF THE RESEARCH:

Condom Promotion and Counseling, HIVNET/HPTN 016A, Version 6.0

SIGNATURE PAGE:

If you have read the informed consent or had it read and explained to you and understand the information, and you voluntarily agree to join this study, please sign your name or make your mark below.

Volunteer's name (print)

Volunteer's signature

Date

Name of staff member
who administered consent
(print)

Staff signature

Date

If the volunteer cannot read, this form must be read to the volunteer exactly as written, in the volunteer's native language, and a witness must sign this form to confirm that the correct information was given to the volunteer and that the volunteer freely consents to be in this study.

Witness' name

Witness' signature

Date

Appendix B: Pelvic Examination Procedures

- A urine sample for a pregnancy test is collected at enrollment, but not at follow-up unless indicated. Subject provides a urine sample in a urine cup marked with her enrollment identifier (see Table 2 for procedures).
- Inguinal lymph nodes palpated and any enlargement and tenderness noted (see Pelvic Exam forms for detailed documentation).
- Vulva and perineum visually inspected for breaks in epithelial integrity, warts, or other lesions (see Pelvic Exam forms for detailed documentation).
- A speculum lubricated with water will be inserted into the vagina.
- Visual inspection of the vagina and cervix (see Pelvic Exam forms for detailed documentation).
- Vaginal pH measured by holding a pH strip against the lateral vaginal wall with a cotton tipped applicator and compared to the pH chart provided with the strips (see Table 2 for procedures).
- A vaginal swab placed in a test tube with 1ml of normal saline for the preparation of the wet-mount (saline). The test tube is marked with the subject number for identification. The swab is swished around in the tube to release as much vaginal debris as possible and is then discarded. The tube is capped and transported to the lab where a slide is prepared and read immediately following lab protocols for the detection of *T. vaginalis*, clue cells, and *Candida albicans*. A second wet mount slide will be prepared and read for the detection of trichomonas only if the first slide fails to detect trichomonas.
- *For ancillary vaginal Gram stain studies:* A second swab rolled against the vaginal wall and then rolled onto a glass slide; slide will be dried and archived for a future Gram stain analysis. (Each site is responsible for the evaluation of specimens taken.)
- A cotton swab is placed into the endocervical canal, rotated 360 degrees, and used to inoculate a modified Thayer-Martin plate for gonorrhea culture. Plates must have the subject's id number written on them. These inoculated plates need to be transported to the laboratory as soon as possible where they will be placed in candle jars then into the incubator.
- A dacron swab provided in the EIA Chlamydia detection kit is placed in the endocervical canal and left in place at least 10 seconds and rotated at least 360 degrees. This swab is placed back in the vial provided in the kit. The end of the swab is broken off and the vial is capped. The vial must be marked with the subject's id number. The vial is transported to the lab where it is placed in the refrigerator until the assay is run per manufacturers instructions.

- If a genital ulcer is detected, the swab from an Amplicor Collection Kit (Roche) will be rolled over the base of the ulcer and placed in the transport media vial. The swab is swished around and then wicked on the side of the vial before being discarded. The vial should be marked with the participant ID and date. The vial will be taken to the lab, placed in a -70°C freezer and eventually shipped to UNC for analysis.
- Finally the speculum is removed and a bimanual pelvic examination is performed (see Pelvic Exam forms for detailed documentation).