HIV Prevention Trials Network
PROTOCOL CLARIFICATION MEMORANDUM #1

HIVNET/HPTN 055: HIV Prevention Preparedness Study
Version 1.0, 12 August 2002

21 January 2004

Summary of Clarification

Section 3.3, Paragraph 2: text is modified to clarify and reconcile procedures outlined in the protocol, with the Study-Specific Procedures Manual (SSP), Visit Checklists, and site-specific Standard Operation Procedures (SOPs) regarding the relative timing of assigning the Participant ID number and obtaining informed consent for screening.

Implementation

The protocol clarification detailed in this memorandum should be implemented immediately. This clarification does not result in a change in the informed consent being used in the study. If The HPTN 055 protocol is amended in the future, this clarification will be incorporated into the next version.

The HPTU will submit HPTN 055 Protocol Clarification Memorandum #1 to all responsible Institutional Review Boards (IRBs) for informational purposes. IRB approval of HPTN 055 Protocol Clarification Memorandum #1 is not required.

The following protocol modifications, indicated by ~~strikethrough~~ or under-score text, made to the HPTN 055 Protocol:

Section 3.3, Paragraph 2:

> During screening, potential participants will be assigned an ID number. After providing written informed consent for screening, potential study participants will be ~~assigned an ID number and~~ asked to provide demographic information, behavioral eligibility information, and locator information.

DATE: **26 February 2003**

RE: **LETTER OF AMENDMENT FOR: HIVNET/HPTN 055, HIV Prevention Preparedness Study, Version 1.0, dated 12 August 2002.**

TO: **HPTN 055 Investigators of Record**

CC: **HPTN 055 Protocol Team**

FROM: **Leigh Peterson, HPTN CORE Protocol Specialist**

THE FOLLOWING INFORMATION IMPACTS THE HIVNET/HPTN 055 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARDS (IRBS) AND/OR ETHICS COMMITTEES (ECS) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. IT MUST BE APPROVED BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE HIVNET/HPTN 055 SAMPLE INFORMED CONSENT FORMS. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

PLEASE FILE THIS LETTER AND ANY IRB CORRESPONDENCE IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES. YOU ARE NOT REQUIRED TO SUBMIT THESE DOCUMENTS TO THE PROTOCOL REGISTRATION OFFICE UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FOR YOUR SITE.

Summary of Revisions

- The listing of study sites throughout the protocol is updated to not include Chililabombwe, Zambia.
- The protocol is clarified throughout to specify that chlamydia and gonorrhea testing will be performed by standard diagnostic methods in use at each study site, rather than by ligase chain reaction (LCR). Standard diagnostic methods to test for chlamydia and gonorrhea currently in use at each site are summarized in the following table:

Site	Chlamydia Test	Gonorrhea Test
Duban, South Africa	SDA	SDA
Hlabisa, South Africa	SDA	SDA
Lusaka, Zambia	ELISA	Culture
Moshi, Tanzania	ELISA	Culture

ELISA, Enzyme-linked Immunosorbent Assay; SDA, Strand Displacement Amplification

- The number of infections listed in Tables 1 and 2 of the protocol's statistical section is corrected.
- The Protocol Team Roster is updated.

Upon receipt of IRB/EC approval, the following protocol modifications, indicated by ~~strikethrough~~ and underscored text, will be implemented:

1. In the List of Abbreviations and Acronyms:

   ~~LCR ligase chain reaction~~

2. In the Protocol Team Roster:

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3. In the Schema:

   ~~Chililabombwe, Zambia~~

4. In the Schema:

   ~~1200 participants total (~~240 participants per site~~)~~.

5. In Section 2.2:

   The is a prospective cohort study to be conducted at HPTN study sites located in ~~Chililabombwe Zambia;~~ Durban, South Africa; Hlabsia South Africa; Lusaka, Zambia; and Moshi, Tanzania.

6. In Section 4.2.2, add bullet:

   - Specimen collection for chlamydia and gonorrhea testing (by standard local method).

7. In Section 4.2.3, second bullet:

   - ~~Urine ligase chain reaction (LCR)~~ Chlamydia and gonorrhea testing by standard local method.

8. In Section 4.3.2, add bullet:

   - Specimen collection for chlamydia and gonorrhea testing (by standard local method).

9. In Section 4.3.3, second bullet:

   - ~~Urine LCR~~ Chlamydia and gonorrhea testing by standard local method if clinically indicated.

10. In Section 4.4.2, add bullet:

- Specimen collection for chlamydia and gonorrhea testing (by standard local method):
  - Quarterly.
  - Additionally when clinically indicated.

11. In Section 4.4.3, second bullet:

- ~~Urine LCR~~ Chlamydia and gonorrhea testing by standard local method:

12. In Section 6.3, Tables 1 and 2:

Table 1
95% Exact Confidence Intervals for Infection Rates
Observed in a Six-Month Follow-up Period

. Infections Observed	Observed Infection Rate	95% Exact Confidence Interval
~~1~~2	1.7%	0.2-6.2%
~~2~~4	3.4%	0.9-8.8%
~~3~~6	5.1%	1.8-11.2%
4~~8~~	6.8%	2.9-13.5%
~~5~~10	8.5%	4.0-15.7%
~~6~~12	10.3%	5.3-17.9%

Table 2
95% Exact Confidence Intervals for Infection Rates
Observed in a Twelve-Month Follow-up Period

. Infections Observed	Observed Infection Rate	95% Exact Confidence Interval
~~2~~4	1.7%	0.4-4.4%
4~~8~~	3.4%	1.4-6.7%
~~6~~12	5.1%	2.6-9.0%
~~8~~16	6.8%	3.9-11.1%
~~10~~20	8.5%	5.2-13.2%
~~12~~24	10.3%	6.5-15.3%

13. In Section 8.1, fourth bullet:

- Urine for pregnancy testing, ~~chlamydia and gonorrhea LCR,~~ dipstick urinalysis, and culture.

14. In Section 8.1, add seventh bullet:

- Specimen for chlamydia and gonorrhea testing by standard local method (type of specimen dependent on local test).

15. In Appendix I, Schedule of Study Visits and Procedures:

~~urine LCR for~~ chlamydia and gonorrhea testing by standard local method

HIVNET/HPTN 055
HIV Prevention Preparedness Study

A Study of the HIV Prevention Trials Network

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institute on Drug Abuse
US National Institutes of Health

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FINAL Version 1.0
12 August 2002

HIVNET/HPTN 055
HIV Prevention Preparedness Study

TABLE OF CONTENTS

HIVNET/HPTN 055
HIV Prevention Preparedness Study

LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
BV	bacterial vaginosis
CORE	Coordinating and Operations Center
DAIDS	Division of AIDS
EC	ethics committee
EIA	enzyme immunoassay
HIV	Human Immunodeficiency Syndrome
HPTN	HIV Prevention Trials Network
HSV-2	Herpes simplex virus 2
IFA	immunofluoresence assay
IRB	institutional review board
LCR	ligase chain reaction
LDMS	Laboratory Data Management System
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCR	polymerase chain reaction
RNA	ribonucleic acid
SDMC	Statistical and Data Management Center
STD	sexually transmitted disease
UNAIDS	United Nations Programme on HIV/AIDS
US	United States
WB	Western blot
WHO	World Health Organization

HIVNET/HPTN 055
HIV Prevention Preparedness Study

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HIVNET/HPTN 055
HIV Prevention Preparedness Study

SCHEMA

Purpose: To prepare for implementation of HPTN 035, A Phase II/III Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women.

Design: Prospective cohort study with a six-month accrual period and 6-12 months of follow-up for each enrolled participant.

Study Population: Sexually active HIV-uninfected women from the study sites listed below.

Study Size: 1200 participants total (240 per site).

Study Duration: Accrual will require six months. Each participant will be maintained in follow-up for a minimum of six months and a maximum of 12 months. At each site, the duration of follow-up will depend on the timing of initiation of HPTN 035.

Primary Objective:

- To estimate rates of HIV seroincidence among women targeted for inclusion in HPTN 035.

Secondary Objectives:

- To develop and describe the accrual process and estimate rates of accrual into a standardized HIV-related research study among women targeted for inclusion in HPTN 035.
- To estimate rates of retention in a standardized HIV-related research study among women targeted for inclusion in HPTN 035.
- To describe the demographic characteristics and HIV risk behaviors of women targeted for inclusion in HPTN 035.
- To estimate prevalence and incidence rates of the following among women targeted for inclusion in HPTN 035:
  - Pelvic exam findings involving deep epithelial disruption
  - Genital ulcer disease
  - Other genital signs and symptoms
  - Bacterial vaginosis
  - Candidiasis
  - Chlamydia infection
  - Gonorrhea infection
  - Syphilis infection
  - Trichomoniasis

Study Sites:

- Chililabombwe, Zambia
- Durban, South Africa
- Hlabisa, South Africa
- Moshi, Tanzania
- Lusaka, Zambia

1 INTRODUCTION

1.1 Background

HIV/AIDS continues to exact a devastating toll on the health, economic and political infrastructure, and social fabric of communities worldwide. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 40 million adults and children were living with HIV/AIDS at the end of 2001, and that about 14,000 new infections are occurring each day. Over 95 percent of new infections are occurring in developing countries where there is little access to the treatments that have prolonged life in industrialized countries.

It has been stated that a safe and effective vaccine remains the best hope for ending the HIV/AIDS pandemic, however the timeline for developing and making available a safe and effective HIV/AIDS vaccine to communities affected by the pandemic remains unclear. While the search for an HIV/AIDS vaccine continues, additional research must be conducted to develop and test non-vaccine strategies to prevent the spread of HIV.

The United States (US) National Institutes of Health (NIH) established the HIV Prevention Trials Network (HPTN) for this purpose. This global network is the NIH's largest multicenter research network dedicated to HIV prevention, and is comprised of a Coordinating and Operations Center (CORE), a Statistical and Data Management Center (SDMC), a Central Laboratory, and 26 research sites and sub-sites located in Africa, Asia, Eastern Europe, South America, and the US. The HPTN focuses on six areas of HIV prevention research, as follows:

- Interventions to prevent mother-to infant HIV transmission.
- Interventions — termed microbicides — designed for vaginal and/or rectal use to prevent sexual transmission of HIV.
- Interventions to reduce behaviors that expose people to HIV.
- Interventions to prevent HIV infection through the reduction of injection drug use.
- Interventions to control other sexually transmitted diseases and thereby reduce the risk of HIV infection.
- Interventions based on antiretroviral therapy to prevent transmission and acquisition of HIV.

The HPTN conducts research in these six areas at all phases of development, ranging from pilot/feasibility studies to Phase I and II safety studies to Phase III efficacy and effectiveness studies. While early phase studies of a particular intervention are underway, work will proceed in parallel to ensure network-wide planning and preparedness to conduct Phase III studies of interventions shown to be safe and acceptable in earlier phase studies. For example, HPTN 035, A Phase II/III Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women, has been developed to determine the effectiveness of two candidate vaginal microbicides that have been shown in Phase I studies to be safe and well tolerated when applied intravaginally as well as topically to the penis.

1.2 Rationale

Previous prevention trial planning efforts have indicated that Phase III studies of HIV prevention interventions will require the participation of large numbers — from several hundred to several thousand — of persons at high risk for HIV infection. In addition to accruing large numbers of participants, research centers conducting Phase III HIV prevention studies must retain participants in extended periods of follow-up — from several months to several years — in order to preserve the statistical power of the study as well as avoid potentially biased results that may not accurately reflect the impact of the intervention in the target population.

The design of Phase III HIV prevention trials to be conducted in the HPTN will depend on the efficacy or effectiveness of the intervention being studied as well as the interplay of the four parameters referenced above: the number of participants enrolled, the HIV incidence rate among enrollees, the duration of follow-up, and the number of participants retained in follow-up. The potential impact of these parameters is illustrated in the tables below, which present the number of study participants required to adequately power a two-arm placebo-controlled phase III HIV prevention study assuming various levels of intervention efficacy (E), annual HIV incidence rates (I), durations of participant follow-up (D), and semiannual retention rates (R).

		R=95%								
		I=2%			I=5%			I=8%		
		D=12	D=18	D=24	D=12	D=18	D=24	D=12	D=18	D=24
E=25%	S=515	31,039	21,330	16,472	12,578	8698	6758	7964	5541	4331
E=50%	S=95	6645	4564	3523	2689	1857	1441	1700	1181	921
E=75%	S=29	2459	1689	1303	994	686	532	628	436	339
E=90%	S=16	1503	1032	796	607	419	325	383	266	207

Notes: S=number of seroconversions observed. Power=90%, Type I error=5%.

		R=85%								
		I=2%			I=5%			I=8%		
		D=12	D=18	D=24	D=12	D=18	D=24	D=12	D=18	D=24
E=25%	S=515	34,604	25,020	20,287	14,016	10,191	8307	8869	6485	5314
E=50%	S=95	7408	5354	4340	2996	2177	1772	1894	1382	1131
E=75%	S=29	2742	1981	1605	1108	804	654	700	510	417
E=90%	S=16	1675	1210	981	677	491	400	427	311	254

Notes: S=number of seroconversions observed. Power=90%, Type I error=5%.

As indicated above, dramatically different study designs may be required depending on the ability of HPTN research centers to recruit study participants and the rate of HIV incidence observed in study populations. As such, in order to realistically plan for future Phase III studies, information must be obtained to characterize these parameters at HPTN sites. HPTN sites also must develop strategies to achieve high rates of participant retention throughout the duration of a prospective study.

HPTN 035 has been designed to determine whether either of two candidate vaginal microbicides — BufferGel and PRO 2000/5 Gel (P) — are at least 33 percent effective in preventing HIV infection. In order to determine effectiveness within a period a three years, HPTN 035 requires accrual of over 8000 women at high risk for HIV infection within 23 months. The study also requires high rates of participant retention for 12-24 months of follow-up and an average HIV seroincidence rate of 5-6 percent among enrolled participants.

Building on prior NIH-sponsored and other work, several of the HPTN sites designated to conduct HPTN 035 have established effective standard operating procedures to recruit and retain high risk populations in research studies, and have characterized HIV incidence rates in these populations. Work is now required to establish a similar research infrastructure and knowledge base at HPTN sites not previously represented in HIV prevention research networks. This HIV Prevention Preparedness Study serves that purpose.

2 STUDY OBJECTIVES AND DESIGN

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to estimate rates of HIV seroincidence among women targeted for inclusion in HPTN 035.

2.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Develop and describe the accrual process and estimate rates of accrual into a standardized HIV-related research study among women targeted for inclusion in HPTN 035.

- Estimate rates of retention in a standardized HIV-related research study among women targeted for inclusion in HPTN 035.

- Describe the demographic characteristics and HIV risk behaviors of women targeted for inclusion in HPTN 035.

- Estimate prevalence and incidence rates of the following among women targeted for inclusion in HPTN 035:
  - Pelvic exam findings involving deep epithelial disruption
  - Genital ulcer disease
  - Other genital signs and symptoms
  - Bacterial vaginosis (BV)
  - Candidiasis
  - Chlamydia infection
  - Gonorrhea infection
  - Syphilis infection
  - Trichomoniasis

2.2 Study Design

This is a prospective cohort study to be conducted at HPTN study sites located in Chililabombwe, Zambia; Durban, South Africa; Hlabisa, South Africa; Lusaka, Zambia; and Moshi, Tanzania. The study design and visit/procedures schedule are summarized in the Schema and in Appendix I. All procedures are consistent with those specified for implementation in HPTN 035.

Each study site will target enrollment of 240 study participants over the course of a six-month accrual period, according to the following schedule of monthly enrollment targets:

- Study month 1: 20 participants
- Study month 2: 30 participants
- Study month 3: 40 participants
- Study month 4: 50 participants
- Study month 5: 50 participants
- Study month 6: 50 participants

The study follow-up period then will extend for at least six months, and up to a maximum of 12 months, from the end of the accrual period.

It is expected that each study site will be activated to implement HPTN 035 by the end of the six-month follow-up period, however if this is not the case, the follow-up period may be extended for up to another six months, pending activation of HPTN 035. Possible reasons for a delay in activation of HPTN 035 include delays in finalizing the HPTN 035 protocol and implementation plans, delays in manufacturing and packaging the investigational products for HPTN 035, delays in obtaining ethical review and approval of the HPTN 035 protocol, and indication based on performance in this study that additional preparedness work is required prior to transitioning to HPTN 035. On a site-by-site basis, upon activation of HPTN 035, this study will be terminated and participants will be invited to screen for HPTN 035.

As described more fully in Section 3.3, potential study participants will be screened for eligibility and enrolled in the study over the course of up to 30 days, and over the course of at least one Screening Visit and one Enrollment Visit.

Enrolled participants then will complete monthly follow-up assessments throughout the duration of their participation. At each visit, participants will complete an interval medical/menstrual history and undergo pregnancy testing. HIV and sexually transmitted disease (STD) risk reduction counseling messages will be reinforced as needed and condoms and other prevention supplies will be distributed.

Each quarter, participants additionally will undergo a structured interview to ascertain HIV risk behaviors and receive HIV/STD pre-test, risk reduction, and post-test counseling. Participants also will undergo pelvic exams with wet mount testing for BV, candidiasis, and trichomoniasis; colposcopic evaluations will be performed at selected sites in accordance with the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2000. For participants found to have a genital ulcer on pelvic exam, the ulcer will be swabbed for multiplex polymerase chain reaction (PCR) testing at the HPTN Central Lab for chancroid, herpes simplex virus 2 (HSV-2), and syphilis. Follow-up testing for chlamydia, gonorrhea, syphilis, and HIV (see Appendix II) will be performed quarterly, and additionally if clinically indicated. A sample of HIV test results will be confirmed for quality assurance purposes by the HPTN Central Laboratory.

Monthly visits other than those in which pelvic exams are scheduled may take place either on-site, in a participant's home, or at other community-based locations, depending on site capacities and site and participant preferences. If genital symptoms are reported during an off-site visit, the participant will be instructed to report to the on-site clinic as soon as possible for a pelvic exam. Other participant-initiated interim visits may occur at any time during follow-up, for example to obtain additional HIV counseling and testing.

All HIV and STD testing will be performed in the context of pre-test, risk reduction and post-test counseling. Study sites will provide this counseling in accordance with locally-accepted standards of practice and will document their counseling policies and procedures prior to study implementation for purposes of staff training, quality assurance, and study monitoring. In accordance with NIH policies, study participants must receive their HIV test results in order to remain eligible for study participation.

Participants who are found to have an STD or other reproductive tract infection will be provided counseling, treatment, and follow-up care in accordance with World Health Organization (WHO) guidelines, free-of-charge. Such participants will be encouraged to refer their partners for STD diagnosis and treatment if applicable. Participants who become pregnant during the study will be maintained in follow-up until the initiation of HPTN 035, as will participants who become infected with HIV. Participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons.

3 STUDY POPULATION

This study will be conducted at the study sites listed in the Schema and in Section 2.2, among women who meet the eligibility criteria listed in Sections 3.1, 3.2, and 3.4 below. These criteria are consistent with those specified for HPTN 035. Participants will be screened and enrolled in the study as described in Section 3.3. Information related to participant retention and withdrawal from the study is provided in Sections 3.5 and 3.6, respectively.

3.1 Inclusion Criteria

Women who meet all of the following criteria are eligible for inclusion in this study:

- Of legal age to provide independent informed consent per local regulations and guidelines.

Note: The above-listed criterion sets a lower bound on the allowable age for study participants, but does not specify an upper bound. In order to accrue a study population at highest risk of HIV infection, individual study sites may set a site-specific upper age limit for participants based on available information about the epidemiology of HIV infection at the site, and target their study accrual efforts accordingly. All site-specific age requirements will be specified in local standard operating procedures.

- Able and willing to provide written informed consent to be screened for and to take part in the study.

- Able and willing to provide adequate locator information for study retention purposes, as defined by local standard operating procedures.

- Sexually active (defined as having had vaginal intercourse at least once in the three months prior to screening).

- HIV-uninfected at screening.

3.2 Exclusion Criteria

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

- History of adverse reaction to latex.

- History of non-therapeutic injection drug use in the 12 months prior to screening.

- Had vaginal intercourse more than an average of two times per day in the two weeks prior to screening.

- At screening:
  - Plans to travel away from the study site for more than three consecutive months in the next 12 months.
  - Plans to relocate away from the study site in the next 12 months.
  - Plans to become pregnant in the next 12 months.

- At screening or enrollment:
  - Enrolled in any other study of a vaginally-applied product.
  - Pregnant.

- At enrollment, is within 42 days of last pregnancy outcome.

- At enrollment, has a clinically apparent pelvic exam finding involving deep epithelial disruption.

Note: Otherwise eligible participants with pelvic exam finding(s) involving deep epithelial disruption may be enrolled after the finding has resolved. If resolution is documented within 30 days after obtaining informed consent for screening, screening procedures need not be repeated.

- At enrollment, diagnosed with a current STD and/or other reproductive tract infection requiring treatment according to WHO guidelines.

  Note: Participants will undergo laboratory testing for chlamydia, gonorrhea, and syphilis at their screening visits, and wet mount testing for BV, candidiasis, and trichomoniasis at their enrollment visits; all results will be available at the enrollment visits. Otherwise eligible participants diagnosed at their enrollment visits with infection(s) requiring treatment per WHO guidelines (other than asymptomatic candidiasis) will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 30 days after obtaining informed consent for screening, screening procedures need not be repeated.

- At enrollment, has any other condition that, in the opinion of the Investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

3.3 Screening and Enrollment Process

Eligibility for the study will be assessed in a step-wise manner at the study Screening and Enrollment Visits. Although all required procedures may be completed in one Screening Visit and one Enrollment Visit, additional visits may be conducted if needed. For example, a participant may want more time to consider whether to participate in the study, may require treatment for an STD or other reproductive tract infection, or may not be able to undergo a pelvic exam due to menstruation. Regardless of the number of visits required, all screening and enrollment procedures must be completed within a 30-day period, beginning on the day the participant provides informed consent for screening. If a participant is not enrolled within 30 days after providing informed consent for screening, the screening process must be repeated.

After providing written informed consent for screening, potential study participants will be assigned an ID number and asked to provide demographic information, behavioral eligibility information, and locator information. They will undergo urine pregnancy testing and HIV and STD counseling and testing. Presumptively eligible participants will be scheduled to return for their Enrollment Visits approximately 7-14 days later, when all screening test results are expected to be available.

Note: For study screening purposes HIV infection status will be ascertained using two different rapid enzyme immunoassay tests; in the event that results from the two tests are discordant, a third test will be performed. Once a participant has enrolled in the study, follow-up HIV testing will be performed according to the algorithm in Appendix II.

At their Enrollment Visits, potential participants will be informed of their screening test results, in the context of post-test counseling, and again undergo testing for pregnancy. Those who test negative will undergo a pelvic exam with wet mount testing for BV, candidiasis, and trichomoniasis; colposcopy will be performed at selected sites. Pap smears will be performed at sites with the capacity and expertise to prepare and interpret the smears and provide appropriate follow-up care to participants with abnormal results.

Potential participants diagnosed with infection(s) requiring treatment per WHO guidelines (other than asymptomatic candidiasis) will be offered treatment at their Enrollment Visits and — provided they meet all other eligibility criteria — enrolled in the study after completing treatment and any symptoms of infection have resolved. If treatment is completed and symptoms have resolved within 30 days after providing informed consent for screening, screening procedures need not be repeated.

Similarly, potential participants with pelvic exam findings involving deep epithelial disruption observed on pelvic exam at the Enrollment Visit may be enrolled after the findings have resolved, provided they meet all other eligibility criteria. If resolution is documented within 30 days after providing informed consent for screening, screening procedures need not be repeated.

Women who meet all the study eligibility criteria will be asked to provide written informed consent to take part in the study. Those who provide informed consent will be enrolled and scheduled for their first three follow-up assessments. They will complete a baseline behavioral risk assessment and will be given instructions to contact study staff to ask questions about the study, report STD symptoms, and/or request additional HIV/STD counseling and testing between scheduled visits.

3.4 Co-Enrollment Guidelines

Participants in this study may not take part in other concurrent research studies, except for the following:

- Participants in this study may take part in microbicide acceptability studies (not involving application of vaginal products) and other ancillary studies approved by the HIVNET/HPTN 055 Protocol Co-Chairs.

- Participants who become infected with HIV may take part in HIV treatment trials.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain her in follow-up to minimize possible bias associated with loss-to-follow-up. It is recommended that participant retention procedures be established at each site such that loss-to-follow-up rates do not exceed the 5-6 percent average annual HIV seroincidence rate expected to be observed in the control groups of HPTN 035. As such, annual retention rates of 95 percent are targeted. Site staff are responsible for developing and implementing local standard operating procedures to achieve this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.

- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.

- Use of mapping techniques to establish the location of participant residences and other locator venues.

- Use of appropriate and timely visit reminder mechanisms.

- Immediate and multifaceted follow-up on missed visits.

- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes and/or other community locations.

- Regular communication with the study community at large to increase awareness of HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

The HPTN CORE will provide the study sites with a participant tracking database to facilitate visit scheduling and timely identification and follow-up on missed visits. The HPTN SDMC will generate weekly reports on the number and percentage of participants completing quarterly follow-up assessments. The Protocol Team as well as the HPTN Study Monitoring Committee will track retention rates closely and work with study sites as needed to take any required action to address below-target retention rates.

3.6 Participant Withdrawal

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The site Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the Protocol Co-Chairs, SDMC Protocol Statistician, and CORE Protocol Specialist. Participants also may be withdrawn if the study sponsors or US or local government authorities terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.

4 STUDY PROCEDURES

See also Appendix I. Detailed instructions to guide and standardize all study procedures across sites will be provided in the study-specific procedures manual. Unless otherwise specified, the laboratory procedures listed below are performed at the local study site laboratories. See Section 8.1 for further information regarding plans to establish local laboratory capabilities for this study.

4.1 Pre-Screening

If desired, study staff may pre-screen potential study participants either on site or at off-site locations. During these interactions, study staff may explain the study to participants and ascertain presumptive eligibility, to be confirmed at an on-site Screening Visit (see Section 4.2). Pre-screening data may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to participant identifiers.

4.2 Screening Visit (up to day -30)

Multiple visits may be conducted to complete all required procedures if necessary. Written informed consent for screening will be obtained before any screening procedures are initiated. For potential participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.

4.2.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening.
- Demographic information.
- Behavioral eligibility checklist.
- Locator information.
- HIV/STD counseling, condoms, other HIV prevention supplies.

4.2.2 Clinical Procedures

- Urine collection.
- Blood collection.
- Test results disclosure.
- Treatment for STD symptoms; offer of STD testing and treatment for partner(s).

4.2.3 Laboratory Procedures

- Urine pregnancy test.
- Urine ligase chain reaction (LCR) for chlamydia and gonorrhea.
- Dipstick urinalysis if clinically indicated; urine culture if dipstick is positive for leukocytes or nitrites.
- HIV serology.
- Syphilis serology.
- HSV-2 serology (at sites in Zambia only).

4.3 Enrollment Visit (day 0)

Multiple visits may be conducted to complete all required procedures if necessary. Written informed consent for study participation will be obtained before any "on-study" procedures are initiated. For potential participants whose eligibility is not confirmed at this visit, the screening and enrollment process will be discontinued when ineligibility is determined.

4.3.1 Administrative, Behavioral, and Regulatory Procedures

- HIV/STD counseling, condoms, other HIV prevention supplies.
- Informed consent for study.
- Informed consent for specimen storage.
- Locator information.
- Behavioral risk assessment.

4.3.2 Clinical Procedures

- Urine collection.
- Blood collection.
- Focused medical history and ascertainment of current medications.
- Physical exam.
- Pelvic exam with:
  - colposcopy (at selected sites);
  - specimen collection for Gram stain;
  - wet mount for BV, candidiasis, and trichomoniasis; and
  - ecto- and endocervical cytobrush for Pap smear (at selected sites).

- Test results disclosure.
- Treatment for STDs and other infections (except asymptomatic candidiasis), when clinically indicated; offer of STD testing and treatment for partner(s).

Note: Otherwise eligible participants with pelvic exam findings involving deep epithelial disruption may be enrolled after the findings have resolved. If resolution is documented within 30 days after obtaining informed consent for screening, screening procedures need not be repeated.

Note: Otherwise eligible participants diagnosed with infections requiring treatment per WHO guidelines (other than asymptomatic candidiasis) will be offered treatment and enrolled in the study after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 30 days after obtaining informed consent for screening, screening procedures need not be repeated.

4.3.3 Laboratory Procedures

- Urine pregnancy test.
- Urine LCR for chlamydia and gonorrhea if clinically indicated.
- Dipstick urinalysis if clinically indicated; urine culture if dipstick is positive for leukocytes or nitrites.
- Gram stain assessment for BV according to the Nugent criteria at the HPTN Central Lab.
- Pap smear interpretation (at selected sites only).
- Syphilis serology if genital ulcer is observed.
- Plasma archive.

  Note: For participants who do not consent to long-term specimen storage and possible future research testing, archived plasma will be discarded after all protocol-required and quality assurance testing has been completed (see also Section 8.3).

4.4 Follow-up Visits

Monthly follow-up visits are scheduled throughout the study follow-up period on the monthly anniversary dates of participants' study enrollment dates. For example, for a participant enrolled on September 15, follow-up visits will be targeted to take place on October 15, November 15, December 15, etc. For participants enrolled on the last day of a month with 31 days, follow-up visits will be targeted to take place on the last day of all subsequent months (e.g., February 28, April 30, June 30, September 30, November 30). Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within a four-week window around the target date (i.e., ± 2 weeks from the target date).

For participants who do not complete scheduled visits within the allowable window, the visit will be considered "missed" and relevant case report forms will be completed to document the missed visit. However, for participants who miss visits scheduled to take place in study months 3, 6, 9, and 12, the pelvic exam and HIV counseling and testing procedures specified to take place at these visits will be conducted at the participants' next visit. Accordingly, every effort should be made to conduct participants' next visit at the study site, rather than at a community-based location. If this is not possible, an interim on-site visit in which the pelvic exam and HIV counseling and testing procedures are performed should be conducted as soon as possible after the off-site visit.

Note: Participants who become pregnant or infected with HIV during follow-up may be maintained in this study until the initiation of HPTN 035. For participants who become pregnant, follow-up procedures may be modified according to guidelines specified in the study-specific procedures manual. For example, after 24 weeks of pregnancy, quarterly pelvic exams may be discontinued and blood collection may be limited to fingersticks for HIV serology only. For participants who become infected with HIV, HIV serology will be discontinued and counseling will be tailored to primary and secondary HIV/STD prevention for infected women.

4.4.1 Administrative, Behavioral, and Regulatory Procedures

- Ongoing informed consent:
  -As needed at all visits.

- Locator information:
  -At all visits and contacts.

- Behavioral risk assessment:
  -Quarterly.

- HIV/STD counseling, condoms, other prevention supplies:
  -Quarterly.
  -Additionally when needed/requested.

4.4.2 Clinical Procedures

- Interval (i.e., since last visit) medical and menstrual history and concomitant medication review:
  -At all visits.

- Pelvic exam with:
  - colposcopy (at selected sites);
  - specimen collection for Gram stain;
  - wet mount for BV, candidiasis, and trichomoniasis; and
  - swab for multiplex PCR if genital ulcer is observed:
    -Quarterly.
    -Additionally when clinically indicated.

- Urine collection:
  -At all visits.

- Blood collection:
  -Quarterly.
  -Additionally when clinically indicated.

- Test results disclosure:
  -As needed at all visits and contacts.

- Treatment for STDs and other infections (except asymptomatic candidiasis); offer of STD testing and treatment for partner(s):
  -When clinically indicated.

4.4.3 Laboratory Procedures

- Urine pregnancy test:
  -At all visits.

- Urine LCR for chlamydia and gonorrhea:
  -Quarterly.
  -Additionally when clinically indicated.

- Dipstick urinalysis; urine culture if dipstick is positive for leukocytes or nitrites:
  -When clinically indicated.

- Gram stain assessment for BV according to the Nugent criteria at the HPTN Central Lab:
  -Quarterly.
  -Additionally when clinically indicated.

- Multiplex PCR at the HPTN Central Lab:
  -When a genital ulcer is observed.

- HIV serology:
  -Quarterly.
  -Additionally when clinically indicated.

  Note: For participants who test HIV-positive at study Month 3, HIV antibody testing will be performed on plasma archived at the participants' Enrollment Visits, to confirm that the participant was HIV-uninfected at enrollment; if additional testing (e.g., RNA PCR, p24 antigen) is required to clarify participants' HIV status at enrollment, such testing will be undertaken in consultation with the HPTN Central Lab.

- Syphilis serology:
  -Quarterly.
  -Additionally when clinically indicated.

- Plasma archive:
  -When phlebotomy is performed for confirmatory HIV testing (i.e., when "sample 2" in Appendix II is obtained).
  - At study exit.

  Note: For participants who do not consent to long-term specimen storage and possible future research testing, archived plasma will be discarded after all protocol-required and quality assurance testing has been completed (see also Section 8.3).

4.5 Interim Contacts and Visits

Interim visits may be performed at any time during the study. Depending on the type of visit, site capacity, and site and participant preferences, interim visits may take place at the study site or at community-based locations. Interim visits may occur:

- For administrative reasons, e.g., the participant may have questions for study staff or may need to re-schedule a follow-up visit.

- For interim STD counseling and testing in response to STD symptoms.

- For interim HIV counseling and testing in response to presumed exposure to HIV.

- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix II.

- In the event that a participant presents to the study site after having missed a scheduled visit (e.g., in response to locator/tracing efforts) on a day that does not fall within a scheduled visit window.

- To complete pelvic exam and HIV counseling and testing procedures after a missed quarterly visit.

- For other reasons at participant request.

All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

4.6 Final Contact

As indicated above, the results of laboratory tests performed at study visits will be provided to participants at their next monthly visit. Depending upon when a site transitions from this study to HPTN 035, some participants will not have received the results of tests performed at their last visit prior to the transition. In such cases, study staff will contact participants with pending test results and deliver their results and appropriate treatment in a timely manner.

5 SAFETY MONITORING AND ADVERSE EVENT REPORTING

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. The protocol team will meet via conference call every two to four weeks during the period of study implementation, and additional ad hoc calls will be convened if required. Since this is an observational study in which participants will not receive any investigational agents, no adverse event reporting will be undertaken.

6 STATISTICAL CONSIDERATIONS

6.1 Review of Study Design

This is a prospective cohort study. Accrual of 240 participants at each participating study site will be completed over the course of six months. Each participant will complete a minimum of six and a maximum of 12 scheduled monthly follow-up assessments. The total length of the study will be 12-18 months.

6.2 Endpoints

6.2.1 Primary Endpoints

Consistent with the primary study objective, HIV seroconversions observed during the study follow-up period will be assessed as primary endpoints.

6.2.1 Secondary Endpoints

Consistent with the secondary study objectives, the following will be assessed as secondary endpoints:

- Potential participants screened for the study, and the screening outcome for each screenee.
- Participants enrolled in the study.

- Participants retained in the study until the site-specific study end date.

- Demographic characteristics of women screened for and/or enrolled in the study, including:
  - Age
  - Race/ethnicity
  - Educational level
  - Employment status
  - Income level

- HIV risk behaviors reported by women enrolled in the study, including:
  - Number of sex partners
  - Frequency of vaginal intercourse
  - Frequency of unprotected vaginal intercourse
  - Frequency of anal intercourse
  - Frequency of unprotected anal intercourse

- Prevalent (i.e., at screening/enrollment) and incident (i.e., during follow-up) occurrences of the following:
  - Pelvic exam findings involving deep epithelial disruption
  - Genital ulcer disease
  - Other genital signs and symptoms
  - Bacterial vaginosis
  - Candidiasis
  - Chlamydia infection
  - Gonorrhea infection
  - Syphilis infection
  - Trichomoniasis

6.3 Accrual, Follow-up, and Sample Size

Each participating study site will target accrual of 240 study participants within the six-month accrual period, with the monthly enrollment targets presented in Section 2.2. Each site also will target retention of 95 percent of enrolled participants annually (or 97.5 percent semi-annually).

As will be described in Section 6.4.2, assessment of the study outcomes related to accrual and retention will not require statistical analysis. However the precision of study estimates of HIV and STD incidence depends on the number of participants enrolled and retained in the study, as well as the "true" seroincidence rate. Shown in Tables 1 and 2 below are the widths of exact 95% confidence intervals around site-specific incidence rates, assuming the accrual schedule presented in Section 2.2 and retention of 97.5 percent of participants semi-annually, with either a six-month (Table 1) or twelve-month (Table 2) follow-up period, and an expected 117 and 234 woman-years of follow-up, respectively.

Table 1
95% Exact Confidence Intervals for Infection Rates
Observed in a Six-Month Follow-up Period

No. Infections Observed	Observed Infection Rate	95% Exact Confidence Interval
1	1.7%	0.2-6.2%
2	3.4%	0.9-8.8%
3	5.1%	1.8-11.2%
4	6.8%	2.9-13.5%
5	8.5%	4.0-15.7%
6	10.3%	5.3-17.9%

Table 2
95% Exact Confidence Intervals for Infection Rates
Observed in a Twelve-Month Follow-up Period

No. Infections Observed	Observed Infection Rate	95% Exact Confidence Interval
2	1.7%	0.4-4.4%
4	3.4%	1.4-6.7%
6	5.1%	2.6-9.0%
8	6.8%	3.9-11.1%
10	8.5%	5.2-13.2%
12	10.3%	6.5-15.3%

6.4 Data Analysis

6.4.1 Primary Analysis

Corresponding to the primary study objective, an HIV seroincidence rate will be computed for each study site, as the total number of confirmed HIV seroconversions divided by the total number of woman-years of follow-up. Confidence intervals will be calculated based on Poisson distribution assumptions.

6.4.2 Secondary Analyses

Corresponding to the secondary study objectives, the following secondary analyses will be performed:

- The study accrual process will be described by tabulating the number and rate of potential participants screened for and enrolled in the study at each site, overall and by month during the accrual period. Each site's actual accrual rates will be compared to the target rates, and reasons for ineligibility for the study will be tabulated.

- The number of enrolled participants retained in the study will be tabulated for each site for the entire site-specific follow-up period as well as for each quarter in the follow-up period. Retention rates also will be calculated. The denominator for these calculations will be the total number of participants enrolled in the study at the site. The numerator will include all participants at the site who complete a scheduled visit during the interval and/or are known to have died during a previous interval. Retention rates for each site will be compared to the annual target of 95 percent.

- The demographic characteristics of persons screened for and/or enrolled in the study at each site will be described. At a minimum, the characteristics listed in Section 6.2 will be tabulated.

- The HIV risk behaviors of persons enrolled in the study at each site will be described. At a minimum, the frequency of each of the outcomes listed in Section 6.2 will be tabulated.

- The baseline prevalence for each of the genital signs and symptoms and infections listed in Section 6.2 will be computed for the enrolled study population at each site, as the total number of endpoints observed among enrollees divided by the number of participants enrolled. Appropriate 95% confidence intervals also will be computed. An incidence rate for each of the genital signs and symptoms and infections listed in Section 6.2 also will be computed for each study site, as the total number of endpoints observed divided by the total number of person-years of follow-up. Confidence intervals will be calculated based on Poisson distribution assumptions.

7 HUMAN SUBJECTS CONSIDERATIONS

7.1 Ethical Review

This protocol and the template informed consent forms contained in Appendices III-V — any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations. (This protocol has been exempted from review by the Division of AIDS (DAIDS)/ NIAID/NIH Prevention Science Review Committee.)

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the institutional review boards (IRBs) and ethics committees (ECs) responsible for oversight of research conducted at the study sites. Subsequent to initial review and approval, the responsible IRBs/ECs will review the study at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months after termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

7.2 Informed Consent

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing, however consent for specimen storage is not required for study participation. Participants will be provided with a copy of their 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 III-V, that describe the purpose 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.

Study staff will document the informed consent process as instructed in the study-specific procedures manual.

7.3 Risks

Study participants may experience discomfort when having pelvic exams and/or undergoing phlebotomy for this study. During phlebotomy, participants may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.

Participants may become embarrassed, worried, or anxious when completing their HIV-related interviews and/or receiving HIV/STD counseling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained counselors will be available to help participants deal with these feelings.

Although study sites will 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.

7.4 Benefits

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study.

Study participants will receive HIV and STD counseling and testing, a physical exam, and pelvic exams. They will be provided STD treatment in accordance with WHO guidelines free-of-charge, and will be offered STD testing and treatment for their partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources care available in their community.

7.5 Access to HIV-Related Care

7.5.1 HIV Counseling and Testing

HIV pre-test, risk reduction, 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, and to all enrolled participants at each follow-up HIV testing timepoint. Counseling will be provided accordance with locally accepted standards of practice. Study sites will document their counseling policies and procedures prior to study implementation for purposes of staff training, quality assurance, and study monitoring.

In accordance with the policies of the US National Institutes of Health, participants must receive their HIV test results in order to take part in this study.

Condoms and other HIV prevention supplies will be provided to participants throughout the duration of their participation.

7.5.2 Care for Participants Identified as HIV-Infected

This study will identify persons who are infected with HIV, either as part of the study screening process or during follow-up of enrolled participants. Study staff will provide participants with their HIV test results in the context of post-test counseling. They also will refer persons found to be HIV-infected to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons.

7.6 Confidentiality

All study procedures will be conducted in private. 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, colposcopic images, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. 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 by the National Institute of Allergy and Infectious Diseases (NIAID) and/or its contractors; representatives of the HPTN CORE, SDMC, and/or Central Lab; and US or local government authorities.

7.7 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for costs associated with travel to study visits, time away from work, and childcare. Site-specific reimbursement amounts will be specified in the local study informed consent forms.

7.8 Communicable Disease Reporting Requirements

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

7.9 Study Discontinuation

The study may be discontinued at any time by NIAID, the HPTN, and US or local government authorities.

8 LABORATORY CONSIDERATIONS

8.1 Local Laboratory Specimens

This study requires that the following types of specimens be collected for testing at the local laboratory:

- Blood for HIV and syphilis serology.
- Blood for HSV-2 serology (at sites in Zambia only).
- Blood for plasma archive.
- Urine for pregnancy testing, chlamydia and gonorrhea LCR, dipstick urinalysis, and culture.
- Vaginal smears for wet mount for BV, candidiasis, and trichomoniasis.
- Ecto- and endocervical specimens for Pap smear (at selected sites only).

At the time of study start-up, some study sites may not have established proficiency in performing each of these tests. In order to maximize the efficiency of timeliness of this study in establishing site preparedness for HPTN 035, study sites will be allowed to begin this study prior to establishing full proficiency in performing tests other than HIV antibody testing (which is required for eligibility determination). As a condition for study activation, however, each site will work with the HPTN Central Lab to prepare a written plan documenting their local laboratory capability at study start-up and action items and timelines for establishing proficiency in the tests listed above.

Each study site will adhere to standards of good laboratory practice; the HPTN Central Laboratory Manual; the study-specific procedures manual; and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the local lab. Specimen collection, testing, and storage at the local lab will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the study-specific procedures manual.

8.2 Central Laboratory Specimens

The following types of specimens will be collected for testing at the HPTN Central Lab:

- Vaginal smears for Gram staining and BV assessment.
- Genital ulcer swabs for multiplex PCR.
- Plasma for quality assurance HIV testing.

Each study site will adhere to standards of good laboratory practice; the HPTN Central Laboratory Manual; and the study-specific procedures manual for proper collection, processing, labeling, and transport of specimens for the Central Lab. All specimens will be shipped in accordance with IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the study-specific procedures manual.

8.3 Quality Control and Quality Assurance Procedures

The HPTN Central Lab has established a proficiency testing program at each study site. Central Lab staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. Central Lab staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

In addition to the above, the HPTN Central Laboratory will verify HIV testing performed at the local laboratories for purposes of eligibility determination and primary outcome ascertainment as follows:

- The Central Lab will test 50 randomly selected study entry specimens from each site for evidence of HIV infection using FDA-licensed tests. "Study entry" specimens are collected at study Enrollment Visits. If any false-negative local lab results are identified, the Central Lab will test another 100 study entry specimens from that site.

- The Central Lab will test the study entry and seroconversion specimens from all study participants identified by the local labs as having become infected with HIV during the study follow-up period. "Study entry" specimens are collected at study Enrollment Visits. "Seroconversion" specimens are collected at the time of phlebotomy for confirmatory HIV testing, i.e., when "sample 2" in Appendix II is obtained. The Central Lab similarly will test the study entry and study exit specimens from a random sample of participants (equal to the number of seroconversions) not identified by the local labs as having become infected with HIV during the study follow-up period. "Study exit" specimens are collected at participants final follow-up visits. If any false-negative or false-positive local lab results are identified, the Central Lab will test all study exit specimens from that site.

8.4 Specimen Storage and Possible Future Research Testing

Study site staff will store plasma collected from each study participant at the time of study entry, seroconversion (if applicable), and study exit. All such specimens will be subject to possible quality assurance testing during and after the study as described in Section 8.3. In addition, study participants will be asked to provide written informed consent for their plasma specimens to be stored after the end of the study for possible future research testing. Any residual specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study, after all protocol-required and quality assurance testing has been completed.

8.5 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 US Centers for Disease Control and Prevention.

9 ADMINISTRATIVE PROCEDURES

9.1 Study Activation

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the study-specific procedures manual — to the HPTN CORE. CORE staff will work with study site staff to complete "protocol registration" procedures in accordance with DAIDS policies. Included in the protocol registration process is CORE and DAIDS review of site-specific informed consent forms.

Pending successful protocol registration and submission of all other required documents, CORE staff will "activate" the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

9.2 Study Coordination

Study implementation at all sites will be directed by this protocol as well as a common study-specific procedures manual. This manual will outline procedures for conducting study visits, collecting and submitting study data, collecting and shipping specimens, and other study operations. Study case report forms will be developed by the protocol team and HPTN SDMC. As part of the study activation process, each Investigator will identify all case report forms to be used as source documents. Data will be transferred to the HPTN SDMC, entered, and cleaned using the DataFax data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Close cooperation between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, address issues in a timely manner, and assure consistent participant management, documentation, and information sharing. Rates of accrual, follow-up, and protocol compliance will be monitored closely by the study team as well as the HPTN Study Monitoring Committee.

9.3 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and locally-accepted HIV counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site Investigators will allow study monitors 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 HPTN CORE, SDMC, Central Lab, NIAID, and US and local government authorities. A site visit log will be maintained at the study site to document all visits.

9.4 Protocol Compliance

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

9.5 Investigator's Records

The Investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study. The Investigator will retain all study records for at least three years after submission of the site's final Financial Status Report to DAIDS, which is due within 90 days after the end of the site's cooperative agreement with DAIDS, unless otherwise specified by DAIDS or the HPTN CORE. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

9.6 Use of Information and Publications

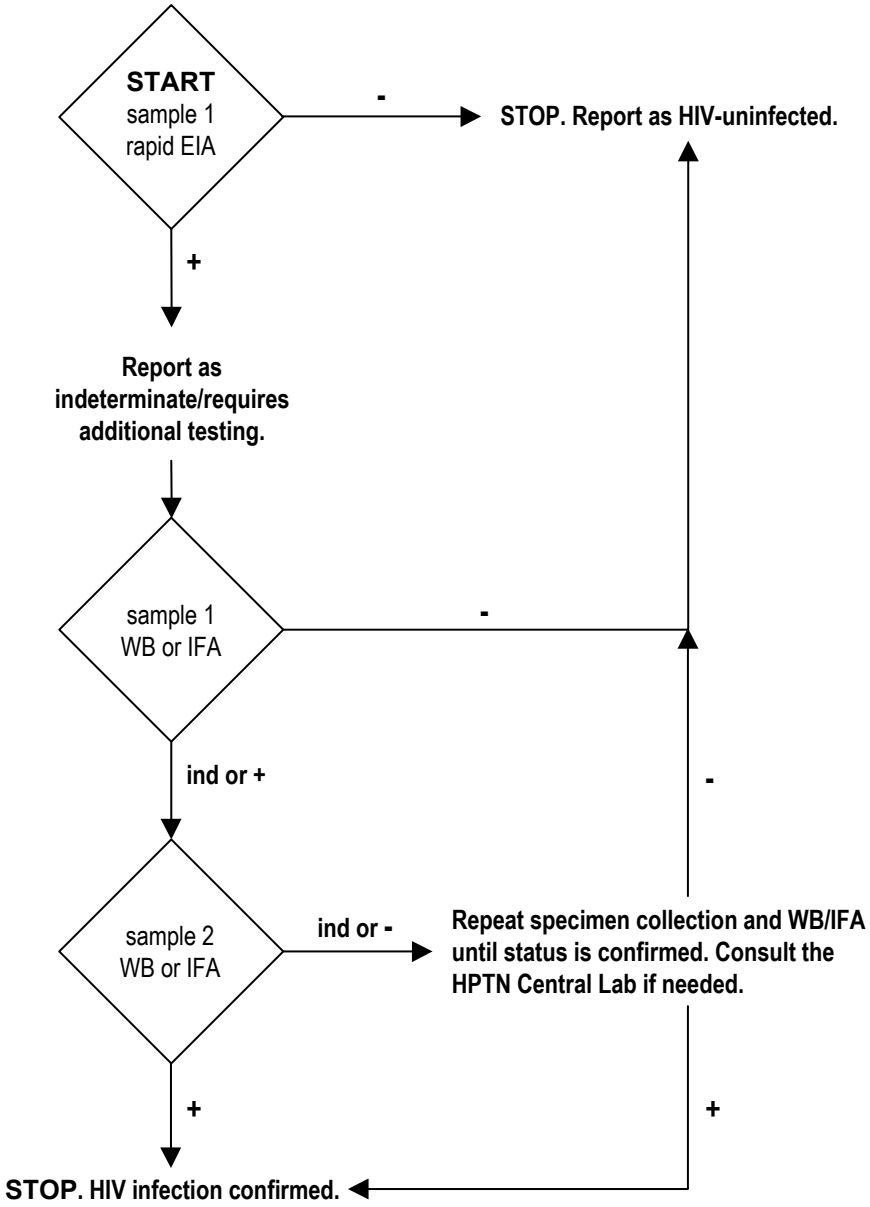
Presentation and publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be made available by the protocol team to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

Appendix I
Schedule of Study Visits and Procedures

Procedure	Screening (up to -30 days)	Enrollment (day/month 0)	Monthly Follow-up mos 1, 2, 4, 5, 7, 8, 10, 11	Quarterly Follow-up mos 3, 6, 9, 12
Obtain informed consent	X	X		
Obtain demographic information	X			
Obtain/update locator information	X	X	X	X
Administer behavioral eligibility checklist	X			
Administer behavioral risk assessment		X		X
Provide HIV/STD pre-test counseling	X		[X]	X
Provide HIV/STD risk reduction counseling	X		[X]	X
Provide HIV/STD post-test counseling	X	X	[X]	X
Obtain medical/menstrual history		X	X	X
Perform physical exam		X		
Perform pelvic exam:				
-naked eye exam of external genitalia		X	[X]	X
-speculum exam of vagina and cervix		X	[X]	X
-colposcopic exam [a]		X	[X]	X
-vaginal pH		X	[X]	X
-dried smear for Gram staining		X	[X]	X
-wet mount for bacterial vaginosis, candidiasis, trichomoniasis		X	[X]	X
-ecto- and endocervical cytobrush for Pap smear [a]		X		
-genital ulcer swab for multiplex PCR			[X]	[X]
Perform laboratory evaluations:				
-urine pregnancy test	X	X	X	X
-urine LCR for chlamydia and gonorrhea	X	[X]	[X]	X
-dipstick urinalysis and urine culture	[X]	[X]	[X]	[X]
-HIV serology	X		[X]	X
-syphilis serology	X	[X]	[X]	X
-HSV-2 serology [b]	X			
-Gram stain assessment for bacterial vaginosis at the HPTN CL		X	[X]	X
-multiplex PCR at the HPTN CL			[X]	[X]
-Pap smear interpretation [a]		X		
-plasma archive [c]		X	[X]	X
Provide test results	X	X	X	X
Provide STD treatment	[X]	[X]	[X]	[X]

[x] = if clinically indicated.
[a] at selected sites only.
[b] at sites in Zambia only.
[c] at study entry, seroconversion (if applicable) and study exit.

Appendix II
HIV Antibody Testing Algorithm for Endpoint Ascertainment at Follow-up



Appendix III
Sample Informed Consent Form for Screening

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

HIVNET/HPTN 055
HIV Prevention Preparedness Study

FINAL Version 1.0
12 August 2002

SCREENING ONLY

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]

INFORMED CONSENT

You are being asked to volunteer for screening tests to find out if you are eligible for the research study named above. The research study is for women who could get HIV. HIV is the virus that causes AIDS. The screening tests include interview questions, urine and blood tests, a physical exam, and an exam of your vagina.

Before you decide whether to have the screening tests, we would like to explain the purpose of the screening tests, the risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the screening tests that will be discussed with you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the screening tests, it is important that you know the following:

- Your participation is entirely voluntary.
- You may decide not to have the screening tests, or to withdraw from the screening tests at any time, without losing the benefits of your routine medical care.
- If you decide not to have the screening tests, you can still join another research study later, if one is available and you qualify.
- You are only being asked to have the screening tests at this time. Even if you agree to have the screening tests, you do not have to join the research study.

PURPOSE OF THE SCREENING TESTS

The purpose of the screening tests is to find out if you are eligible for a research study.

[Institution] is part of a group of scientists from all over the world doing research on ways to prevent HIV infection. The purpose of the research study is to set up a system at [institution] for doing research with this group. Specifically, this study will help the [institution] prepare for another study that may begin within the next year to find out if 2 gels can protect women from getting HIV during sex.

Some people may not be able to join the research study because of information found during the screening tests.

PROCEDURES

If you agree to have the screening tests, you will have 2 visits here over about 1-2 weeks. Depending on your screening test results, more visits may be needed, as described below.

All screening tests must be done within 30 days. If all tests are not done within 30 days, and you still want to find out if you are eligible for the research study, you will have to start the screening tests over from the beginning.

Visit 1:

Your first visit will continue today, after you read, discuss, and sign this form. The visit will take about 1 hour. The study staff will ask you where you live and other questions about you, your health, and your sexual practices.

If your answers to the questions show that you may be eligible for the study, you will give urine for a pregnancy test. If you are pregnant, you will not be eligible for the research study. The study staff will refer you to available sources of medical care and other services you may need.

If you are not pregnant, you will have counseling about HIV and other infections passed during sex. These infections are called syphilis, gonorrhea, [*for Zambia sites only:* genital herpes,] and chlamydia. If you are having health problems that may be due to these infections, the study staff will give you medicine to treat them. The study staff will talk with you about the HIV test and tests for other infections passed during sex. You will talk about what it may mean to know the results of these tests, and whether you are prepared to receive the test results. You will talk about ways to avoid these infections.

If you are prepared to have an HIV test, study staff will draw about 1 teaspoon [or local equivalent] of blood from your arm with a needle. They will test your blood for HIV. It will take about 15-20 minutes to get your test result. You will be told your result as soon as it is available, on the same day you give blood and have the test. You will talk with the study staff about the meaning of your result and how you feel about it. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will draw your blood again and repeat the tests until we know the result for sure. You must receive your HIV test results to be in the research study.

If the test shows that you have HIV, you will not be eligible for the research study. The study staff will tell you about other studies you may be eligible for, if any. They will refer you to available sources of medical care and other services you may need.

If the test shows that you do not have HIV, the study staff will test your blood for syphilis [*for Zambia sites only:* and genital herpes]. They will test your urine for gonorrhea and chlamydia. These tests take 1-2 weeks. You will come back for another visit when your results are available.

Visit 2:
This visit will take about 90 minutes. The study staff will tell you your test results from Visit 1, and what they mean. They will talk with you again about HIV and other infections passed during sex, and how to avoid these. If the tests show that you have syphilis, gonorrhea, or chlamydia, and you did not get medicine for these infections at Visit 1, the study staff will give you medicine to treat them at this visit.

You will give urine for a pregnancy test. If you are pregnant, you will not be eligible for the research study. The study staff will refer you to available sources of medical care and other services you may need.

If you are not pregnant, you will talk with the study staff about your health. You will have a physical exam, including an exam of your genital area and inside your vagina. [*At selected sites only:* During this exam, the study staff will look through a lens called a "colposcope." The lens works like a magnifying glass to help the nurse or doctor see any abnormalities. The lens also is attached to a camera that will take a picture of the inside of your vagina.] The study staff will collect fluid from your vagina with a swab to test for infections. These infections are called trichomoniasis, candidiasis, and bacterial vaginosis. If you have these infections, we will tell you about them and give you medicine to treat them, if needed. If you have an infection that your partner also may have, you can bring him here for testing and treatment that he may need too.

[*For selected sites only:* The study staff also will collect samples from your cervix to test for abnormalities that could mean you have cervical cancer, or that could lead to cervical cancer. This test is called a "Pap smear." It takes about [x] weeks before Pap smear results are available. We will give you the results as soon as they are available.]

If you have no infections or other health problems, you will be eligible for the research study. The study staff will fully explain the study to you and answer any questions you have. If you decide to take part in the research study, you will be asked to sign another consent form.

If the screening tests show that you have an infection that needs treatment, you will be given medicine and asked to come back here after taking all the medicine. At that time, you will be eligible for the research study.

If you have a sore seen during the exam of your vagina, you will be given medicine to treat it, if needed, and asked to come back here after several days for another exam. If the sore is healed when you come back, you will be eligible for the research study.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, or infection where the needle goes into your arm. You may feel discomfort during the exam of your vagina.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or anxious while waiting for your test results. If you have HIV or other infections, knowing this could make you worried or anxious. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the screening tests. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you have HIV, or are at "high risk" for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

BENEFITS

You may get no direct benefit from the screening tests. However, you will have a physical exam and a genital exam. You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. You will get counseling and testing for other infections. If you have these infections, you will get medicine to treat them, if needed. You can bring your partner here for tests and treatment for these infections if he needs them. [*For selected sites only:* If your Pap smear result is abnormal, you will be referred for treatment at the [insert name of provider/center].]

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT

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

- The research study is stopped or canceled.
- The study staff feel that having the screening tests would be harmful to you.
- You are not willing to find out your HIV test result.
- You are not able to attend clinic visits or complete the screening tests.
- Other administrative reasons.

COSTS TO YOU

There is no cost to you for the screening tests. [*Sites to insert information about local incentives:*] You will receive [$xx] for your time and effort at each scheduled screening visit. You also will receive payment for the costs of [lost work, travel, and/or childcare] due to your visits.

CONFIDENTIALITY

The records of your screening tests [, including the pictures of your vagina,] will be confidential to the extent permitted by law. You will be identified by a code. 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. However, your records may be reviewed, under the guidelines of the United States Federal Privacy Act, by the United States National Institutes of Health, study monitors, and [insert applicable local authorities].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the screening tests, or if you have a research-related injury, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the screening tests, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

Appendix IV
Sample Informed Consent Form for Enrollment

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

HIVNET/HPTN 055
HIV Prevention Preparedness Study

FINAL Version 1.0
12 August 2002

ENROLLMENT

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]

INFORMED CONSENT

You are being asked to volunteer for the research study named above. This is a study for women who could get HIV. HIV is the virus that causes AIDS. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives 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 your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is entirely voluntary.
- You may decide not to take part in the study, or to withdraw from the study at any time, without losing the benefits of your routine medical care.
- If you decide not to take part in the study, you can still join another study later, if one is available and you qualify.

PURPOSE OF THE STUDY

[Institution] is part of a group of scientists from all over the world doing research on ways to prevent HIV infection. One purpose of this study is to set up a system at [institution] for doing research with this group. This study will help the [institution] prepare for another study that may begin in the next year to find out if 2 gels can protect women from getting HIV during sex. A second purpose is to find out about how likely people living in [city/area] are to become infected with HIV and other infections passed during sex.

The United States National Institutes of Health is funding this study. A total of 1200 women will be in this study. About 240 women will be from [site name]. The study also is going on in [list other locations]. The whole study will take 12-18 months to finish. Each woman will be in the study for 6-12 months.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign this form. You will answer interview questions about your sexual practices. You will give 2 teaspoons [or local equivalent] of blood that the study staff will keep frozen here while you are in the study. If needed, they will test this blood later in the study to help check on your health. Your blood also may be sent to Johns Hopkins University in the United States. Johns Hopkins University will test your blood for HIV, and compare their results with our results. This will help us make sure we are doing the best possible HIV testing here.

After today, you will be in the study for 6-12 months, depending on when you join. You will have a study visit every month while you are in the study. These visits will take 30-60 minutes. [Some visits must happen here at the [institution]. Study staff may be able to do other visits in your home or other places if you wish.] You will have a genital exam and testing for HIV and other infections passed during sex every 3 months.

Every month, you will:

- Tell the study staff if you had any health problems since your last visit.
- Give urine for a pregnancy test.
- Get condoms.
- Get the results of tests done at the visit and at the previous visit.
- Get treatment for infections passed during sex if you need it.
- Get referrals for medical care and other services if you need them.

Every 3 months, you also will:

- Have an exam of your genital area and inside your vagina. [*At selected sites only:* During this exam, the study staff will look through a lens called a "colposcope." The lens works like a magnifying glass to help the nurse or doctor see any abnormalities. The lens also is attached to a camera that will take a picture of the inside of your vagina.] The study staff will collect fluid from your vagina with a swab to test for infections (trichomoniasis, candidiasis, and bacterial vaginosis).
- Answer interview questions about your sexual practices.
- Talk with study staff about ways to avoid HIV and other infections passed during sex.

- Have blood tests for syphilis and urine tests for gonorrhea and chlamydia. These are infections passed during sex.
- Talk with study staff about the HIV test and give about 2 teaspoons [or local equivalent] of blood from your arm for the test. When we do HIV testing for this study, we first do a test that gives results in 15-20 minutes. You will get the result of that test when it is available, on the same day you give blood and have the test. If the test shows that you may have HIV infection, we will do another different test to confirm this result. This test takes about 1-2 weeks, so you will have to come back here at that time to get the results. If that test shows that you have HIV, we will draw your blood again and repeat the test one more time. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will draw your blood again and repeat the tests until we know the result for sure. You must receive your HIV test results to stay in the study.

At any time in the study, if you are having health problems that may be caused by infections passed during sex, you will:
- Have an exam of your genital area and inside your vagina.
- Give blood or urine to test for infections passed during sex.
- Get treatment for infections passed during sex if you need it.

You are asked to tell the study staff about medical problems you have during the study, especially genital problems. You also can contact the study staff between regular visits to report these problems. The study staff will examine you as needed. They will either provide or refer you for medical care that you may need.

If you become pregnant during the study, you can stay in the study if you wish. The study staff will refer you to available sources of medical care and other services you or your baby may need.

If you are found to have an infection that is passed during sex, the study staff will give you medicine to treat it, if needed. If you have an infection that your partner also may have, you can bring him here for testing and treatment that he may need too.

You can have extra counseling and testing for HIV if needed between regular visits. If you wish, your partner can have counseling with you. If you become infected with HIV, you can stay in the study if you wish. The study staff will give you counseling and refer you to available sources of medical care and other services you may need.

At each study visit, the study staff will update information on where you live and how to keep in contact with you. They will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [site-specific methods]. They also may visit your home to find you. They will try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you.

Other blood tests: At your last study visit, blood that is left over from your HIV test will be kept frozen here at the clinic. Leftover blood also will be kept if you become infected with HIV. This blood may be sent to Johns Hopkins University. Johns Hopkins University will test your blood for HIV, and compare their results with our results. This will help us make sure we are doing the best possible HIV testing here.

The study staff also would like to draw blood from you to keep after the study is over. You will be asked to sign a separate consent form to give permission for that. Even if you do not give permission to store your blood after the study, you can still be in the study.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, or infection where the needle goes into your arm. You may feel discomfort during the exam of your vagina.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or anxious while waiting for your test results. If you have HIV or other infections passed during sex, knowing this could make you worried or anxious. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are in the study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you have HIV, or are at "high risk" for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

BENEFITS

You may get no direct benefit from being in this study. You or others may benefit in the future from information learned in this study. You may get some personal satisfaction from being part of research on HIV.

You will have exams of your vagina and tests for infections passed during sex. If you have these infections, you will get medicine to treat them, if needed.

You will have pregnancy tests. If these tests show that you are pregnant, you will be referred for medical care and other services that you and your baby may need.

You will get counseling and testing for HIV. You will get free condoms. You can bring your partner here for counseling, tests for infections passed during sex, and treatment for these infections. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

NEW FINDINGS

You will be told any new information learned during this study that might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

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

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
- You are not willing to find out your HIV test results.
- You are not able to attend study visits or complete the study procedures.
- Other administrative reasons.

ALTERNATIVES TO PARTICIPATION

[*Sites to include/amend the following if applicable:* There may be other HIV research studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. 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.]

COSTS TO YOU

There is no cost to you for being in the study. [*Sites to insert information about local incentives:*] You will receive [$xx] for your time and effort at each scheduled screening visit. You also will receive payment for the costs of [lost work, travel, and/or childcare] due to your visits.

CONFIDENTIALITY

Your study records [, including the pictures of your vagina] will be confidential to the extent permitted by law. You will be identified by a code. 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. However, your records may be reviewed, under the guidelines of the United States Federal Privacy Act, by the United States National Institutes of Health, study monitors, and [insert applicable local authorities].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of taking part in this study. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or if you have a research-related injury, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the study, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

Appendix V
Sample Informed Consent Form for Specimen Storage and Possible Future Research Testing

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

HIVNET/HPTN 055
HIV Prevention Preparedness Study

FINAL Version 1.0
12 August 2002

SPECIMEN STORAGE

INTRODUCTION

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

HOW WILL YOU GET THE BLOOD FROM ME?

The researchers doctors want to take blood from you at your first study visit and your last study visit for storage. If you agree to this, you will have you will have about 2 teaspoons [or local equivalent] of blood drawn at each of these visits. This blood will be kept and used for future research.

HOW WILL YOU USE MY BLOOD?

Your blood will only be used to look for additional evidence of infection with HIV or other agents, damage caused by infection, or your body's response to infection (such as examining cells, proteins, and other chemicals in your body). 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 susceptible to becoming infected, your responses to infection or to treatment stronger or weaker, or make HIV progress more rapidly or slowly. No other kinds of genetic test will be done by anyone on your stored blood without first explaining the test to you and obtaining your permission.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored blood. 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. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers notify your study doctor and your study doctor will 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 blood will not be sold or used directly to produce commercial products. Research studies using your samples will be reviewed by the National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board).

HOW LONG WILL YOU KEEP MY BLOOD?

There is no time limit on how long your blood will be stored.

HOW WILL MY BLOOD BE STORED?

Your blood will be stored at special facilities that are designed to store blood samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the blood samples. Some employees of the storage facilities will need to have access to your blood samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you. An Institutional Review board will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY BLOOD BENEFIT ME?

There are no direct benefits to you. The benefit of doing research on stored blood includes learning more about HIV infection.

WHAT ARE THE RISKS?

There are few risks related to storing your blood. When tests are done on the stored blood, 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 true parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?

In order to keep your information private, your blood 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 blood to study, they will not be given your personal information. The results of future tests will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

WHAT ARE MY RIGHTS?

Allowing your blood to be stored is completely voluntary. You may decide not to have any blood 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 blood 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 blood will then not be used.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your blood, contact [insert the name of the investigator] at [insert telephone number].

For questions about your rights related to the storage of your blood for research, contact [insert the name or title of person on the Institutional Review Board] at [insert telephone number].

SIGNATURES

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your care.

I agree to have blood taken for the purpose of storage and testing for future research related to HIV infection.

_____ Yes

_____ No

[Insert signature blocks as required by the local IRB/EC:]

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date