

HPTN 035
Phase II/IIb Safety and Effectiveness Study of the
Vaginal Microbicides BufferGel and 0.5% PRO 2000/5 Gel (P)
for the Prevention of HIV Infection in Women

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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ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
BV	bacterial vaginosis
CORE	(HPTN) Coordinating and Operations Center
CRPMC	Clinical Research Products Management Center
DAIDS	Division of AIDS
DSMB	Data and Safety Monitoring Board
EC	ethics committee
EIA	enzyme immunoassay
FDA	(United States) Food and Drug Administration
HIV	Human Immunodeficiency Virus
hCG	human chorionic gonadotropin
HPTN	HIV Prevention Trials Network
HSV-2	herpes simplex virus-2
IFA	immunofluorescence assay
IND	Investigational New Drug application
IRB	institutional review board
LDMS	Laboratory Data Management System
M_n	number-average molecular weight
M_w	weight-average molecular weight
N-9	nonoxynol-9
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
PCR	polymerase chain reaction
Pr	probability
p-y	person-years
RNA	ribonucleic acid
SAE	serious adverse event
SDA	strand displacement amplification
SDMC	(HPTN) Statistical and Data Management Center
SHIV	Simian-Human Immunodeficiency Virus
SMC	(HPTN) Study Monitoring Committee
STD	sexually transmitted disease
TE	true effectiveness
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WB	Western blot
WHO	World Health Organization
w/w	weight/weight

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I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for each of the two study products for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee, DAIDS, and the product Co-Sponsors for review prior to submission.

I have read and understand the information in the Investigator's Brochures, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

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SCHEMA

- Purpose:** To assess the safety and effectiveness of two candidate vaginal microbicides: BufferGel and 0.5% PRO 2000/5 Gel (P).
- Design:** Phase II/IIb, four-arm, multisite, randomized, controlled trial comparing BufferGel and 0.5% PRO 2000/5 Gel (P) with a placebo gel and with no treatment. The three study gel arms will be double-blinded. The Phase II portion of the study will be conducted as an uninterrupted lead-in to the Phase IIb portion. Each study participant will complete approximately 12-30 months of follow-up.
- Study Population:** Sexually active HIV-uninfected women from the study sites listed below.
- Study Size:** Approximately 3100 women total, 800 of whom will take part in the Phase II portion of the study.
- Treatment Regimen:** Participants assigned to one of the three study gels will apply a single dose of the product — BufferGel, PRO 2000/5 Gel (P), or placebo gel — intravaginally up to 60 minutes before each act of vaginal intercourse while in the study, using single-use, pre-filled applicators. Participants in all four groups will receive ongoing HIV risk reduction counseling, condoms, and diagnosis and treatment of sexually transmitted diseases.
- Study Duration:** Approximately 30 months total. Accrual will require approximately 18 months and follow-up will continue until 192 incident HIV infections are observed in the study, which is expected to occur approximately 12 months after the end of the accrual period.
- Primary Objectives:**
- To evaluate the safety of BufferGel and 0.5% PRO 2000/5 Gel (P) when applied intravaginally by women at risk for sexually-transmitted HIV infection.
 - To estimate the effectiveness of BufferGel and 0.5% PRO 2000/5 Gel (P) in preventing HIV infection among at-risk women.
- Secondary Objectives:**
- To estimate the effectiveness of BufferGel and 0.5% PRO 2000/5 Gel (P) in preventing the following among women at risk for sexually-transmitted HIV infection:
 - bacterial vaginosis
 - chlamydia infection
 - genital ulcer disease
 - gonorrhea infection
 - herpes simplex virus-2 infection
 - pregnancy
 - syphilis infection
 - trichomoniasis

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SCHEMA
(continued)

Secondary Objectives (continued):

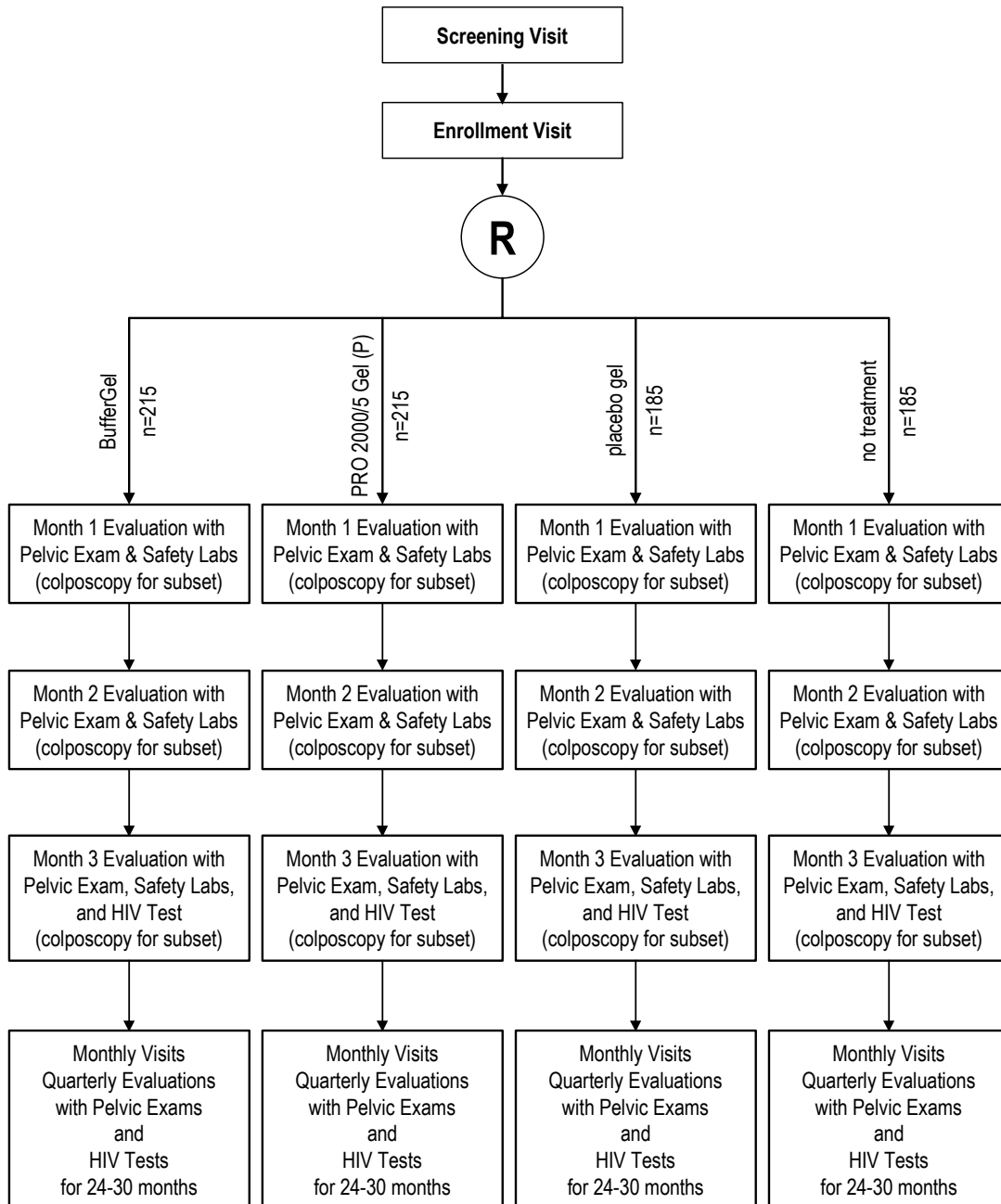
- To assess the acceptability of BufferGel and 0.5% PRO 2000/5 Gel (P) for use as a vaginal microbicide.

Study Sites:

- Blantyre, Malawi
- Chitungwiza and Harare, Zimbabwe
- Durban and Hlabisa, South Africa
- Lilongwe, Malawi
- Lusaka, Zambia
- Moshi, Tanzania
- Philadelphia, PA, USA
- Pune, India

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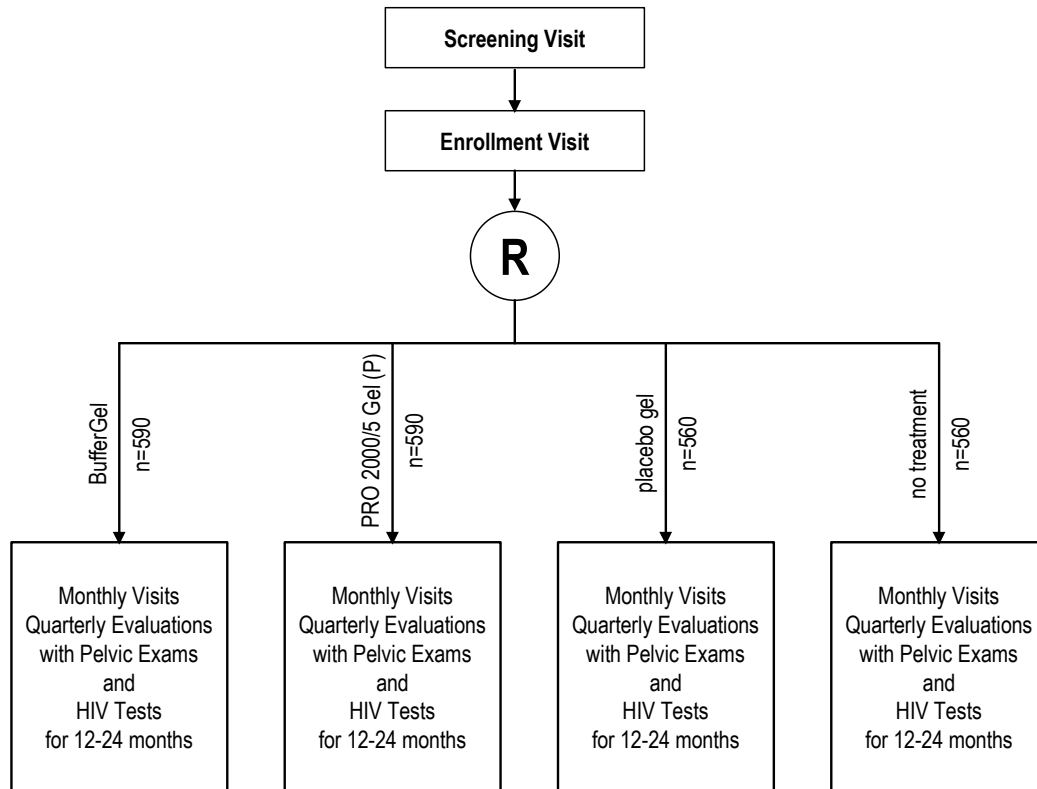
Figure 1
OVERVIEW OF STUDY DESIGN FOR PHASE II/IIb PARTICIPANTS



R=random assignment

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Figure 2
OVERVIEW OF STUDY DESIGN FOR PHASE IIb PARTICIPANTS



R=random assignment

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Figure 3
OVERVIEW OF RANDOMIZATION SCHEME

	TREATMENT GROUP				TOTAL
	BufferGel	PRO 2000/5 Gel	Placebo Gel	No Treatment	
Phase II/IIb					
US	40	40	10	10	100
Non-US	175	175	175	175	700
Total	215	215	185	185	800
Phase IIb					
US	40	40	10	10	100
Non-US	550	550	550	550	2200
Total	590	590	560	560	2300
Total					
US	80	80	20	20	200
Non-US	725	725	725	725	2900
Total	805	805	745	745	3100

Note: The absolute numbers of participants shown above are approximations and may change if observed accrual, retention rate, and/or HIV seroincidence rates differ from rates assumed in sample size calculations.

1 INTRODUCTION

1.1 Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that 42 million adults and children were living with HIV/AIDS at the end of 2002, and that about 14,000 new infections are occurring each day [1]. The majority of new infections are transmitted through heterosexual contact. As such, there is a clear need for new technologies to prevent the sexual transmission of HIV. Correct and consistent use of male condoms has been shown to prevent HIV transmission [2], but women often are unable to negotiate use of condoms by their male partners [3-5]. The female condom has been marketed as an alternative barrier method [4], but this device is relatively costly and requires a certain level of skill, and acceptance by the male partner.

Topical microbicides are products designed to prevent the sexual transmission of HIV and other disease pathogens [3-6]. Potentially, they can be applied vaginally to prevent both male-to-female and female-to-male transmission. They also offer a female-controlled option in cases where male condom use cannot be negotiated. Several marketed chemical spermicides, which have shown some activity against HIV and sexually transmitted disease (STD) pathogens in vitro, have been evaluated as topical microbicides. Notable among these is nonoxynol-9 (N-9). N-9 has been tested as a microbicide in several different doses and formulations, but has not been shown in effectiveness studies to prevent HIV infection [7-9]. In addition, N-9 products have been shown to cause mucosal erosion and ulceration in a dose-dependent manner [10-11].

In light of the N-9 trial results, increasing attention has been given to developing new approaches to topical microbicides to prevent HIV infection, particularly approaches that do not adversely affect the integrity of the vaginal and cervical epithelium. Two such products are BufferGel, developed by ReProtect, Inc. and PRO 2000/5 Gel (P), developed by Indevus Pharmaceuticals, Inc. (formerly Interneuron Pharmaceuticals, Inc.). BufferGel is designed to protect against HIV infection by maintaining the normally acidic pH of the vagina in the presence of ejaculate [12]. PRO 2000/5 Gel (P) is designed to protect against HIV infection by inhibiting viral entry into susceptible cells. After a thorough review of these and other potential candidate microbicide products — based on available pre-clinical and clinical data, as well as estimated product availability — the HIV Prevention Trials Network (HPTN) Microbicide Science Working Group Product Selection Committee, together with the HPTN 035 Protocol Team, selected BufferGel and 0.5% PRO 2000/5 Gel (P) for evaluation in this study.

1.2 Prior Research

1.2.1 BufferGel

Carbopol 974P, which constitutes the major nonaqueous component of BufferGel, is used as a gelling or tableting agent in many pharmaceuticals [13] and has a well-documented safety record of mucosal safety in animals and humans [14]. Described below are pre-clinical and clinical studies pertinent to use of BufferGel as a vaginal microbicide.

Pre-Clinical Research

Semen [12] and many STD pathogens are inactivated at pH less than 5 in vitro, including herpes simplex viruses 1 and 2 (HSV-1, HSV-2) [15], *Neisseria gonorrhoeae* [16,17] *Treponema pallidum* [18], *Hemophilus ducreyi* [19], and a variety of bacteria associated with bacterial vaginosis (BV) [20]. The pH required for HIV inactivation has been reported between 4 and 5.8 in different studies [21-23]. BufferGel is protective against transmission of HSV, papillomavirus, and *Chlamydia trachomatis* in animal models and is contraceptive in rabbits [24]. BufferGel was not protective against a cell-free viral simian-human immunodeficiency virus (SHIV) challenge in the progesterone-treated-macaque model, but the vaginas of these progesterone-treated animals were neutral in pH; thus, unlike the acidic human vagina did not support the acidifying action of BufferGel. BufferGel was highly protective against a cell-associated HIV vaginal challenge in the humanized SCID-mouse model [25].

Given the well-documented safety record of Carbopol 974P, rabbit vaginal irritation studies of BufferGel have been judged unnecessary. No adverse effects have been observed in six-month intravaginal toxicity studies of BufferGel in rats and dogs, and no toxicity was detected following multiple intravaginal doses of BufferGel in the pig-tailed macaque. BufferGel was not mutagenic in *S. typhimurium* or genotoxic in Chinese hamster ovary cells, and showed no developmental toxicity in a rat embryo-fetal development study, a rat fertility and embryonic development study or a rabbit developmental toxicity study.

Clinical Research

The safety and acceptability of BufferGel have been tested in a large Phase I safety study conducted in both the United States (US) [26] and several international sites [27].

In the US component, 27 HIV-uninfected women at low risk for HIV applied BufferGel vaginally once daily for 14 days, followed by twice daily for 14 days. Signs and symptoms reported in the study were minor, and product use was discontinued in only three cases. Three colposcopic abnormalities (cervical petechiae, a condyloma, and vaginal erythema) but no cases of epithelial disruption were observed. Quantitative vaginal cultures showed reduction in the prevalence and quantity of BV-associated anaerobes. (A separate pilot study also has shown that BufferGel can improve symptoms and clinical findings in women with BV [28].) There was no change in the prevalence of H2O2+ or H2O2- lactobacilli, although a moderate reduction in the quantity of H2O2+ lactobacilli was observed [29].

Acceptability was good, with the majority of women stating they would use BufferGel if it were proven effective and if they perceived themselves at risk for STD infection [30].

In the international component, 98 women (30 sexually abstinent and 68 sexually active) from India, Malawi, Thailand, and Zimbabwe applied BufferGel twice daily for 14 days. Epithelial abnormalities detected by pelvic exam or colposcopy were uncommon (8 cases in 271 examinations). Irritation was reported by approximately one quarter of the women (0.58 events per woman-week), but was generally mild and of short duration, and did not differ in frequency from historical controls using no product. The prevalence of BV fell significantly, from 30 percent at enrollment to 6 percent and 7 percent after one and two weeks of BufferGel use, respectively. Thirty-two women acquired microscopically detectable yeast during BufferGel exposure, but only three developed symptomatic yeast vaginitis.

In summary, it was judged that BufferGel was safe and well tolerated, and that its effect on BV and yeast colonization merits further study. Further detailed information is available in the BufferGel Investigator's Brochure.

1.2.2 PRO 2000/5 Gel (P)

PRO 2000/5, the active ingredient of PRO 2000/5 Gel (P), is a polyanionic polymer consisting of alternating 2-naphthalene sulfonic acid sodium salt and methylene units. Gels containing concentrations of 0.5%, 2%, and 4% PRO 2000/5 have been evaluated in pre-clinical and clinical studies, as described below.

Pre-Clinical Research

In vitro, PRO 2000/5 has been shown to suppress infection by a wide range of HIV-1 isolates [31-33] apparently by inhibiting viral entry into susceptible cells. PRO 2000/5 also is active in vitro against certain other STD pathogens, including herpes viruses, *C. trachomatis* and *N. gonorrhoeae*. Vaginally applied PRO 2000/5 Gel at concentrations as low as 0.5% inhibits vaginal HSV-2 infection in mice [33] and vaginal SHIV infection in macaques, as shown in the table below. Though not spermicidal, PRO 2000/5 Gel (P) is contraceptive in rabbits.

Treatment Received	No. Macaques Challenged	No. Macaques with Recoverable Virus
Control	7	7
0.5% PRO 2000/5 Gel	7	0
2% PRO 2000/5 Gel	7	1
4% PRO 2000/5 Gel	7	1

PRO 2000/5 has been found to be nonmutagenic in a standard battery of genotoxicity tests, and 4% PRO 2000/5 Gel (P) had no effect on embryo/fetal development in rats or rabbits. Gels containing up to 4% PRO 2000/5 have been well-tolerated in rabbit models for vaginal, penile, and ocular irritation. In repeat-dose intravaginal toxicity studies, concentrations up to 4% were reasonably well tolerated for six months in rats and four-and-a-half months in rabbits. No adverse effects were associated with exposure to 0.5% PRO 2000/5 Gel (P) in either species, though the 2% and 4% concentrations were associated with microscopic signs of vaginal irritation in both. Excess mortality was seen in rabbits treated with 4% PRO 2000/5 Gel (P), though some of the deaths were judged to be unrelated to PRO 2000/5 exposure. The relatedness of the others has not yet been determined.

In a small dose-ranging study in dogs, daily intravaginal administration of 2% and 4% PRO 2000/5 Gel (P) for 10 days was associated with microscopic inflammation and ulceration of cervicovaginal (though not uterine) tissue. In pig-tailed macaques, multiple intravaginal doses of 0.5% PRO 2000/5 Gel (P) produced no evidence of genital irritation, whereas cervical and vaginal abnormalities, including epithelial disruption, were observed colposcopically in animals exposed to 2% and 4% PRO 2000/5 Gel (P).

PRO 2000/5 was not detected in rabbit plasma following up to 14 intravaginal doses of 4% PRO 2000/5 Gel (P). Likewise, repeated intravaginal application of up to 4% PRO 2000/5 Gel (P) for four-and-a-half months in rabbits, six months in rats, and 10 days in dogs had no significant effect on blood coagulation times, indicating negligible systemic absorption. Low levels of PRO 2000/5 were reported in plasma samples collected from pregnant rats after twelve intravaginal gel applications. PRO 2000/5 at concentrations up to 4% had no effect on the growth of vaginal lactobacilli. Intravenous administration of PRO 2000/5 to laboratory animals and humans produced toxicological effects typical of polyanions, including reversible coagulopathy, leukocytosis, thrombocytopenia and liver and kidney pathology.

Clinical Research

The safety and acceptability of intravaginal PRO 2000/5 Gel have been tested in Phase I studies conducted among 136 women from four countries [34-36].

In Belgium and the United Kingdom [34, 35], 73 healthy, sexually abstinent women were enrolled in a randomized, double-blind, placebo-controlled study and asked to apply a 2 gram intravaginal dose of 0%, 0.5% or 4% PRO 2000/5 Gel (sterile non-preserved formulation) once per day for two weeks. In the US and South Africa [35, 36], 50 healthy, HIV-uninfected sexually active women and 13 sexually abstinent HIV-infected women were asked to apply a 2 gram dose of 2% or 4% PRO 2000 Gel (P) one or two times per day for two weeks. Assessments included pelvic exams (with colposcopy), laboratory safety tests, vaginal pH measurements, and microbiology tests, microscopic evaluation of vaginal biopsies (UK only), daily subject diaries, and acceptability questionnaires.

Adherence to product use was high in all studies, and 130 of 136 participants (96 percent) completed the studies. No serious adverse events were reported, and there was no evidence for significant systemic absorption or toxicity. Treatment-emergent adverse events were reported in 84 percent of participants, with the most common being vaginal discharge, vaginal bleeding/spotting, and vulvovaginal pruritus, burning, and pain.

Cervical and vulvovaginal ulceration was seen colposcopically in four percent and three percent of participants respectively during product use, but was usually linked to trauma or HSV infection. Findings resolved during or shortly after cessation of dosing. Vaginal pH and ecology, plasma HIV RNA, and microscopic signs of inflammation were largely unaffected by treatment. The spectrum of findings was similar across populations and exposure levels, though some findings tended to be more common in the 4% gel recipients.

Acceptability was good in all studies. In Belgium and the UK, most participants found the consistency, color and odor of the gel acceptable (“liked a lot” or “like somewhat”). In the US and South Africa, all study participants queried reported that they would use the gel if they perceived themselves to be at risk for HIV infection, and all reported that they would recommend the gel to other women.

In summary, PRO 2000/5 Gel was judged to be safe and well-tolerated in the study populations. Further detailed information is available in the PRO 2000/5 Gel Investigator’s Brochure.

Rationale for Dose Selection

Although gels containing concentrations of up to 4% PRO 2000/5 have been judged to be safe and well-tolerated in clinical research studies, certain pre-clinical findings noted above have raised concerns about proceeding to effectiveness studies with gel concentrations greater than 0.5%. In particular, colposcopic findings including cervical and vaginal epithelial disruption were observed at greater frequency among macaques treated with 2% and 4% PRO 2000/5 Gel (P) than among macaques treated with a placebo gel, whereas no such findings were observed among macaques treated with 0.5% gel. These findings, together with the fact that the 0.5% gel provided complete protection in a macaque challenge study, and significant protection in other animal STD models, form the rationale for the selection of the 0.5% gel for evaluation in this study.

1.2.3 Penile Safety

In addition to the Phase I vaginal studies described above, Phase I studies also have been conducted to assess the safety of BufferGel and PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa [37].

In one study, HIV-uninfected men applied either 4% PRO 2000/5 Gel (P) (n=24) or a gel containing the inactive ingredients of PRO 2000/5 Gel (P) (n=12) to the penis for seven consecutive days. About one in six users of both gels reported mild transient symptoms of genital itching, tingling, irritation, or abrasion. Additional users of both gels reported dryness or flaking of the dried gel. In a similar study comparing BufferGel and K-Y Jelly (a marketed sexual lubricant), about one in eight users of BufferGel and one in six users of K-Y Jelly reported similar symptoms.

A third study (HPTN 032) was conducted to assess the effects of BufferGel and 4% PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa of HIV-infected men. Mild symptoms similar to those reported by HIV-uninfected men were reported at similar frequencies in this study. In addition moderate yeast balanitis was observed in one (uncircumcised) participant during use of PRO 2000/5 Gel (P).

Based on the above, neither BufferGel nor PRO 2000/5 Gel (P) are expected to have significant adverse effects on the partners of study participants, should they be exposed to the gels while having sexual intercourse with participants in the absence of a condom.

1.3 Rationale

There is an urgent need to develop safe and effective vaginal microbicides to prevent sexual transmission of HIV. Based on available pre-clinical and clinical data, both BufferGel and 0.5% PRO 2000/5 Gel (P) are promising candidates, as recognized by their selection for testing in this study by the HPTN Microbicide Science Working Group Product Review Committee and the Protocol Co-Chairs.

Responding to the recently-updated recommendations of the International Working Group on Microbicides [38], this study tests two candidate microbicides, in multiple populations with different characteristics, and includes a Phase II safety study “lead in” to an effectiveness study. This study also includes two control groups, one in which a placebo gel serves as the comparator and one in which no treatment serves as the comparator. The importance of and rationale for these design features are summarized below.

1.3.1 Multiple Products

Both BufferGel and 0.5% PRO 2000/5 Gel (P) will be evaluated in this study, compared to the two common control groups noted above. By including both products in a single study, the number of women enrolled as control participants is greatly minimized, compared to the number of control participants who would be required to take part in separate studies of the two candidate products.

1.3.2 Multiple Populations

This study will be conducted among populations from Africa, India, and the US, with different baseline profiles of overall health status, STD prevalence, and sexual practices. Although primary analyses of product effectiveness will of necessity be conducted using data pooled from multiple study sites, inclusion of a number of diverse sites will provide for secondary assessment of potential site-specific product safety and acceptability issues pertinent to each population. In addition, inclusion of a US site will provide a basis for seeking licensure from the US Food and Drug Administration (FDA) of products shown to be highly effective in this study.

1.3.3 Phase II Lead-In to Phase IIb

BufferGel and PRO 2000/5 Gel (P) both have been evaluated in Phase I clinical studies in several international settings. In a “traditional” clinical development pathway, the previously completed Phase I studies would be followed by Phase II studies — generally considered expanded safety and “proof-of concept studies” — conducted among hundreds of women at risk for HIV infection.

In microbicide research, “proof-of-concept” for HIV prevention can only be measured in studies with very large numbers of participants. Similarly, the potential for increased risk of HIV and/or other STDs associated with product use (a principle safety outcome) can only be observed in very large numbers of participants. As such, and in light of the urgency of microbicide development, this study employs a Phase II “lead-in” to a Phase IIb effectiveness study, which provides for the following efficiencies:

- Phase II safety endpoints are evaluated at participating Phase IIb study sites.
- Phase II participants contribute to the Phase IIb effectiveness analyses.
- Study operations are maintained at the participating study sites throughout the Phase II/IIb transition.

Note: As described more fully in Sections 2 and 7, although study operations will be maintained throughout the Phase II/IIb transition, Phase IIb accrual will continue at the same rate as in Phase II, such that less than half of the eventual number of participants to be assigned to the two candidate microbicide groups will be exposed prior to the data cut-off for the Phase II Data and Safety Monitoring Board (DSMB) review. Further information on the planned safety and effectiveness analyses involving both Phase II and Phase IIb data is provided in Section 7.

The Phase IIb study design provides a screening assessment of product effectiveness in preventing HIV infection. As described more fully in Section 7, the Phase IIb design utilized in this study provides clear indications of whether candidate products are:

- not plausibly effective, and therefore should be discontinued from development;
- plausibly effective, and require further evaluation in a subsequent Phase III study; or
- demonstrably effective based on the Phase IIb study alone.

1.3.4 Placebo Control and No Treatment Control

The inclusion of two control groups in this study represents a departure from the designs of previous microbicide effectiveness studies, however for the reasons described below this design has been identified as scientifically desirable for this study.

The randomized placebo-controlled clinical trial remains the “gold-standard” for establishing the efficacy of investigational products. Inclusion of the placebo control group in this study provides a means to blind study investigators and participants to product assignments and thereby often maximizes the likelihood of obtaining an unbiased estimate of the efficacy of the two candidate microbicides.

However, interpretation of comparisons made across the candidate microbicide and placebo control groups in this study vis-à-vis the efficacy of the candidate microbicides is predicated on an assumption that the placebo control gel is inert. Microbicide research to date has been hampered by a lack of information on the possible protective effects of placebo gels used in prior studies. For example, a placebo gel could have protective effects even in the absence of an active ingredient by virtue of lubricating properties or by serving as a physical barrier to HIV infection. Other possible mechanisms of action include antimicrobial effects from preservatives contained in the gels, effects on vaginal flora, and volume-related effects on the concentration of HIV in the vagina after ejaculation in the presence of the gel.

The adverse impact of lack of information on the potential effects of the placebo control gel was most recently demonstrated in the UNAIDS-sponsored study of COL-1492 [9]. The placebo used in that study was a bioadhesive gel with lubricating and other properties that could potentially protect against HIV infection. Although a higher rate of HIV infection was observed in the COL-1492 group of this study than in the placebo group, it is unclear whether the results of the study should be interpreted as demonstrating a deleterious effect of COL-1492 or a possible protective effect of the placebo gel. In the absence of information that inclusion of a no treatment group in that study could have provided, either interpretation is valid.

For this study, every effort was made to formulate a placebo gel with no microbicidal properties (see also Section 4.1.3). Until this formulation is tested in vivo, however, it is not possible to determine whether it may have protective effects when used by women at high risk for HIV infection. As such, inclusion of a no treatment group in this study will provide information that may prove critical for interpretation of the study results. It also will likely contribute significantly to the overall field of microbicide development, since if the formulation is shown to be inert, it may be a suitable control preparation for other future microbicide studies.

Inclusion of the no treatment group in this study also serves a second useful purpose. Since study participants may not use the product to which they are assigned for every sex act while in the study, and may vary their sexual behaviors when using a study product versus when not, microbicide research is limited to evaluating product effectiveness, a construct comprised of both efficacy and use variables. In this setting, it can be argued that the comparison of HIV infection rates observed in the candidate microbicide groups versus the no treatment group may be as informative as the comparison of rates observed in the candidate microbicide groups versus the placebo gel group. While the use of a placebo gel is intended to approximate the traditional model of determining the efficacy of a candidate active product, the no treatment group provides a comparator for the two candidate microbicides that may better reflect the effectiveness of the products by taking into account potential changes in a complex set of behaviors associated with use or non-use of a microbicide product.

For these reasons, as noted in Section 7.6.2, the estimated effectiveness of each candidate microbicide compared to each control group will be considered when determining the overall public health benefit of the candidate microbicides.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objectives of this study are to:

- Evaluate the safety of BufferGel and 0.5% PRO 2000/5 Gel (P) when applied intravaginally by women at risk for sexually-transmitted HIV infection.
- Estimate the effectiveness of BufferGel and 0.5% PRO 2000/5 Gel (P) in preventing HIV infection among at-risk women.

Note: The first primary objective listed above, related to safety, is the focus of the Phase II portion of the study. Both primary objectives will be addressed in the Phase IIb portion of the study.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Estimate the effectiveness of BufferGel and 0.5% PRO 2000/5 Gel (P) in preventing the following among women at risk for sexually-transmitted HIV infection:
 - BV
 - chlamydia infection
 - genital ulcer disease
 - gonorrhea infection
 - HSV-2 infection
 - pregnancy
 - syphilis infection
 - trichomoniasis

Note: Data on the incidence of chlamydia and gonorrhea infection will be collected throughout the study, however due to expected low incidence rates in some study sites, statistical power to detect differences in incidence rates across study treatment groups may be limited.

- Assess the acceptability of BufferGel and 0.5% PRO 2000/5 Gel (P) for use as a vaginal microbicide.

2.3 Study Design

2.3.1 Overview

This is a Phase II/Ib, four-arm, multisite, randomized, controlled trial comparing two candidate vaginal microbicides, BufferGel and 0.5% PRO 2000/5 Gel (P), with a placebo gel and with no treatment. The three study gel arms will be double-blinded.

The study will be conducted among sexually active HIV-uninfected women from eight sites in seven countries:

- Blantyre, Malawi
- Chitungwiza and Harare, Zimbabwe
- Durban and Hlabisa, South Africa
- Lilongwe, Malawi
- Lusaka, Zambia
- Moshi, Tanzania
- Philadelphia, PA, USA
- Pune, India

The study design is summarized in the Schema, Overview Figures 1-3 (on pages 11-13), and Appendices I-III. For both the Phase II and Phase IIb portions of the study, non-US participants will be assigned at random to the four study treatment groups in a 1:1:1:1 ratio. US participants will be assigned in a 4:4:1:1 ratio, such that four times as many US participants will be assigned to the candidate microbicide groups as to the control groups, in order to provide a relatively larger amount of candidate product safety information among the US participant population.

The Phase II portion of the study will be conducted among 800 women — 100 from the US and ideally 100 from each of the non-US sites. Accrual will begin after the US site and at least three non-US sites have obtained all required regulatory approvals and are activated to begin study implementation by the HPTN Coordinating and Operations Center (CORE; see also Section 10.1). Depending on the timing of activation across sites, it is possible that not all non-US sites will take part in the Phase II portion of the study. Activated sites each will accrue up to 25 Phase II participants per month until a total of 800 Phase II participants are enrolled. These participants will complete three monthly follow-up assessments for Phase II study endpoints. For planning purposes, as shown in Appendix I, it is assumed that accrual for the Phase II portion of the study will require approximately six months.

Within two months of completing Phase II follow-up, the Phase II data will be compiled for review by the DAIDS Vaccine and Prevention DSMB. In addition, if enrollment in the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be compiled for DSMB review no more than 12 months after study initiation. The DSMB meets routinely every four months and will review the Phase II data at its first meeting after the data have been compiled and analyzed. Statistical considerations for the Phase II portion of the study are presented in Section 7.3.1.

Concurrent with the follow-up portion of the Phase II study and the time required to complete the Phase II data analyses and DSMB review, accrual of Phase IIb participants will begin and follow-up of the Phase II participants for Phase IIb study endpoints will continue. That is, accrual will continue uninterrupted during the transition from the Phase II portion of the study into the Phase IIb portion. However, prior to the DSMB review, accrual into the Phase IIb portion of the study will be capped at a maximum of 25 participants per site per month. As described in detail in Section 7.1, this approach of a Phase II “lead-in” to the Phase IIb study provides for continuity of study operations at the study sites while also allowing a thorough review of safety data among target populations prior to full-scale exposure of study participants to the investigational study products.

Assuming a favorable DSMB review of the Phase II data, accrual into the Phase IIb study will continue for approximately nine additional months, such that approximately 3100 participants total will be enrolled over approximately 18 months total.

Follow-up of enrolled participants will continue until a total of 192 incident HIV infections are observed in the study, or for a maximum of 30 months for each participant, whichever occurs first. Based on the participant accrual rate, retention rate, and HIV seroincidence rate assumed for sample size determination (see Section 7.3.2), the targeted number of incident infections is expected to be reached approximately 12 months after the date upon which the last participant enrolls in the study. Thus it is expected that participants will be followed for a minimum of 12 months and a maximum of 30 months, depending on when they enroll in the study and when the targeted number of infections is reached. Additional statistical considerations for the Phase IIb portion of the study are presented in Section 7.3.2.

2.3.2 Study Visits and Procedures

Study visits and procedures are nearly identical for Phase II and Phase IIb study participants, with the exception that Phase II participants will undergo additional safety evaluations — including pelvic exams and laboratory testing — during each of the first three months of their study participation (see Appendices II and III). In addition, all US Phase II participants (n=100) and the first 150 non-US Phase II participants at selected sites will undergo colposcopic examination as part of their pelvic exams during each of their first three months in the study.

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 Part 1 Visit and one Screening Part 2/Enrollment Visit. Eligible participants who provide informed consent to take part in the study will be assigned at random to one of the four study treatment groups according to the randomization schemes described above.

Enrolled participants then will complete monthly follow-up visits for the duration of their participation. At each visit, participants will complete an interval medical and menstrual history and undergo pregnancy testing. HIV/STD risk reduction counseling messages will be reinforced if needed and study supplies (i.e., condoms and the assigned study product, if applicable) will be provided.

Each quarter, participants additionally will undergo a structured interview to ascertain key HIV risk behaviors (e.g., frequency of sexual intercourse, number of sexual partners), contraceptive use, condom use, and use of study products. They also will receive HIV pre- and post-test counseling and HIV/STD risk reduction counseling. Product acceptability will be ascertained via interview at study Month 3 and at study exit.

Note: Participant risk behaviors and condom and study product use data will be collected via standardized interviewer-administered questionnaires developed by the Protocol Team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data. In order to minimize “socially-desirable” reporting, these questionnaires will be administered prior to the delivery of HIV/STD risk reduction and adherence counseling, by staff members other than those who deliver the HIV/STD risk reduction and adherence counseling. All interviewer-administered questionnaires will be pilot-tested at each site and refined accordingly prior to study start-up.

During their first three months in the study, Phase II participants will undergo pelvic exams with wet mount testing for BV, candidiasis, and trichomoniasis as well as hematology, liver and renal function, and coagulation testing each month (see Appendix IV for a listing of tests to be performed). Colposcopic evaluations also will be performed for the US Phase II participants and the first 150 non-US Phase II participants enrolled across selected sites, in accordance with the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2000. Thereafter, and for all other study participants, pelvic exams with wet mount testing for BV, candidiasis, and trichomoniasis will be performed routinely each quarter, and additionally if indicated clinically based on participant reports of symptoms at other visits. 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, HSV-2, and syphilis.

Follow-up hematology and coagulation testing will be performed quarterly at the US site. Follow-up HIV (see Appendix V) testing will be performed quarterly, and additionally if clinically indicated. Follow-up chlamydia, gonorrhea, and syphilis testing will be performed annually, and additionally if clinically indicated. HSV-2 testing will be performed on specimens obtained at enrollment and at study exit, however since information on HSV-2 serostatus is not required for clinical management, this testing will be performed in batches in the final year of study implementation at each site. STD and HIV testing will be performed in the context of pre-test, risk reduction, and post-test counseling. In accordance with the policies of the US National Institutes of Health, study participants must receive their HIV test results in order to remain eligible for study participation. A sample of HIV test results will be confirmed for quality assurance purposes by the HPTN Central Laboratory (see Section 9.3).

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 study supplies or to report symptoms between scheduled visits.

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. Observed single-dose treatment will be provided whenever possible. Participants with STDs will be encouraged to refer their partners for testing and treatment if applicable. Participants who become pregnant during the study will discontinue product use while they are pregnant, however they will remain in follow-up and may resume product use 42 days after birth or other termination of the pregnancy. Participants who become infected with HIV will be maintained in follow-up for ascertainment of secondary endpoints. They 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

The study will include approximately 3100 sexually active women from the study sites listed in the Schema and in Section 2.3.1. Participants will be recruited from a variety of sources across sites, including STD clinics, family planning clinics, and post-natal clinics, as well as community-based locations. Participants also may be referred to the study from other local research projects and other health and social service providers serving the target study population.

Ideally 415 women will be enrolled at each of the non-US sites and 200 women will be enrolled at the US site. Eight hundred of these women (700 non-US and 100 US) will take part in the Phase II portion of the study.

As is described in Section 7 and elsewhere below, the Protocol Team, HPTN Study Monitoring Committee (SMC), and the DAIDS Vaccine and Prevention DSMB will monitor rates of accrual into the study as well as observed HIV seroincidence rates. Upon recommendation from one or more of these groups, if accrual problems are encountered at any site, the Protocol Team will consider whether to shift site-specific accrual targets across sites in order to ensure that the overall sample size is achieved in as timely a manner as possible.

Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2 and the guidelines in Section 3.4. Participants will be screened for and enrolled in the study as described in Section 3.3 and assigned to a study treatment group as described in Section 7.4. 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 must meet all of the following criteria (by self-report, unless otherwise indicated) in order to be eligible for inclusion in the study:

- Of legal age to provide independent informed consent for research 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 based on testing performed by study staff.

3.2 Exclusion Criteria

Women who meet any of the following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

- History of adverse reaction to latex.
- History of non-therapeutic injection drug use in the 12 months prior to screening.
- History of vaginal intercourse more than an average of two times per day in the two weeks prior to screening.

- For Phase II participants, Grade 3 or higher laboratory abnormality, as defined by the DAIDS Toxicity Tables, based on hematology, liver and renal function, and coagulation testing performed by study staff.
- Plans any of the following during the next 30 months:
 - To become pregnant.
 - To travel away from the study site for more than three consecutive months.
 - To relocate away from the study site.
- Enrolled in any other study of a vaginally-applied product.
- Pregnant, based on self-report or testing performed by study staff.

Note: Self-reported pregnancy is adequate for exclusion from the study. A documented negative pregnancy test performed by study staff is required for inclusion.

- Within 42 days of last pregnancy outcome.

Note: Breastfeeding is not exclusionary.

- Has a clinically apparent pelvic exam finding (observed by study staff) involving deep epithelial disruption.

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

- Diagnosed by study staff 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 Part 1 Visits, and wet mount testing for BV, candidiasis, and trichomoniasis at their Screening Part 2/Enrollment visits; all results will be available by the time of enrollment/randomization. Otherwise eligible participants diagnosed during screening 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.

- Has any other condition that, based on 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 Part 1 and Screening Part 2/Enrollment Visits. Although all required procedures may be completed in as few as two visits, 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/randomized within 30 days of providing informed consent for screening, the screening process must be repeated.

At their Screening Part 1 Visits, 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 (chlamydia, gonorrhea, and syphilis) counseling and testing. Phase II study participants also will undergo hematology, liver and renal function, and coagulation testing. Presumptively eligible participants will be provided educational materials about the study to review prior to their Screening Part 2/Enrollment visit, which will be scheduled to take place approximately 7-14 days later, when all Screening Part 1 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 Western blot test will be performed. Once a participant is enrolled/randomized in the study, follow-up HIV testing will be performed according to the algorithm in Appendix V.

At their Screening Part 2/Enrollment Visits, potential participants will be informed of their Screening Part 1 test results, in the context of post-test counseling, and again undergo testing for pregnancy. Those who test negative will undergo a physical exam and pelvic exam with pH assessment and wet mount testing for BV, candidiasis, and trichomoniasis; colposcopy will be performed for the first 250 participants enrolled at selected sites. Pap smears will be performed at sites with the capacity and expertise to prepare and interpret the smears and provide referrals to appropriate follow-up care to participants with abnormal results.

Potential participants diagnosed with STD(s) or other reproductive tract infection(s) requiring treatment per WHO guidelines (other than asymptomatic candidiasis) will be offered treatment 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 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 assigned at random to one of the four study treatment groups and provided with:

- Supplies of condoms and the assigned study product (if applicable).
- Instructions for product use and product adherence counseling (if applicable).
- Instructions to contact study staff with questions about the study, requests for additional counseling, requests for additional condoms and study product (if applicable), and/or reports of adverse events (AEs, see Section 6).

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 other than the HPTN 035 study products) and other ancillary studies approved by the HPTN 035 Protocol Chair.
- Participants who become infected with HIV may take part in HIV treatment trials.

3.5 Participant Retention

Once a participant is enrolled/randomized 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. Each site will establish participant retention procedures to target loss-to-follow-up rates that do not exceed the incidence rate of the primary study endpoint. As such, an average annual retention rate of 95 percent is targeted across sites. Study 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.
- Thorough explanation of the importance of all four study treatment groups to the overall success of the study.
- Collection of detailed locator information at the study screening visits, 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 Statistical and Data Management Center (SDMC) will generate bi-weekly reports on the number and percentage of participants completing the follow-up visits throughout the course of the study. The Protocol Team as well as the HPTN SMC 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 Chair, SDMC Protocol Statistician, DAIDS Medical Officer, and CORE Protocol Specialist. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or site Institutional Review Boards (IRBs)/Ethics Committees (ECs) terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation (see Section 5.4 and Appendices II and III) of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff will record the reason(s) for all withdrawals in participants’ study records.

4 STUDY TREATMENT CONSIDERATIONS

The “treatment” for this study consists of HIV risk reduction and condom counseling provided to all study participants as well as vaginal application of one of three study products by participants assigned at random to three of the four study treatment groups. Counseling will be provided in accordance with standard study counseling methods (see also Section 8.5.1). Participants will be counseled that consistent use of condoms is the only known way to prevent sexual transmission of HIV, and condoms will be provided free of charge to all participants at each study visit. In addition, counseling will emphasize the unknown efficacy of the study products in preventing HIV infection.

Described in the remainder of this section are considerations related to the three study products: BufferGel, PRO 2000/5 Gel (P), and a placebo gel.

4.1 Product Formulation

4.1.1 BufferGel

The active ingredient of BufferGel is the hydrogen ion, H⁺. BufferGel is formulated to buffer the concentration of free hydrogen ions at the level normally found in the vaginal lumen, 0.1 mM (pH 3.8 – 4.0). BufferGel itself is formulated at a pH of 3.85. Hydrogen ions are buffered (released or bound) by abundant carboxyl groups on the Carbopol 974P polymer which constitutes the major nonaqueous component (4% polymer, 94% water) of BufferGel. Carbopol 974P is a high molecular weight, cross-linked, polyacrylic acid that is used as a gelling or tableting agent in many pharmaceuticals [11]. It has a well-documented record of mucosal safety in animals and humans [12]. The additional constituents of BufferGel are all USP23/NF18: dibasic potassium phosphate, magnesium sulfate, dibasic sodium phosphate, sorbic acid, monobasic sodium phosphate, and disodium EDTA.

4.1.2 PRO 2000/5 Gel (P)

PRO 2000/5, the active ingredient of PRO 2000/5 Gel (P), is a polyanionic polymer consisting of alternating 2-naphthalene sulfonic acid sodium salt and methylene units. The weight-average molecular weight (M_w) is 5 ± 1 kilodaltons and the polydispersity (M_w/M_n), a measure of molecular weight distribution, is low (less than or equal to 1.2). PRO 2000/5 is synthesized by the acid catalyzed condensation of 2-naphthalene sulfonic acid with formaldehyde, followed by neutralization and molecular weight fractionation. PRO 2000/5 Gel (P), 0.5%, is an aqueous gel formulation containing 0.5% (w/w) PRO 2000/5, Carbomer 1382, lactic acid, trolamine, methylparaben, propylparaben, and sodium benzoate. It is buffered to pH 4.5.

4.1.3 Placebo

The placebo gel is formulated to minimize any possible effects — negative or positive — on study endpoints. It is isotonic to avoid epithelial cell swelling or dehydration. It is formulated at a pH of 4.4 but has minimal buffering capacity. When mixed with an equal volume of semen, the placebo gel induced only a trivial decrease in semen pH (from 7.8 to 7.7).

The placebo gel contains hydroxyethylcellulose as a gelling agent, and its viscosity is comparable to that of BufferGel and PRO 2000/5 Gel (P). Hydroxyethylcellulose does not have anti-HIV properties. The gel also contains sorbic acid as a preservative. Sorbic acid has no anti-HIV activity and is readily metabolized by human cells.

Minimal toxicity was observed when the placebo gel was tested in a highly sensitive mouse epithelial toxicity model (Thomas Moench, personal communication). When tested in a mouse HSV-2 vaginal challenge model, the placebo afforded no protection when compared to no treatment or when compared to pretreatment with phosphate buffered saline. The placebo also did not enhance susceptibility to HSV-2 when administered 12 hours before vaginal challenge. In contrast, N-9 and other detergent microbicides tested in the same protocol caused a 10-25 fold increase in susceptibility (Thomas Moench, personal communication).

4.2 Product Use Regimen

Study staff will instruct participants assigned to one of the three study product groups in proper methods of storing and applying the products. In particular, these participants will be instructed to insert one dose — the entire contents of one applicator — of product into the vagina up to 60 minutes before each act of vaginal intercourse (however intercourse may take place immediately after product insertion).

Participants will be educated and counseled about the risks of douching and encouraged to avoid this practice. They also will be instructed to:

- Only apply the products vaginally.
- Not douche or otherwise clean the vagina, or insert other vaginal products, within one hour before and one hour after having vaginal intercourse.
- Not use other participants' study gel.
- Not distribute their own study gel to other women.

4.3 Product Supply, Dispensing, and Accountability

DPT Laboratories will manufacture and package BufferGel, 0.5% PRO 2000/5 Gel (P), and placebo gel under good manufacturing practices conditions. All three products will be provided in identically packaged single-use opaque plastic applicators.

Site pharmacists will obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) according to the ordering instructions provided in the study-specific procedures manual. All three study products will be stored in a secure, limited-access area at the site.

Study product will be dispensed only to enrolled study participants, upon receipt of a written prescription from an authorized prescriber, in quantities expected to be sufficient until the participant's next monthly follow-up visit (up to a maximum of 60 applicators per month, which corresponds to the maximum frequency of exposure — twice per day — evaluated in Phase I studies of the candidate products). Allowances will be made for up to a three-month supply of product to be dispensed to participants under exceptional circumstances. All such circumstances will be documented fully by the Investigator or designee as described in the study-specific procedures manual. In the event that a participant needs additional supplies between visits, she will be instructed to contact the study site to request additional supplies.

Site pharmacists are required to maintain complete records of all study product received from the CRPMC and subsequently dispensed. Instructions and sample forms will be provided in the study-specific procedures manual. All unused study product must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the DAIDS Pharmaceutical Affairs Branch.

All study sites will be provided with a single brand of condoms — not impregnated or coated with nonoxynol-9 or any other spermicide — to distribute to participants throughout the study. Condoms will be provided to participants in quantities expected to be sufficient until their next monthly follow-up visit. In the event that a participant needs additional condoms between visits, she may request these of study staff at any time.

4.4 Adherence Counseling

Adherence counseling will be provided to study participants assigned to the three study product groups upon enrollment into the study, and as needed thereafter to help ensure high rates of product use. Counseling will be provided in accordance with standard study methods that will address such topics as client-centered strategies to remember to use the products for each episode of vaginal intercourse; to ensure the availability of the products both in the home and away from home; and to negotiate product use with “primary” and “non-primary” partners. Counseling also will include reminders to contact study staff with questions about product use and requests for additional supplies. For participants who have adherence problems, every effort will be made to identify adherence strategies to increase their rates of product use throughout the course of the study.

4.5 Adherence Assessment

Data on adherence to the product use regimen will be collected quarterly via interviewer-administered questionnaires. These questionnaires will ascertain participants’ frequency of sexual intercourse, condom use, and product use. They will be administered prior to the delivery of HIV/STD risk reduction and adherence counseling, by staff members other than those who deliver HIV/STD risk reduction and adherence counseling. The Protocol Team will monitor adherence rates over time, and adherence counseling methods will be updated if needed to address lower-than expected rates. Adherence rates also will be reported to the HPTN SMC and the DSMB.

4.6 Product Use Management

Study participants will be discontinued from product use by the study site Investigator or designee in the event that they become pregnant or experience a serious adverse event (SAE, see Section 6) that is judged by the site Investigator or designee to be probably or definitely related to product use. Participants who become pregnant may resume product use 42 days after giving birth or other termination of the pregnancy.

Participants at selected sites performing Pap smears will be discontinued from product use if they are found to have a high-grade squamous intraepithelial lesion or more severe abnormality, however such participants may resume product use after treatment and resolution of the abnormality. For participants at sites where local standards of care require clinical colposcopy and biopsy to assess lower grade abnormalities, product use will be discontinued during the three-week period beginning one week before the required procedure and ending two weeks after the required procedure (assuming no further intervention or treatment is needed). If further intervention or treatment is needed, the period of product discontinuation will be extended until after treatment and resolution of the abnormality.

Investigators/designees also may at their discretion discontinue product use — temporarily or permanently — among participants who:

- Experience an SAE judged possibly related to product use.
- Have a pelvic exam finding involving deep epithelial disruption that does not resolve over the course of an additional month of continued product use.
- Are unable or unwilling to comply with required study procedures.
- Otherwise might be put at undue risk to their safety and well-being by continuing product use.

The Investigator or designee will document all changes in product application regimen, and the reason for the change, on applicable case report forms.

Participants who discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified follow-up visits and procedures with these participants. In addition, participants who become pregnant will be maintained in follow-up through their originally scheduled study exit date or until their pregnancy outcome is ascertained, whichever is longer.

4.7 Concomitant Medications

Enrolled study participants may continue use of all concomitant medications, including prescription, non-prescription, traditional, and other preparations during this study. However, as noted in Section 4.2, participants will be encouraged to avoid douching and the use of vaginally-applied medications/preparations within one hour before and one hour after having vaginal intercourse. All concomitant medications used by participants throughout the course of the study, beginning at the time of randomization/enrollment, will be reported on applicable case report forms. Medications used for the treatment of endpoints and AEs that occur during study participation also will be recorded on applicable case report forms.

5 STUDY PROCEDURES

See also Appendices II-V. 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 in this section are performed at the local study site laboratories.

5.1 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 visit. Pre-screening information 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.

5.2 Screening Part 1 Visit

Unless otherwise noted, the following procedures are performed at Screening Part 1 Visits for both Phase II and Phase IIb participants. 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.

5.2.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening.
- Demographic information.
- Behavioral eligibility information.
- Locator information.
- HIV pre-test and post-test counseling.
- HIV/STD risk reduction counseling, condoms, other HIV prevention supplies.
- Offer HIV counseling and testing for partner(s).

5.2.2 Clinical Procedures

- Urine collection.
- Blood collection.
- Test results disclosure.
- Treatment for STDs and other genitourinary symptoms requiring treatment per WHO guidelines; offer of STD testing and treatment for partner(s).

Note: Pelvic exams may be performed at Screening Part 1 Visits at study sites where local standards of care require an exam to guide treatment of STD symptoms. Such exams will not substitute for the pelvic exams required at Screening Part 2/Enrollment Visits for all participants (see Section 5.3.2).

5.2.3 Laboratory Procedures

- Urine pregnancy test.
- Urine strand displacement amplification (SDA) for chlamydia and gonorrhea.
- Dipstick urinalysis if clinically indicated; urine culture if dipstick is positive for leukocyte esterase or nitrites.
- HIV serology.
- Syphilis serology.
- Complete blood count (Phase II participants only).
- Liver and renal function tests (Phase II participants only).
- Coagulation tests (Phase II participants only).

5.3 Screening Part 2/Enrollment Visit

Unless otherwise noted, the following procedures are performed at the study Screening Part 2/Enrollment Visit for Phase II and Phase IIb participants. Multiple visits may be conducted to complete all required procedures if necessary. Written informed consent for study participation will be obtained before any Enrollment (or “on-study”) procedures are conducted. For participants whose eligibility is not confirmed at this visit, the screening and enrollment process will be discontinued when ineligibility is determined.

5.3.1 Administrative, Behavioral, and Regulatory Procedures

Screening Part 2

- HIV pre-test and/or post-test counseling if needed.
- Condoms, other HIV prevention supplies if needed.
- Behavioral eligibility information.
- Informed consent for study.

Enrollment

- Informed consent for specimen storage and possible future research testing.
- Locator information.
- Behavioral risk assessment.
- Random assignment.
- For participants assigned to a study gel, provide study product, instructions, and adherence counseling.
- For participants assigned to no gel, provide explanation/counseling.

5.3.2 Clinical Procedures

Screening Part 2

- Urine collection.
- Blood collection if genital ulcer is observed.
- Focused medical and menstrual history and ascertainment of current medications (includes detailed intermenstrual bleeding history).
- Physical exam.
- Pelvic exam with:
 - colposcopy (US Phase II participants and first 150 non-US Phase II participants from selected sites only)
 - specimen collection for Gram stain
 - pH, assessment for homogenous discharge, and wet mount for BV, candidiasis, and trichomoniasis
 - ecto- and endocervical cells for Pap smear (at selected sites only)
- Test results disclosure.
- Treatment for STDs and other genitourinary infections requiring treatment per WHO guidelines (except asymptomatic candidiasis); 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.

Enrollment

- Blood collection.

5.3.3 Laboratory Procedures

Screening Part 2

- Urine pregnancy test.
- Urine SDA for chlamydia and gonorrhea if clinically indicated.
- Dipstick urinalysis if clinically indicated; urine culture if dipstick is positive for leukocyte esterase 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.

Enrollment

- Plasma archive.

Note: HSV-2 testing will be performed on plasma archived at enrollment and at study exit in batches during the final year of study implementation at each site.

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 9.3).

5.4 Follow-up Visits

Monthly follow-up visits are scheduled throughout the study follow-up period on the same date as the participant's enrollment date (i.e., on the monthly "anniversary" of the enrollment date). 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 quarterly visits, 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 will be maintained in follow-up as originally planned based on their study enrollment date. For participants who become pregnant, follow-up procedures may be modified according to guidelines specified in the study-specific procedures manual. For example, pregnancy testing will be discontinued and 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 risk reduction counseling will be tailored to primary and secondary HIV/STD prevention for infected women.

5.4.1 Administrative, Behavioral, and Regulatory Procedures

- Ongoing informed consent:
 - As needed at all visits.
- Locator information:
 - At all visits and contacts.
- Behavioral risk, adherence, and social harms assessment:
 - Quarterly.
 - At study exit.
- Acceptability assessment:
 - At Month 3.
 - At study exit.
- Unblinding assessment:
 - At study exit.

Note: Not done for participants assigned to the no treatment group.

- HIV pre- and post-test counseling:
 - Quarterly.
 - At study exit.
 - Additionally when needed/requested.
- HIV/STD risk reduction counseling, offer HIV counseling and testing for partner(s):
 - Quarterly.
 - At study exit.
 - Additionally when needed/requested.
- Condoms and other HIV prevention supplies:
 - Monthly.
 - Additionally when needed/requested.
- Study product supplies, instructions, and adherence counseling:
 - Monthly (except at study exit).
 - Additionally when needed/requested.

Note: Not done for participants assigned to the no treatment group.

5.4.2 Clinical Procedures

- Interval (i.e., since last visit) medical and menstrual history and concomitant medication review (includes detailed intermenstrual bleeding history).
 - At all scheduled visits.
 - Additionally at unscheduled visits in response to intercurrent symptoms/illnesses.
- Pelvic exam with:
 - Specimen collection for Gram stain
 - pH, assessment for homogenous discharge, and wet mount for BV, candidiasis, and trichomoniasis
 - Swab for multiplex PCR if genital ulcer is observed:
 - At Months 1, 2, and 3 for Phase II participants.
 - Quarterly for all participants.
 - Additionally for all participants when clinically indicated.

Note: A swab sample will be collected from each genital ulcer observed during the study. See also Section 5.4.3.

- Additionally with colposcopy:
 - At Months 1, 2, and 3 for the first 250 Phase II participants from selected sites.
- Additionally with collection of ecto- and endocervical cells for Pap smear (at selected sites only):
 - During last scheduled exam.
 - Additionally when clinically indicated and/or if required by local standard of care.
- Urine collection:
 - At all scheduled visits.
 - Additionally when clinically indicated.
- Blood collection:
 - At Months 1, 2, and 3 for Phase II participants.
 - Quarterly and at study exit for all participants.
 - Additionally for all participants when clinically indicated.
- Test results disclosure:
 - As needed at all visits and contacts.
- Treatment for STDs and other genitourinary infections requiring treatment per WHO guidelines (except asymptomatic candidiasis); offer of STD testing and treatment for partner(s):
 - When clinically indicated.

5.4.3 Laboratory Procedures

- Urine pregnancy test:
 - At all scheduled visits.
 - Additionally at unscheduled visits when a participant reports a missed menstrual period or has not had a pregnancy test in the last month.
- Urine SDA for chlamydia and gonorrhea:
 - Annually and at study exit.
 - Additionally when clinically indicated.
- Dipstick urinalysis; urine culture if dipstick is positive for leukocyte esterase or nitrites:
 - When clinically indicated.
- Gram stain assessment for BV according to the Nugent criteria at the HPTN Central Lab:
 - At Months 1, 2, and 3 for Phase II participants.
 - Quarterly for all participants.
 - Additionally for all participants when clinically indicated.
- Multiplex PCR at the HPTN Central Lab:
 - When a genital ulcer is observed.

Note: A swab sample will be collected from each genital ulcer observed during the study, and all samples will be shipped to the HPTN Central Lab. The Central Lab will perform multiplex PCR testing on a random sample of approximately 500 samples. The exact number of samples to be tested from each site will be determined in consultation with the Protocol Biostatistician once preliminary data are obtained on the total number of genital ulcers likely to be observed at each site.

- Pap smear interpretation (at selected sites only):
 - At the participant's last scheduled quarterly visit.
 - Additionally when clinically indicated and/or if required by local standard of care.
- HIV serology:
 - Quarterly and at study exit.
 - Additionally when clinically indicated.
- Syphilis serology:
 - Annually and at study exit.
 - Additionally when clinically indicated.
- Complete blood count:
 - At Months 1, 2, and 3 for Phase II participants only.
 - Quarterly and at study exit for all participants at the US site only.

- Liver and renal function tests:
-At Months 1, 2, and 3 for Phase II participants only.
- Coagulation tests:
-At Months 1, 2, and 3 for Phase II participants only.
-Quarterly and at study exit for all participants at the US site only.
- Plasma archive:
-When blood is collected for confirmatory HIV testing (i.e., when “sample 2” in Appendix V is obtained).
- At study exit.

Note: HSV-2 testing will be performed on plasma archived at enrollment and at study exit in batches during the final year of study implementation at each site.

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 9.3).

5.5 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., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.
- For product-related reasons, e.g., a participant may need additional study product or want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 6); all AEs associated with genital symptoms will be evaluated according to the quarterly pelvic exam procedures described above. Reports of genital bleeding will be evaluated and documented according to standard study procedures across sites.
- 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 V.

- In the event that a participant presents to the study site on a day that does not fall within a scheduled visit window to complete required study visits procedures that were not completed at the participant's last scheduled visit.
- 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.

5.6 Final Contact

Since participants' last study follow-up visits (or "exit" visits) will include laboratory testing for HIV and other infections, a final contact is required to provide her final study test results, post-test counseling, and treatment, if needed. In addition, for participants who become pregnant within nine months prior to the study end date, an additional contact may be required to ascertain the participant's birth outcome. Study sites may complete these contacts at the study site or at community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

6 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

The study site Investigators are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. In addition, the HPTN SDMC will prepare routine study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment) for review by the Protocol Team. Protocol Team members will meet via conference call at least once per month throughout the period of study implementation, and additional ad hoc calls will be convened if required.

As noted in Section 2, and described more fully in Section 7, the DAIDS Vaccine and Prevention DSMB will complete a formal review of the Phase II study data after the 800 Phase II participants have completed three months of product use and follow-up. In addition, if enrollment in the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be prepared for DSMB review no more than 12 months after study initiation. Based on the results of that (these) review(s), the DSMB will advise as to whether the Phase IIb portion of the study should proceed as designed, should proceed with design modifications, or should be discontinued.

Assuming continuation of the Phase IIb study, the DSMB will conduct interim reviews of study progress, including rates of participant accrual, retention, and HIV incidence, and product safety. These reviews will take place approximately every six months. At the time of these reviews, or at any other time, the DSMB may recommend that the Phase IIb portion of the study proceed as designed, proceed with design modifications, or be discontinued. Formal comparisons of HIV incidence across treatment groups will be made only at final analysis.

6.2 Adverse Event Reporting Requirements

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition will be applied to all four study treatment groups, even though one group is not assigned to administer an investigational product, and will be applied to all groups beginning from the time of random assignment. The term “investigational product” for this study refers to BufferGel, PRO 2000/5 Gel (P) and the placebo gel.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study case report forms. All participants reporting an untoward medical occurrence will be followed clinically, until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document on case report forms all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. All AEs will be graded using the DAIDS Table for Grading Severity of Adverse Experiences (also referred to as the “Toxicity Table”). The investigator or designee will assess the relationship of all AEs to the study product based on the DAIDS SAE Reporting Manual for the HPTN, the Investigator’s Brochures, and his/her clinical judgment. Both the DAIDS SAE Reporting Manual for the HPTN and the Toxicity Table are provided in the study-specific procedures manual and are available at the following web sites:

http://www.hptn.org/network_information/regulatory_resources.htm

<http://rcc.tech-res-intl.com>

6.3 Serious Adverse Event Reporting Requirements

Site staff also will report to the DAIDS Regulatory Compliance Center all AEs that meet serious adverse event (SAE) reporting requirements according to the procedures set forth in the DAIDS SAE Reporting Manual for the HPTN. Specifically:

- DAIDS-defined “intensive” reporting requirements will be followed during the Phase II portion of the study.
- DAIDS-defined “standard” reporting requirements will be followed during the Phase IIb portion of the study.

Information on all AEs will be included in reports to the FDA, and other applicable government and regulatory authorities. Site staff will report information on all AEs and SAEs to their IRBs/ECs in accordance with all applicable regulations and local IRB/EC requirements.

7 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

As noted in Section 1.3, the design of this study follows several of the current recommendations of the International Working Group on Microbicides. In particular, a multi-site Phase II study among 800 participants will “lead in” to the Phase IIb study which will include the Phase II study participants plus approximately 2300 additional women. By capping, rather than stopping, enrollment during the transition between Phase II and Phase IIb, continuity of study operations is maintained without exposing more women than necessary to the candidate microbicide products. Specifically, with a cap of 25 participants enrolled per site per month, and assuming the Phase II accrual rates shown in Appendix I and three months of Phase II follow-up, plus two additional months for Phase II data cleaning, analysis, and DSMB review, approximately 390 women will be exposed to each candidate microbicide prior to the data cut-off for the DSMB safety review. This includes the 215 Phase II participants assigned to each of these products. These 780 participants constitute less than half of the total number of participants planned to be exposed to a candidate microbicide during the full Phase II/IIb study.

The Phase IIb portion of this study (which will incorporate data from the Phase II study) is designed to provide a screening evaluation for the hypothesis of no benefit versus the hypothesis of a 33 percent reduction in HIV seroincidence among participants using a candidate microbicide (i.e., BufferGel or PRO 2000/5 Gel (P)) relative to participants using placebo or no treatment. This effect size is based on a series of discussions that began as part of the Study Monitoring Committee review of the Advantage-24 trial previously conducted in Mombasa, Kenya.

Previous microbicide effectiveness trials had been powered to detect an effect of 50 percent. However, the potential biological effect of a microbicide is impacted by less than full adherence to product use. In previous microbicide trials, microbicide use was reported in approximately 80 percent of sexual acts. Therefore, this Phase IIb study is designed to target effectiveness (biological efficacy combined with adherence) of 33 percent. In Microbicide Efficacy Trial Design Meetings convened in January 1998 and August 2000, comprehensive groups of scientists considered key methodological issues, and agreed at both meetings that an effect size of 33 percent was justifiable. This effect size also is consistent with the current recommendations of the International Working Group on Microbicides. Given this target, the decision guidelines for this study (described in detail in Section 7.6.2) have been set such that if a candidate product is 33 percent effective, the probability of declaring the product demonstrably or plausibly effective is 87.5 percent, and the probability of declaring the product unworthy of further study in its current formulation is 2.5 percent.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to evaluate the safety of BufferGel and 0.5% PRO 2000/5 Gel (P), the following primary safety endpoints will be assessed:

- Deep epithelial disruption observed on pelvic exam (speculum and/or colposcopic).
- Other genital signs and symptoms observed in or reported by study participants.
- Laboratory measures of systemic effects including hematology, liver and renal function, and coagulation test results (among Phase II participants only; see also Appendix IV).

Consistent with the primary study objective to estimate the effectiveness of BufferGel and 0.5% PRO 2000/5 Gel (P) in preventing HIV infection, HIV infection as measured by seroconversion (see Appendix V) will be assessed as the primary effectiveness endpoint.

7.2.2 Secondary Endpoints

Consistent with the secondary study objectives listed in Section 2.2, the following secondary endpoints will be assessed:

- BV ascertained by gram stain assessment at the HPTN Central Lab according to the Nugent criteria.
- Chlamydia infection ascertained by urine SDA.
- Genital ulcer disease ascertained by pelvic exam.
- Gonorrhea infection ascertained by urine SDA.
- HSV-2 infection ascertained by serologic testing.
- Pregnancy ascertained by urine human chorionic gonadotropin (hCG) testing.
- Syphilis infection ascertained by serologic testing.
- Trichomoniasis ascertained by wet mount testing.
- Acceptability of the study products based on adherence to the product use regimen as well as responses to acceptability questionnaire items.

Note: The HPTN Central Lab will perform multiplex PCR testing on a random sample of genital swabs obtained from all genital ulcers observed on pelvic exam during the study follow-up period. As described below, secondary analyses of this endpoint will examine candidate microbicide effects on all genital ulcer disease as well as on genital ulcer disease in which an infectious etiology is not ascertained by multiplex PCR.

7.3 Accrual, Follow-up, and Sample Size

7.3.1 Phase II Study

A total of 800 women (100 from the US site and 700 from at least three non-US sites) will be enrolled in the Phase II portion of the study over a period of approximately six months, and each woman will be followed monthly for three months in the Phase II portion of the study. Thus, the total duration of the Phase II portion is approximately nine months. After completing their three months of Phase II follow-up, Phase II participants will complete another 21-27 months of follow-up for the Phase IIb portion of the study.

Consistent with recommendations received from the FDA, non-US participants will be assigned at random to the four study treatment groups in a 1:1:1:1 ratio, whereas US participants will be assigned in a 4:4:1:1 ratio, such that four times as many US participants will be assigned to the candidate microbicide groups as to the control groups. Assuming a five percent significance level for a two-sided test (i.e., a 2.5 percent false-positive error rate), and five percent loss-to-follow-up over the Phase II study period, 51 and 44 person-years (p-y) of follow-up will be accumulated in the active and control groups, respectively, of the Phase II portion of the study.

Assuming each candidate microbicide will be compared separately to the placebo gel and to no treatment, Table 7-1 presents the power of the Phase II study to detect various differences in rates of epithelial disruption for given baseline rates of this outcome (i.e., rates in the placebo and no treatment groups). As shown, the Phase II portion of the study will have greater than 80 percent power to detect five-fold or larger differences between the candidate microbicide groups and the placebo or no treatment groups in rates of epithelial disruption, assuming a baseline rate of at least 5 per 100 p-y. The Phase II portion also will have greater than 90 percent power to detect three-fold or larger differences between the candidate microbicide groups and placebo or no treatment groups if the baseline rate is at least 20 per 100 p-y.

Table 7-1
Statistical Power to Detect Differences in Safety Outcome Rates
in the Phase II Portion of HPTN 035

Baseline Rate (per 100 p-y)	Power to Detect a:			
	two-fold Difference	three-fold difference	five-fold difference	ten-fold difference
5	.15	.41	.88	>.99
10	.26	.68	>.99	>.99
15	.37	.85	>.99	>.99
20	.47	.93	>.99	>.99
25	.55	.97	>.99	>.99

In previous microbicide studies conducted in African populations, epithelial disruption was observed among control participants at a rate of approximately 20 per 100 p-y. If this same rate is observed among placebo and no treatment participants in this study, the Phase II portion of the study will have at least 90 percent power to detect a difference between a candidate microbicide group and a control group if epithelial disruption is observed at a rate of at least 58 per 100 p-y in the candidate microbicide group.

7.3.2 Phase IIb Study

The Phase IIb study will enroll a total of approximately 3100 women, with enrollment ending approximately nine months after the DSMB review of the Phase II data, resulting in a total enrollment period of approximately 18 months for the Phase II/IIb study.

The US site will enroll a total of 200 women. Non-US sites are expected to enroll at least 200 women each, and ideally will enroll approximately 415 women each, to achieve the total non-US sample size of approximately 2900.

Approximately every three months during the accrual period, and/or additionally at the recommendation of the HPTN SMC or DSMB, the Protocol Team will review performance data from each study site — including accrual rates, retention rates, protocol adherence measures, data quality measures, and HIV incidence rates — to determine whether enrollment slots should be shifted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual. The Protocol Team will make every effort to discontinue accrual approximately 12 months prior to when the targeted number of incident HIV infections (n=192) will be observed.

Each enrolled participant will be followed through the study end date or for a maximum of 30 months, whichever occurs first. The study end date will be set as the date upon which a total of 192 incident HIV infections are observed. Based on the assumptions listed below, the targeted number of incident infections is expected to be reached approximately 12 months after the date upon which the last participant enrolls in the study. Thus, it is expected that participants will be followed for a minimum of 12 months and a maximum of 30 months, depending on when they enroll in the study and when the targeted number of infections is reached.

Sample size calculations are based on the randomization schemes described in Section 7.4 and the following assumptions:

- Participant accrual rates sites as shown in Appendix I.
- An average annual HIV seroincidence rate of 5.67 per 100 p-y in the placebo and no treatment groups in the non-US sites.
- An annual HIV seroincidence rate of 0.5 per 100 p-y in the placebo and no treatment groups at the US site.
- An average annual retention rate of 81 percent.

Note: The assumed HIV seroincidence rates are averages of best available estimates based on ongoing or recently completed research studies an/or other available epidemiologic information from populations as similar as possible to the study population. In particular, estimates from populations receiving condom counseling were used when available.

As noted in Section 3, each study site will establish participant retention procedures to target loss-to-follow-up rates that do not exceed the HIV infection rate among local study participants, to minimize potential bias associated with loss-to-follow-up. However, the assumed average retention rate of 81 percent reflects past performance at the study sites and was factored into the sample size calculations to adjust for the increase in variability associated with these rates.

Given the above assumptions, and assuming a 33 percent effect of the candidate products, a total of approximately 1000 p-y of follow-up are expected to be accrued in each study treatment group, and approximately 192 incident HIV infections are expected to be observed throughout the course of the study.

7.4 Random Assignment

Enrolled participants will be assigned at random to one of the four study treatment groups. The randomization scheme will be stratified by site. At non-US sites, participants will be assigned to the four study treatment groups in a 1:1:1:1 ratio. At the US site, participants will be assigned in a 4:4:1:1 ratio, such that four times as many participants are assigned to the candidate microbicide groups as to the control groups. The randomization code will be generated and maintained by the HPTN SDMC.

The SDMC will provide two sets of sealed, opaque randomization envelopes to each study site. The two sets will be linked by sequential envelope number. One set of envelopes will be stored and used in the study clinic. The other set will be stored and used in the study pharmacy. The clinic envelopes will contain an assignment to “gel” or “no gel/condoms only.” Clinic staff will assign these envelopes in sequential order by envelope number to eligible study participants. The corresponding pharmacy envelopes will contain coded (blinded) information indicating the specific product to which participants in the three study gel groups are assigned or “no gel/condoms only.”

Assignment of the clinic envelope is considered the effective act of participant enrollment/randomization. For participants assigned to “gel” in the clinic, clinic staff will prepare a written prescription that, among other things, documents the randomization envelope number to which the participant was assigned. Prescriptions for these participants will be delivered to pharmacy staff who will complete the randomization process by opening the pharmacy envelope corresponding to the assigned clinic envelope and dispensing product according to the letter code contained in the envelope. For participants assigned to “no gel/condoms only” in the clinic, in lieu of a “prescription” per se, documentation of the random assignment will be forwarded to the pharmacy, however pharmacy staff will not open a corresponding envelope or dispense product for these participants.

Clinic staff will store assigned clinic randomization envelopes and their contents in participants’ study charts. Pharmacy staff will store assigned pharmacy randomization envelopes and their contents in a secure location in the pharmacy.

7.5 Blinding

Both study staff and participants will be blinded to the random assignments of participants assigned to the three study treatment groups that include a study product; the assignment of participants to the no treatment group cannot be blinded.

As noted in Section 4, the three study products will be supplied in identically-packaged, opaque, single-use applicators. Randomization documentation and other pharmacy records will be stored in a secure location in the site pharmacy (apart from the rest of the participant file). This information must not be accessible to study staff who complete other study procedures with participants.

Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the study informed consent process.

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 4.7, in the event that an Investigator is concerned that a participant might be put at undue risk by continuing product use, the Investigator may discontinue product use by this participant, however knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the Protocol Chair, Protocol Biostatistician, and DAIDS Medical Officer (or designees) to consider and jointly rule upon the request.

All study participants will be administered a brief unblinding assessment at their study exit visits in which they will be asked to report which study product they think they received while in the study. A sample of study staff will complete a similar assessment after the close of the study at the site.

The DSMB will be provided with unblinded product coding information with closed study reports upon request.

7.6 Data Analysis and DSMB Review

All analyses will be performed on an intent-to-treat basis.

To assess the success of randomization, a summary of the baseline variables by treatment group will be tabulated, but no formal statistical testing of these variables will be performed.

DSMB reviews of study safety data will be conducted after the Phase II portion of the study is completed, and approximately every six months during the Phase IIb portion of the study. If enrollment into the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be compiled for DSMB review no more than 12 months after study initiation. O'Brien-Fleming methods for interim analyses will be used in this case. In addition to safety data presentations, analyses will be performed for these reviews to assess the assumptions used to determine sample size (i.e., accrual, retention, and HIV incidence rates at each site) and alterations will be made to the overall sample size if recommended by the DSMB.

7.6.1 Phase II Study

Data from participants in the BufferGel and PRO 2000/5 Gel (P) groups of the Phase II portion of the study will be compared (separately) to data from participants in the placebo group and in the no treatment group (separately). Incidence rates of epithelial disruption will be compared using Andersen Gill Proportional Hazards Models stratified by site and with robust variance estimates. The proportion of participants experiencing study endpoints — including genital signs and symptoms as well as and/or abnormal laboratory test results — during follow-up will be compared using Chi-square tests. In addition, listings and tabulations of all endpoints and AEs will be provided for DSMB review. The DSMB will review these analyses at the end of the Phase II study to determine whether the Phase IIb study should proceed. The DSMB also will review participant accrual and retention rates and pooled HIV seroincidence rates to assess the adequacy of rates assumed for sample size determination.

7.6.2 Phase IIb Study

Based on discussions with the FDA, a false-positive error rate of 0.0025, which is approximately midway on a log scale between the false-positive error rates associated with the strength of evidence from one and two traditional Phase III studies (0.025 and 0.000625, respectively) will be used for hypothesis testing in the Phase IIb portion of the study.

Primary Analyses

To assess safety throughout the Phase IIb portion of the study, analyses of epithelial disruption observed on pelvic examination and reported genital signs and symptoms will be performed for DSMB review approximately every 6 months, including data from all sites, using the same methods described above for the Phase II analysis. Listings and tabulations of all endpoints and AEs also will be provided for each DSMB review.

To assess effectiveness, at the final analysis HIV incidence rates will be calculated for each study treatment group and the effect of each candidate product on cumulative HIV incidence will be determined using Cox Proportional Hazards models stratified by site. Product effectiveness will be expressed as a percent reduction in the HIV incidence rate (i.e., 1 minus the hazard ratio).

The primary analysis will be formally based on a four-point decision guideline that was used to determine the study sample size and operating characteristics. The decision guideline should not be interpreted as strict decision rule, but as a guideline derived from formal statistical procedures that will be factored into a broader scientific perspective regarding the public health benefit of the candidate microbicides and how they compare to both control arms.

The decision guideline is as follows:

1. If the estimated effectiveness of a candidate microbicide is less than 15.3 percent, exclude the candidate microbicide from further testing for HIV prevention.
2. If the estimated effectiveness is greater than 15.3 percent but less than or equal to 33 percent, consider the product plausibly effective and meriting further evaluation. Either two subsequent Phase III studies each with a false-positive error rate of 0.025 or a single subsequent Phase III study with a false-positive error rate of 0.0025 may be required for licensure.

3. If the estimated effectiveness is between 33 and 43.6 percent, consider the product effective with strength evidence equal to that of at least a single Phase III study (i.e., with a false-positive error rate of 0.025). A subsequent Phase III study with a false-positive error rate of 0.025 may be required for licensure.
4. If the estimated effectiveness is greater than 43.6 percent, consider the product effective with the strength of evidence of at least one-and-a-half Phase III studies (i.e., with a false-positive error rate of 0.0025).

*Note: The above-listed statements represent a decision guideline. The point estimates of microbicide effectiveness and associated false-positive error rates specified in the guideline are based on the assumptions related to study size in Section 7.3.2 and although every effort will be made to fulfill these assumptions, in the event that they are not borne out, alternative *p* values may be associated with observed point estimates. In this case action taken with regard to declaring effectiveness, seeking licensure, and/or planning further studies will be consistent with the intent of the guideline, but based on the actual point estimates and *p* values observed.*

The operating characteristics of this study are as follows:

- The false-positive rate of the screening procedure is low. If a candidate microbicide truly is ineffective (0% effect), there is only an 18 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.0025, a 2.2 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.025, and only a 0.25 percent chance of declaring the microbicide effective. If a candidate microbicide truly reduces risk by only 10 percent, there is a 31 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.0025, a 6.3 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.025, and only a 1.1 percent chance of declaring the microbicide effective.
- The false-negative rate of the screening procedure is low. If a candidate product truly reduces risk by 33 percent, there is a 12.5 percent chance of discarding the product from further testing, a 37.5 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.0025, a 30.1 percent chance of proceeding to a Phase III trial designed with a false-positive error rate of 0.025, and a 19.9 percent chance of declaring the microbicide effective.
- The power to provide a definitive result for a highly effective candidate product is high. If a product truly reduces risk by 50 percent then there is a 72.2 percent chance that the product would be declared effective and only a 0.49 percent chance it would be discarded from further testing.

Table 7-2 summarizes the probabilities (Pr) of each possible decision for a variety of true effectiveness (TE) levels comparing a candidate product to one of the control groups. Probabilities were calculated assuming asymptotic normality of the natural logarithm of the risk ratio.

Table 7-2
Probability of Outcomes Corresponding to the HPTN 035 Decision Guideline
for Various Levels of True Product Effectiveness

TE	Pr(estimated TE ≤ 15.3%)	Pr(15.3% < estimated TE ≤ 33%)	Pr(33% < estimated TE ≤ 43.6%)	Pr(43.6 < estimated TE)
0%	.792	.183	.022	.0025
5%	.713	.243	.038	.005
10%	.617	.309	.063	.011
15%	.507	.371	.100	.022
15.3%	.500	.375	.102	.023
20%	.390	.418	.149	.043
25%	.276	.434	.209	.081
30%	.175	.410	.270	.145
33%	.125	.375	.301	.199
35%	.097	.344	.316	.243
40%	.046	.249	.325	.381
43.6%	.023	.176	.301	.500
45%	.017	.150	.284	.549
50%	.005	.071	.202	.722
55%	.001	.025	.109	.866
60%	<.001	.006	.040	.954

In addition to the decision guidelines based on the estimated effectiveness of the candidate microbicides compared to each of the control groups, the estimated effectiveness of each candidate compared to each control group will be considered when determining the overall public health benefit of the candidate microbicides.

Secondary Analyses

The criteria and guidelines used in the primary analysis for defining a product as effective or harmful with regard to HIV infection also will be used in secondary analyses. Incidence rates of the infections other than HSV-2 listed in Section 7.2.2 and of pregnancy will be calculated. The effect of both BufferGel and PRO 2000/5 Gel (P) on the cumulative incidence of these outcomes will be determined using Anderson Gill Proportional Hazards models stratified by site and with robust variance estimates.

Similar analyses will be performed on the incidence of genital ulcer disease overall and on the incidence of ulcers for which no infectious etiology is identified via multiplex PCR. Prevalence of HSV-2 infection at study exit (among women who were HSV-2-seronegative at enrollment) will be analyzed using logistic regression. Product acceptability will be assessed by comparing adherence rates and reported acceptability across treatment groups using the Mann Whitney U test and Chi-square tests.

Note: Data on the incidence of chlamydia and gonorrhea infection will be collected throughout the study, however due to expected low incidence rates in some study sites, statistical power to detect differences in incidence rates across study treatment groups may be limited.

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent forms contained in Appendices VI-X — and any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the IRBs/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 study 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. In addition, the results of all DSMB reviews of the study will be provided to the IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, via the HPTN CORE, in accordance with the current DAIDS Protocol Registration Policy and Procedures Manual.

8.2 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. Study staff will document the informed consent process in accordance with the DAIDS Standard Operating Procedure for Source Documentation. Participants will be provided with copies of the informed consent forms if they are willing to receive them.

Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices VI-X, that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

In addition to the informed consent forms, Protocol Team members will work with study staff and community representatives to develop locally-appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at all study sites. Written educational materials as well as other more innovative approaches will be considered. The process and materials will be pilot tested prior to study start-up to ensure cultural appropriateness at each site.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process will specifically address the following topics of import to this study:

- The unknown safety and unproven efficacy of the study products.
- The need to practice safer sex behaviors regardless of study treatment group.
- The importance of participants in all four study groups to the success of the study.
- The importance of adherence to the study visit and procedures schedule.
- The potential medical risks of study participation (and what do if such risks are experienced).
- The potential social harms associated with study participation (and what do if such harms are experienced).
- The real yet limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

The informed consent process will include an assessment of each potential participant's understanding prior to enrollment and randomization of concepts identified by the Protocol Team as essential to the informed consent decision. Based on input from study site staff and community representatives, this assessment may take the form of a self-administered "quiz," interviewer-administered instrument (qualitative and/or quantitative) or other method. Regardless of method, participants who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study. For quality assurance purposes, similar assessments of participant understanding will be undertaken among a sub-sample of participants throughout the accrual period; results will be used to provide feedback and recommendations to the Protocol Team and relevant study site staff to optimize the informed consent process.

8.3 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. Based on the results of prior studies, study participants assigned to apply the candidate microbicides may experience the following:

- Vulvar ulceration, abrasion, erythema, burning, itching, and soreness.
- Vaginal ulceration, abrasion, erythema, bleeding, irritation, inflammation, burning, itching, soreness, and dryness.
- Increased vaginal discharge.
- Cervical ulceration, abrasion, ecchymosis, erythema, subepithelial and/or petechial hemorrhage, inflammation, and soreness.
- Dysuria and/or dyspareunia.
- Pelvic and/or abdominal pain.
- Nausea.
- Diarrhea.

In addition, both BufferGel and PRO 2000/5 Gel (P) may be contraceptive.

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.

Participants in sites requiring partner notification in response to diagnosed STD or HIV infection could have problems in their relationships with their sexual partners. Participants assigned to the study product groups also could have problems in their partner relationships associated with use or attempted use of the products. In addition, participants could misunderstand the current experimental status of the study gels (i.e., their unknown safety and unproven efficacy) and as a result increase their HIV risk behaviors while in the study.

As noted above, data on participant risk behaviors and the occurrence of other potential social harms will be collected from all participants on a quarterly basis. The Protocol Team will monitor trends in risk behaviors over time based on these data, as well as the occurrence of other potential social harms, and initiate any required follow-up action. This information also will be reported to the HPTN Study SMC and the DSMB.

8.4 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. Specifically, information learned in this study may lead to the development of a safe and effective vaginal microbicide that prevents HIV infection.

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.

8.5 Access to HIV-Related Care

8.5.1 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 in accordance with a standard study counseling manual, and will emphasize the unknown efficacy of the candidate microbicides in preventing HIV infection.

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.

8.5.2 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. For any participants found to be HIV-infected who also become pregnant during follow-up, every effort will be made to facilitate access to single-dose nevirapine (and/or other interventions) to reduce the probability of HIV transmission to the participant's infant.

8.6 Access to Effective Products

Should this study provide evidence of the effectiveness of BufferGel and/or PRO 2000/5 Gel (P) in preventing HIV infection, it will be critical to provide access to the effective product(s) to study participants, their communities, and the worldwide population at risk for HIV infection in a timely manner. In preparation for this study, representatives of DAIDS and the HPTN leadership have begun discussions with ReProtect and Indevus to ensure such access. Considerations under discussion include licensing agreements and preferred pricing arrangements for the study communities and other resource-poor settings.

While this study is ongoing, DAIDS and the HPTN will continue these discussions. In addition, discussions will be initiated with other public and private funding sources such as the WHO, UNAIDS, Gates Foundation, and appropriate site government agencies that may be able to purchase product supplies in bulk and offer them at low or no cost to the study communities and other resource-poor communities most in need of the product(s). Operations and marketing research also may be conducted to determine how best to package and distribute the products, and maximize their acceptability and use, in at-risk populations.

8.7 Confidentiality

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

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, 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 ReProtect, Inc. and Indevus Pharmaceuticals, Inc.
- Representatives of the HPTN CORE, SDMC, and/or Central Lab
- The US FDA and/or other (US and non-US) government and regulatory authorities
- Site IRBs/ECs

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

8.8 Incentives

Participants may 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 child care. Site-specific reimbursement amounts will be specified in the local study informed consent forms and approved by all responsible IRBs/ECs.

8.9 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.

8.10 Study Discontinuation

This study may be discontinued at any time by NIAID, the HPTN, the product manufacturers, the US FDA, other government or regulatory authorities, or site IRBs/ECs.

9 LABORATORY CONSIDERATIONS

9.1 Local Laboratory Specimens

The following types of specimens will be collected for testing at the local laboratory:

- Blood for complete blood count, liver and renal function testing, and coagulation testing
- Blood for HIV, HSV-2, and syphilis serology
- Blood for plasma archive
- Urine for pregnancy testing and chlamydia and gonorrhea SDA
- Vaginal smears for wet mount for BV, candidiasis, trichomoniasis
- Ecto- and endocervical specimens for Pap smear (at selected sites only)

The HPTN Central Lab has completed testing to confirm that the study gels, which may contaminate specimens collected for pregnancy, gonorrhea, and chlamydia testing, do not inhibit or otherwise interfere with the pregnancy test kits and SDA testing methodology selected for the study.

Each study site will adhere to standards of good clinical 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.

9.2 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

The HPTN Central Lab has completed testing to confirm that the study gels do not inhibit or otherwise interfere with the multiplex PCR testing methodology.

Each study site will adhere to standards of good clinical 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 International Air Transport Association specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the study-specific procedures manual.

9.3 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. In addition, the 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 study entry specimens from a 10 percent random sample of participants enrolled at each site for evidence of HIV infection using FDA-licensed tests. “Study entry” specimens are collected at participants’ Enrollment Visits. If any false-negative local lab results are identified, the Central Lab will test the study entry specimens from another 20 percent of enrolled participants 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 participants’ Enrollment Visits. “Seroconversion” specimens are collected at the time of specimen collection for confirmatory HIV testing, i.e., when “sample 2” in Appendix V 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. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For seroconverters, study entry specimens also will be tested by RNA PCR. If any false-negative or false-positive local lab antibody test results are identified, the Central Lab will test all study exit specimens from that site.

Central Lab staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing, on-site assessments, and/or confirmatory HIV testing.

9.4 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 9.3. In addition, study participants will be asked to provide written informed consent for additional plasma specimens to be collected at study entry and exit and 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.

9.5 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. All infectious specimens will be transported in accordance with applicable US regulations. Refer to individual carrier guidelines for specific instructions.

10 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

Following IRB/EC 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 site staff to complete DAIDS Protocol Registration procedures in accordance with the current DAIDS Protocol Registration Policy and Procedures Manual. Included in this step is CORE and DAIDS review of site-specific informed consent forms.

Pending successful protocol registration and submission of all other required study activation documents, HPTN 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.

10.2 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study (#62,366). Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to ReProtect and Indevus, for cross-referencing with the companies’ other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and each company.

Study implementation will be directed by this protocol as well as a common study-specific procedures manual. This manual — which will contain reference copies of the DAIDS SOPs for Source Documentation and Essential Documents, as well as the DAIDS SAE Reporting Manual for the HPTN and DAIDS Toxicity Tables — will outline procedures for conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. The manual will be available upon request to the FDA, other government and regulatory authorities, and site IRBs/ECs.

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 coordination between Protocol Team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, and CORE Protocol Specialist will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the HPTN SMC.

10.3 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 study counseling manual.
- 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, ReProtect, Indevus, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRBs/ECs and the DAIDS Regulatory Compliance Center prior to implementing the amendment.

10.5 Investigator's Records

The Investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study. In accordance with US regulations, for each of the two investigational products tested, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. 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 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.

10.6 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 submitted by the Protocol Team to the HPTN Manuscript Review Committee, DAIDS, and the product manufacturers for review prior to submission.

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Appendix I
HPTN 035 Phase II/Ib Accrual and Follow-up Plan and Timeline

Study Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19-30
No. Enrolled Per Month Non-US	70	105	140	140	175	175	175	175	175	175	175	175	175	175	175	175	175	170	0
No. Enrolled Per Month US	10	15	15	20	20	20	15	15	15	10	10	10	10	10	5	0	0	0	0
Total No. Enrolled Per Month	80	120	155	160	195	195	190	190	190	185	185	185	185	185	180	175	175	170	0
Cumulative No. Enrolled	80	200	355	515	710	905	1095	1285	1475	1660	1845	2030	2215	2400	2580	2755	2930	3100	3100
Cumulative No. Exposed (a)	43	108	190	276	379	483	582	682	781	877	972	1068	1163	1259	1350	1438	1525	1610	1610
Cumulative % Exposed (b)	3%	7%	12%	17%	24%	30%	36%	42%	49%	54%	60%	66%	72%	78%	84%	89%	95%	100%	100%
Phase II/Ib Screening	●—————▶																		
Phase II Enrollment	●—————▶																		
Phase II/Ib Follow-up									●—————▶										
Phase II Data Cleaning and DSMB Review										●—————▶									
Phase IIb Enrollment						●—————▶													
Phase IIb Follow-up							●—————▶												
Interim Phase IIb DSMB Reviews (c)																		●	●

(a) Refers to the total number of participants exposed to one of the two study investigational products, BufferGel and 0.5% PRO 2000/5 Gel (P).

(b) Refers to the percentage of participants exposed to one of the two study investigational products among those who will eventually be exposed over the course of the entire study

(c) Phase IIb are assumed to occur at least every six months after the Phase II data review, however the DSMB may request more frequent reviews.

Appendix II Schedule of Study Visits and Procedures for Phase II/IIb Participants

Procedure	Screening Part 1 (up to -30 days)	Screening Part 2 (up to -30 days)	Enrollment (day/month 0)	Monthly-Phase II (mo 1, 2)	Quarterly-Phase II (mo 3)	Monthly-Phase IIb (mo 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29)	Quarterly-Phase IIb (mo 6, 9, 15, 18, 21, 27)	Annually-Phase IIb (mo 12, 24)	Study Exit
Obtain informed consent	X	X	X						
Obtain demographic information	X								
Obtain/update locator information	X		X	X	X	X	X	X	X
Obtain behavioral eligibility information	X	X							
Provide HIV pre-test and post-test counseling	X	[X]		[X]	X	[X]	X	X	X
Provide HIV/STD risk reduction counseling	X			[X]	X	[X]	X	X	X
Obtain medical and menstrual history		X		X	X	X	X	X	X
Perform physical exam		X							
Perform pelvic exam:									
-naked eye exam of external genitalia		X		X	X	[X]	X	X	[X]
-speculum exam of vagina and cervix		X		X	X	[X]	X	X	[X]
-colposcopic exam ^a		X		X	X				
-vaginal pH		X		X	X	[X]	X	X	[X]
-dried smear for Gram staining/BV assessment at the HPTN CL		X		X	X	[X]	X	X	[X]
-wet mount for BV, candidiasis, trichomoniasis		X		X	X	[X]	X	X	[X]
-genital ulcer swab for multiplex PCR at the HPTN CL				[X]	[X]	[X]	[X]	[X]	[X]
-ecto- and endocervical cells for Pap smear ^b		X		[X]	[X]	[X]	X	[X]	[X]
Perform laboratory evaluations:									
-urine pregnancy test	X	X		X	X	X	X	X	X
-urine SDA for chlamydia and gonorrhea	X	[X]		[X]	[X]	[X]	[X]	X	X
-dipstick urinalysis/urine culture	[X]	[X]		[X]	[X]	[X]	[X]	[X]	[X]
-HIV serology (rapid EIA, WB when indicated)	X			[X]	X	[X]	X	X	X
-syphilis serology	X	[X]		[X]	[X]	[X]	[X]	X	X
-herpes simplex virus 2 serology ^c			X						X
-Pap smear interpretation ^b		X		[X]	[X]	[X]	X	[X]	[X]
-plasma archive ^d			X	[X]	[X]	[X]	[X]	[X]	X
-complete blood count ^e	X			X	X		X	X	X
-liver and renal function testing	X			X	X				
-coagulation testing ^e	X			X	X		X	X	X
Provide test results	X	X		X	X	[X]	X	X	X
Provide STD treatment	[X]	[X]		[X]	[X]	[X]	[X]	[X]	[X]
Obtain random assignment			X						
Provide study product and instructions for use			X	X	X	X	X	X	
Administer baseline behavioral risk assessment			X						
Administer follow-up behavioral risk, adherence, and social harms assessment					X		X	X	X
Administer acceptability assessment ^f					X				X
Administer unblinding assessment									X

[X] = if clinically indicated.

^aFor the first 250 participants enrolled across selected sites only.

^bPerformed at selected sites only, at study entry and at last scheduled quarterly visit, and additionally if clinically indicated.

^cPerformed in batches during the final year of study implementation on archived samples collected at enrollment and study exit.

^dPerformed at study entry, seroconversion (if applicable) and study exit.

^ePerformed at Screening Part 1 and Months 1-3 for all Phase II participants. Performed quarterly and at study exit for US participants only.

^fPerformed at Month 3 and study exit.

Appendix III
Schedule of Study Visits and Procedures for Phase IIb Participants

Procedure	Screening Part 1 (up to -30 days)	Screening Part 2 (up to -30 days)	Enrollment (day/month 0)	Monthly (mo 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29)	Quarterly (mo 3, 6, 9, 15, 18, 21, 27)	Annually (mo 12, 24)	Study Exit
Obtain informed consent	X	X	X				
Obtain demographic information	X						
Obtain/update locator information	X		X	X	X	X	X
Obtain behavioral eligibility information	X	X					
Provide HIV pre-test and post-test counseling	X	[X]		[X]	X	X	X
Provide HIV/STD risk reduction counseling	X			[X]	X	X	X
Obtain medical and menstrual history		X		X	X	X	X
Perform physical exam		X					
Perform pelvic exam:							
-naked eye exam of external genitalia		X		[X]	X	X	[X]
-speculum exam of vagina and cervix		X		[X]	X	X	[X]
-vaginal pH		X		[X]	X	X	[X]
-dried smear for Gram staining/BV assessment at the HPTN CL		X		[X]	X	X	[X]
-wet mount for BV, candidiasis, trichomoniasis		X		[X]	X	X	[X]
-genital ulcer swab for multiplex PCR at the HPTN CL				[X]	[X]	[X]	[X]
-ecto- and endocervical cells for Pap smear ^a		X		[X]	X	[X]	[X]
Perform laboratory evaluations:							
-urine pregnancy test	X	X		X	X	X	X
-urine SDA for chlamydia and gonorrhea	X	[X]		[X]	[X]	X	X
-dipstick urinalysis/urine culture	[X]	[X]		[X]	[X]	[X]	[X]
-HIV serology (rapid EIA, WB when indicated)	X			[X]	X	X	X
-syphilis serology	X	[X]		[X]	[X]	X	X
-herpes simplex virus 2 serology ^b			X				X
-Pap smear interpretation ^a		X		[X]	X	[X]	[X]
-plasma archive ^c			X	[X]	[X]	[X]	X
-complete blood count ^d					X	X	X
-coagulation testing ^d					X	X	X
Provide test results	X	X		[X]	X	X	X
Provide STD treatment	[X]	[X]		[X]	[X]	[X]	[X]
Obtain random assignment			X				
Provide study product and instructions for use			X	X	X	X	
Administer baseline behavioral risk assessment			X				
Administer follow-up behavioral risk, adherence, and social harms assessment					X	X	X
Administer acceptability assessment ^e					X		X
Administer unblinding assessment							X

[x] = if clinically indicated.

^aPerformed at selected sites only, at study entry and at last scheduled quarterly visit, and additionally if clinically indicated.

^bPerformed in batches during the final year of study implementation on archived samples collected at enrollment and study exit.

^cPerformed at study entry, seroconversion (if applicable), and study exit.

^dPerformed quarterly and at study exit for US participants only.

^ePerformed at Month 3 and at study exit.

Appendix IV
Safety Laboratory Evaluations to be Performed Among Phase II Participants
at Screening and at Study Months 1, 2, and 3

Hematology Tests

- Complete blood count

Liver Function Tests

- Alkaline phosphatase
- Alanine transaminase
- Aspartate aminotransferase
- Gammaglutamyl transaminase
- Total bilirubin

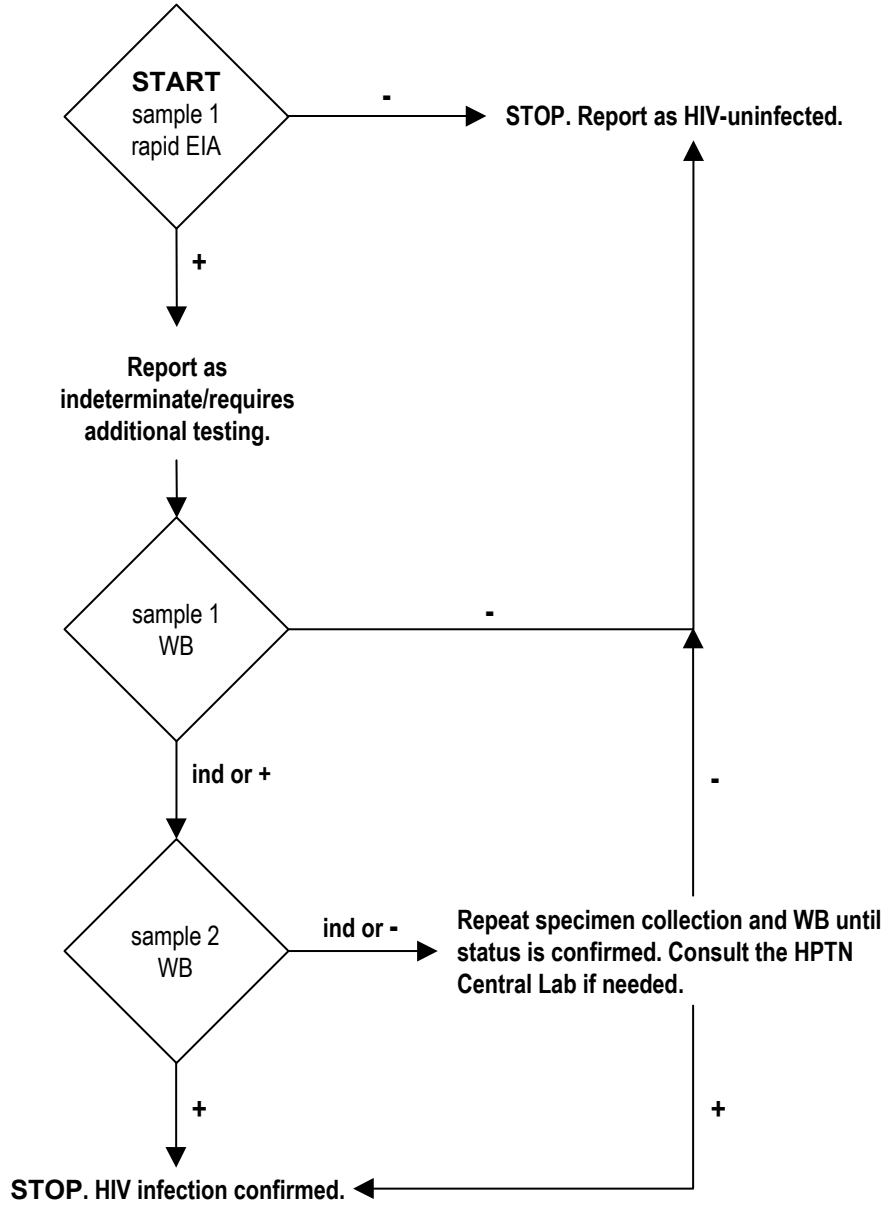
Renal Function Tests

- Blood urea nitrogen
- Creatinine

Coagulation Tests

- Activated partial prothrombin time
- Prothrombin time

Appendix V
HIV Antibody Testing Algorithm for Primary Endpoint Ascertainment at Follow-up Visits



EIA=enzyme immunoassay; WB=Western blot; +=positive; -= negative; ind=indeterminate

Appendix VI. Sample Informed Consent Form for Screening Phase II/IIb Participants

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

HPTN 035

Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women

Version 1.0
24 September 2003

SCREENING ONLY / PHASE II/IIb

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 Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or 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. The research study will find out if 2 gels protect women from getting HIV during sex. The gels are called “BufferGel” and “PRO 2000 Gel.” The United States National Institutes of Health is funding the study.

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 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 or make your mark on 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 the study is still open after your pregnancy, you can come back here to find out if you are eligible then.

If you are not pregnant, you will have counseling about HIV and other infections passed during sex. These infections are called syphilis, gonorrhea, and chlamydia. If you are having health problems that may be due to syphilis, gonorrhea, or chlamydia, 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 also 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. They also will do tests to find out how healthy your blood, liver, and kidneys are. 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 the infections at this visit.

If the tests of your blood, liver, and kidneys show that you might have some health problems, 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. Later, if the problems resolve, you can come back here to find out if you are eligible then.

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 the study is still open after your pregnancy, you can come back here to find out if you are eligible then.

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 test.” It takes about [x] weeks before Pap test results are available. We will give you the results as soon as they are available. The results of your Pap test may affect whether you can use the gels being tested in the research study. If the test shows a serious abnormality, you will be asked to stop using the gels until after you receive treatment and the abnormality has resolved.

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 resolved when you come back, you will be eligible for the research study.

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws:

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.

Risks of Genital Exams:

You may feel discomfort during the exam of your genital area and inside your vagina.

Other Possible Risks:

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, because of this, 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 have tests of your blood, liver, and kidneys. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].]

You will get counseling and testing for HIV. You will get free 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.

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:

- You are found to not be eligible for the study of BufferGel and PRO 2000 Gel.
- The research study of BufferGel and PRO 2000 Gel 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 visits or complete the screening tests.
- Other administrative reasons.

COSTS TO YOU

There is no cost to you for the screening tests. Treatments available to you from the study for infections passed during sex will be given to you free of charge.

REIMBURSEMENT

[*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

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

[US site only: insert this paragraph:] In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.

[All sites continue with this paragraph:] Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the companies that make the gels being tested in the research study

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 VII. Sample Informed Consent Form for Screening Phase IIb Participants

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

HPTN 035

**Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women**

**Version 1.0
24 September 2003**

SCREENING ONLY / PHASE IIb

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 Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or 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. The research study will find out if 2 gels protect women from getting HIV during sex. The gels are called “BufferGel” and “PRO 2000 Gel.” The United States National Institutes of Health is funding the study.

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 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 or make your mark on 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 the study is still open after your pregnancy, you can come back here to find out if you are eligible then.

If you are not pregnant, you will have counseling about HIV and other infections passed during sex. These infections are called syphilis, gonorrhea, and chlamydia. If you are having health problems that may be due to syphilis, gonorrhea, or chlamydia, 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 also 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. 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 the infections 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 the study is still open after your pregnancy, you can come back here to find out if you are eligible then.

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. 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 test.” It takes about [x] weeks before Pap test results are available. We will give you the results as soon as they are available. The results of your Pap test may affect whether you can use the gels being tested in the research study. If the test shows a serious abnormality, you will be asked to stop using the gels until after you receive treatment and the abnormality has resolved.

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 resolved when you come back, you will be eligible for the research study.

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws:

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.

Risks of Genital Exams:

You may feel discomfort during the exam of your genital area and inside your vagina.

Other Possible Risks:

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, because of this, 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. *[For selected sites only: If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].]*

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.

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:

- You are found to not be eligible for the study of BufferGel and PRO 2000 Gel.
- The research study of BufferGel and PRO 2000 Gel 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. Treatments available to you from the study for infections passed during sex will be given to you free of charge.

REIMBURSEMENT

[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

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

[US site only: insert this paragraph:] In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.

[All sites continue with this paragraph:] Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the companies that make the gels being tested in the research study

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 VIII. Sample Informed Consent Form for Enrolling Phase II/IIb Participants

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

HPTN 035

**Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women**

**Version 1.0
24 September 2003**

ENROLLMENT / PHASE II/IIb

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 is for women who could get Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or 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

The main purpose of this study is to find out if 2 gels can protect women from getting HIV during sex. The gels are called “BufferGel” and “PRO 2000 Gel.” They are inserted in the vagina before sex. Another purpose is to find out if there any bad effects when women use BufferGel and PRO 2000 Gel in the vagina.

BufferGel and PRO 2000 Gel are “experimental.” This means we do not know all the effects they may have. We do not know if they work to protect against HIV. This study is being done to find that out. Because the gels are experimental, the United States Food and Drug Administration (FDA) [and the local authority] [has/have] not approved them for use in the general community. The FDA has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

The United States National Institutes of Health is funding this study. About 3100 women from Africa, India, and the United States will be in the study. About [200/400] women will be in the study here at [study site]. The whole study will take about 3 years to finish. Each woman will be in the study for up to two-and-a-half (2½) years.

STUDY GROUPS

If you decide to take part in the study, you will be placed in 1 of 4 study groups. Women in 3 of the groups will get a study gel to insert in the vagina before sex. One group will get BufferGel. One group will get PRO 2000 Gel. One group will get a placebo gel. The placebo gel is a gel that looks and feels like BufferGel and PRO 2000 Gel, but it does not have the ingredients from BufferGel and PRO 2000 Gel that may protect against HIV. The fourth group will not get a gel.

The study group that you will be in will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin or throwing dice]. You cannot choose your group, and the study staff cannot choose your group for you. [*For Non-US Sites:* You have an equal chance of being placed in each group.] [*For the US Site:* You have an 8-out-of-10 chance of being placed in a group that will get either BufferGel or PRO 2000 Gel. You have a 1-out-of-10 chance of being placed in the group that gets the placebo gel and a 1-out-of-10 chance of being placed in the group that gets no gel.]

All 4 groups are very important to this study. Women in all groups will have the same study visits. All women will get condoms and counseling on how to avoid HIV and other infections passed during sex.

No matter what study group you are in, you must remember that we do not know if any of the study gels work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a condom every time you have sex.

If you are in one of the groups that gets a gel, neither you nor the study staff will know which gel you are getting. All the gels come in the same type of applicator. They all look and feel about the same. Within about six months after the end of the study, you will be able to find out which gel you got. Until then, no one will be told.

If you are in one of the groups that gets a gel:

- You will be given applicators containing the gel at each study visit. You can come back here to get more gel between visits if you need it.
- You will be given instructions on how to use the gel. For your safety, it is important that you only use the gel in your vagina, as instructed by the study staff.
- You will be asked to insert the gel in your vagina every time you have sex. You can have sex right after you insert the gel, or you can wait up to 1 hour.
- You will be asked not to give your gel to other women.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. You will find out which study group you will be in. 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 up to 2½ years, depending on when you join. You will have a study visit every month while you are in the study. These visits will take 30-90 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 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 new gel applicators (if you are in a gel group).
- 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.

In your first 3 visits, 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 abnormalities. The lens 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).
- Give 2 teaspoons [or local equivalent] of blood for tests of your blood, liver, and kidneys. The results of these tests will be available at your next visit.

Every 3 months (4 times per year), you also will:

- Have an exam of your genital area and inside your vagina. The study staff will collect fluid from your vagina with a swab to test for infections (trichomoniasis, candidiasis, and bacterial vaginosis). [*For selected sites only:* During your last genital exam you will have samples collected 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 test.” The study staff will make arrangements with you to give you your Pap test results when they are available.]
- Answer interview questions about your sexual practices.
- Answer interview questions about the study gel.
- Talk with study staff about ways to avoid HIV and other infections passed during sex.
- Talk with study staff about the HIV test and give about 1 teaspoon [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.
- [*For the US site only:* Give about 1 teaspoon [or local equivalent] of blood from your arm for tests of your blood cells and how well your blood clots.]

Every 12 months (once per year), you also will:

- Have a blood test for syphilis and a urine test for gonorrhea and chlamydia. Syphilis, gonorrhea, and chlamydia are infections passed during sex.

At your last study visit, you also will answer interview questions about your sexual practices and the study gel. You will have final tests for HIV, syphilis, gonorrhea, and chlamydia. The study staff will make arrangements with you to give you your test results when they are available.

If you decide to leave the study before your planned study end date, you will be asked to have a last study visit with all the exams and tests listed above.

At any time in the study, if the study staff think you may have become pregnant, you will give urine for a pregnancy test. Also, 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 any 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 necessary. They will either provide or refer you for medical care that you may need.

If the staff find that a study gel is causing you problems, they may ask you to stop using the gel, either for a short time or permanently. Even if you stop using the gel, you will be asked to stay in the study and have your monthly visits as originally planned.

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 and keep using the gel (if you are in a gel group). 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.

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

Other blood tests: At your last study visit, blood that is left over from your HIV test and other tests will be kept frozen here at the clinic. Leftover blood also will be kept if you become infected with HIV. Blood kept from your first and last study visits will be tested for herpes. Herpes is an infection passed during sex. Your blood also 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

Risks of Blood Draws:

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.

Risks of Genital Exams:

You may feel discomfort during the exams of your genital area and inside your vagina.

Risks of the Study Gels:

If you are in one of the study groups that will be using a gel, the gel could cause some bad effects. We do not yet know all the effects of the gels, but women who used the gels in other studies have had:

- redness, itching, burning, dryness, or other irritation of the genital area and vagina
- genital soreness or pain
- genital blisters or sores
- genital bleeding
- increased vaginal fluids or discharge
- difficulty or pain when urinating
- abdominal pain
- nausea or feeling sick to your stomach
- diarrhea

You could have these effects or other effects that we do not know about. It is unlikely that the study gels will be absorbed from your vagina into your blood. If this happens, we do not know if it might cause bad effects.

If the study gels cause genital sores, this could increase your risk of getting HIV and other infections passed during sex. Because of this, study staff will remind you of the importance of using condoms to protect against HIV.

Other Possible Risks:

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, because of this, 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.

If you are in one of the study groups that will be using a gel, using the gel could cause problems between you and your partner. For example, your partner could have questions about the gel and why you want to use it. If you have problems like this, study counselors are available to talk to you and your partner to try to help resolve the problems.

PREGNANCY

We do not know if BufferGel and PRO 2000 Gel have any effect on pregnancy. It is possible that both gels may prevent pregnancy.

We do not know if BufferGel and PRO 2000 Gel have any effect on the fetus of women who use the gels when pregnant. Because of this, pregnant women may not join this study. This also is why study participants must have pregnancy tests while in the study.

If you become pregnant during the study, the study staff will refer you to available sources of medical care and other services you or your baby may need. You will stop using the study gel, but keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. For example, we will not examine or collect fluids from your vagina after 24 weeks of pregnancy. If you have a baby, we will ask you to have a study visit after the birth, so that we can find out about the birth.

Depending on when you become pregnant, you may be able to start using the gel again after your pregnancy (if you are in a gel group). The study staff will talk more with you about this after your pregnancy.

BENEFITS

You may get no direct benefit from being in this study. **We do not know if BufferGel or PRO 2000 Gel work to protect against HIV.** You may not be placed in a group that gets BufferGel or PRO 2000 Gel. If you are placed in one of the gel groups, you will not know which gel you are getting. Because of this, study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV. This is true no matter what study group you are in.

You will get counseling and testing for HIV. You will have exams of your vagina and tests for infections passed during sex. You will get free condoms. You can bring your partner here for counseling and testing for HIV and other infections passed during sex. If you or your partner have infections passed during sex, other than HIV infection, you will get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

You will have tests of your blood, liver, and kidneys. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you.

[For selected sites only: If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].] If you have other health problems during the study, you will be referred for medical care 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

There are no gels known to protect against HIV during sex. **The only known way to protect against HIV during sex is to use a condom every time you have sex.**

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community 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 this study. Treatments available to you from the study for infections passed during sex will be given to you free of charge.

REIMBURSEMENT

[Sites to insert information about local incentives:]

You will receive [\$xx] for your time and effort at each scheduled study visit. You also will receive payment for the costs of [lost work, travel, and/or childcare] due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

[US site only: insert this paragraph:] In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.

[All sites continue with this paragraph:] Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the company that makes BufferGel (ReProtect)
- the company that makes PRO 2000 Gel (Indevus Pharmaceuticals)

RESEARCH-RELATED INJURY

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. You will have genital exams every 3 months. If you have any genital problems or other health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

[Sites to specify institutional policy:] If you are injured as a result of being in this study, 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 IX. Sample Informed Consent Form for Enrolling Phase IIb Participants

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

HPTN 035

**Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women**

**Version 1.0
24 September 2003**

ENROLLMENT / PHASE IIb

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 is for women who could get Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or 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

The main purpose of this study is to find out if 2 gels can protect women from getting HIV during sex. The gels are called “BufferGel” and “PRO 2000 Gel.” They are inserted in the vagina before sex. Another purpose is to find out if there any bad effects when women use BufferGel and PRO 2000 Gel in the vagina.

BufferGel and PRO 2000 Gel are “experimental.” This means we do not know all the effects they may have. We do not know if they work to protect against HIV. This study is being done to find that out. Because the gels are experimental, the United States Food and Drug Administration (FDA) [and the local authority] [has/have] not approved them for use in the general community. The FDA has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

The United States National Institutes of Health is funding this study. About 3100 women from Africa, India, and the United States will be in the study. About [200/400] women will be in the study here at [study site]. The whole study will take about 3 years to finish. Each woman will be in the study for up to two-and-a-half (2½) years.

STUDY GROUPS

If you decide to take part in the study, you will be placed in 1 of 4 study groups. Women in 3 of the groups will get a study gel to insert in the vagina before sex. One group will get BufferGel. One group will get PRO 2000 Gel. One group will get a placebo gel. The placebo gel is a gel that looks and feels like BufferGel and PRO 2000 Gel, but it does not have the ingredients from BufferGel and PRO 2000 Gel that may protect against HIV. The fourth group will not get a gel.

The study group that you will be in will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin or throwing dice]. You cannot choose your group, and the study staff cannot choose your group for you. [*For Non-US Sites:* You have an equal chance of being placed in each group.] [*For the US Site:* You have an 8-out-of-10 chance of being placed in a group that will get either BufferGel or PRO 2000 Gel. You have a 1-out-of-10 chance of being placed in the group that gets the placebo gel and a 1-out-of-10 chance of being placed in the group that gets no gel.]

All 4 groups are very important to this study. Women in all groups will have the same study visits. All women will get condoms and counseling on how to avoid HIV and other infections passed during sex.

No matter what study group you are in, you must remember that we do not know if any of the study gels work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a condom every time you have sex.

If you are in one of the groups that gets a gel, neither you nor the study staff will know which gel you are getting. All the gels come in the same type of applicator. They all look and feel about the same. Within about six months after the end of the study, you will be able to find out which gel you got. Until then, no one will be told.

If you are in one of the groups that gets a gel:

- You will be given applicators containing the gel at each study visit. You can come back here to get more gel between visits if you need it.
- You will be given instructions on how to use the gel. For your safety, it is important that you only use the gel in your vagina, as instructed by the study staff.
- You will be asked to insert the gel in your vagina every time you have sex. You can have sex right after you insert the gel, or you can wait up to 1 hour.
- You will be asked not to give your gel to other women.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. You will find out which study group you will be in. 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 up to 2½ years, depending on when you join. You will have a study visit every month while you are in the study. These visits will take 30-90 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 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 new gel applicators (if you are in a gel group).
- 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 (4 times per year), you also will:

- Have an exam of your genital area and inside your vagina. The study staff will collect fluid from your vagina with a swab to test for infections (trichomoniasis, candidiasis, and bacterial vaginosis). [*For selected sites only*: During your last genital exam you will have samples collected 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 test.” The study staff will make arrangements with you to give you your Pap test results when they are available.]
- Answer interview questions about your sexual practices.
- Answer interview questions about the study gel.
- Talk with study staff about ways to avoid HIV and other infections passed during sex.

- Talk with study staff about the HIV test and give about 1 teaspoon [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.
- *[For the US site only: Give about 1 teaspoon [or local equivalent] of blood from your arm for tests of your blood cells and how well your blood clots.]*

Every 12 months (once per year), you also will:

- Have a blood test for syphilis and a urine test for gonorrhea and chlamydia. Syphilis, gonorrhea, and chlamydia are infections passed during sex.

At your last study visit, you also will answer interview questions about your sexual practices and the study gel. You will have final tests for HIV, syphilis, gonorrhea, and chlamydia. The study staff will make arrangements with you to give you your test results when they are available.

If you decide to leave the study before your planned study end date, you will be asked to have a last study visit with all the exams and tests listed above.

At any time in the study, if the study staff think you may have become pregnant, you will give urine for a pregnancy test. Also, 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 any 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 necessary. They will either provide or refer you for medical care that you may need.

If the staff find that a study gel is causing you problems, they may ask you to stop using the gel, either for a short time or permanently. Even if you stop using the gel, you will be asked to stay in the study and have your monthly visits as originally planned.

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 and keep using the gel (if you are in a gel group). 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.

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

Other blood tests: At your last study visit, blood that is left over from your HIV test and other tests will be kept frozen here at the clinic. Leftover blood also will be kept if you become infected with HIV. Blood kept from your first and last study visits will be tested for herpes. Herpes is an infection passed during sex. Your blood also 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

Risks of Blood Draws:

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.

Risks of Genital Exams:

You may feel discomfort during the exams of your genital area and inside your vagina.

Risks of the Study Gels:

If you are in one of the study groups that will be using a gel, the gel could cause some bad effects. We do not yet know all the effects of the gels, but women who used the gels in other studies have had:

- redness, itching, burning, dryness, or other irritation of the genital area and vagina
- genital soreness or pain
- genital blisters or sores
- genital bleeding
- increased vaginal fluids or discharge
- difficulty or pain when urinating
- abdominal pain
- nausea or feeling sick to your stomach
- diarrhea

You could have these effects or other effects that we do not know about. It is unlikely that the study gels will be absorbed from your vagina into your blood. If this happens, we do not know if it might cause bad effects.

If the study gels cause genital sores, this could increase your risk of getting HIV and other infections passed during sex. Because of this, study staff will remind you of the importance of using condoms to protect against HIV.

Other Possible Risks:

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, because of this, 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.

If you are in one of the study groups that will be using a gel, using the gel could cause problems between you and your partner. For example, your partner could have questions about the gel and why you want to use it. If you have problems like this, study counselors are available to talk to you and your partner to try to help resolve the problems.

PREGNANCY

We do not know if BufferGel and PRO 2000 Gel have any effect on pregnancy. It is possible that both gels may prevent pregnancy.

We do not know if BufferGel and PRO 2000 Gel have any effect on the fetus of women who use the gels when pregnant. Because of this, pregnant women may not join this study. This also is why study participants must have pregnancy tests while in the study.

If you become pregnant during the study, the study staff will refer you to available sources of medical care and other services you or your baby may need. You will stop using the study gel, but keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. For example, we will not examine or collect fluids from your vagina after 24 weeks of pregnancy. If you have a baby, we will ask you to have a study visit after the birth, so that we can find out about the birth.

Depending on when you become pregnant, you may be able to start using the gel again after your pregnancy (if you are in a gel group). The study staff will talk more with you about this after your pregnancy.

BENEFITS

You may get no direct benefit from being in this study. **We do not know if BufferGel or PRO 2000 Gel work to protect against HIV.** You may not be placed in a group that gets BufferGel or PRO 2000 Gel. If you are placed in one of the gel groups, you will not know which gel you are getting. Because of this, study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV. This is true no matter what study group you are in.

You will get counseling and testing for HIV. You will have exams of your vagina and tests for infections passed during sex. You will get free condoms. You can bring your partner here for counseling and testing for HIV and other infections passed during sex. If you or your partner have infections passed during sex, other than HIV infection, you will get medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

[For selected sites only: If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].] If you have other health problems during the study, you will be referred for medical care 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

There are no gels known to protect against HIV during sex. **The only known way to protect against HIV during sex is to use a condom every time you have sex.**

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community 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 this study. Treatments available to you from the study for infections passed during sex will be given to you free of charge.

REIMBURSEMENT

[Sites to insert information about local incentives:]

You will receive [\$xx] for your time and effort at each scheduled study visit. You also will receive payment for the costs of [lost work, travel, and/or childcare] due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

[US site only: insert this paragraph:] In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.

[All sites continue with this paragraph:] Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the company that makes BufferGel (ReProtect)
- the company that makes PRO 2000 Gel (Indevus Pharmaceuticals)

RESEARCH-RELATED INJURY

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. You will have genital exams every 3 months. If you have any genital problems or other health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

[Sites to specify institutional policy:] If you are injured as a result of being in this study, 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 X. Sample Informed Consent Form for Specimen Storage
and Possible Future Research Testing**

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

HPTN 035

**Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P) for the Prevention of HIV Infection in Women**

Version 1.0

24 September 2003

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. You will be asked to sign or make your mark on this form to indicate whether you agree to have your blood stored and tested. You will be offered a copy to keep.

HOW WILL YOU GET THE BLOOD FROM ME?

The research 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. Any publication about the results of future tests will not use your name or identify you personally.

The researchers will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential, but absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

[US site only: insert this paragraph:] In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to yourself or others, they will be required to tell the proper authorities.

[All sites continue with this paragraph:] Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the company that makes BufferGel (ReProtect)
- the company that makes PRO 2000 Gel (Indevus Pharmaceuticals)

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