HIV Prevention Trials Network

CLARIFICATION #2

Protocol 032: Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

7 March 2002
IND # 62,366

Summary of Revisions

- Notations are added the protocol to clarify that study wash-out periods may be extended for reasons of convenience and enhancing adherence to the product use and evaluation schedule.

Implementation

The following modifications are made to the HPTN 032 protocol:

1. At the end of protocol Section 2.3, the following text is added:

   Note: Study washout periods also may be extended for convenience and/or enhancing adherence to the product use and evaluation schedule, e.g., to accommodate product use and visit scheduling around vacations or other time away from the study site.

2. At the end of protocol Section 5.5, the following text is added:

   Note: Study washout periods also may be extended for convenience and/or enhancing adherence to the product use and evaluation schedule, e.g., to accommodate product use and visit scheduling around vacations or other time away from the study site.

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

A Study of the HIV Prevention Trials Network

Sponsored by:

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

IND # 62,366

Protocol Chair:

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FINAL Version 2.0
20 August 2001

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ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
CORE	Coordinating and Operations Center
DAIDS	Division of AIDS
FDA	(United States) Food and Drug Administration
g	gram
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IRB	Institutional Review Board
LE	Leukocyte esterase
mL	Milliliter
mM	Millimolar
M_w	Weight-average molecular weight
M_w/M_n	Polydispersity
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
ROC	Regulatory Operations Center
SAE	Serious adverse event
SDMC	Statistical and Data Management Center
STD	Sexually transmitted disease
US	United States
w/w	Weight to weight

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

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HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS (DAIDS)
US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institutes of Health (NIH)

I, the Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol and will comply with all requirements regarding the obligations of clinical investigators as fully outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for a minimum of two years after FDA clearance or until DAIDS/NIAID/NIH and pharmaceutical co-sponsor(s) advise that it is no longer necessary. Publication of the results of this study will be governed by DAIDS and HPTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to DAIDS, the HPTN Manuscript Review Committee, and the pharmaceutical 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 Principal Investigator

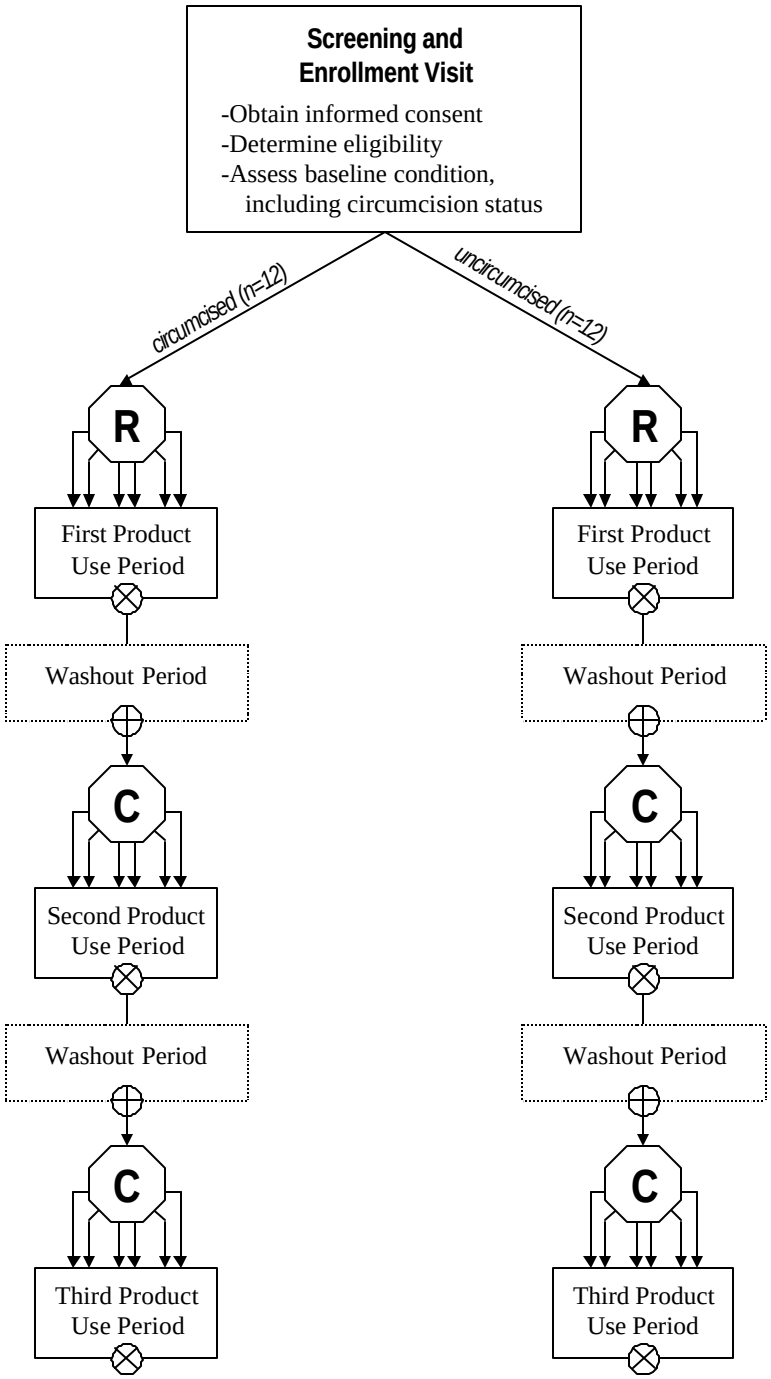
_____ _____
Signature of Principal Investigator **Date**

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

PROTOCOL SUMMARY

Design:	Phase I, randomized, blinded, crossover study with one week of exposure to each of two investigational products and one placebo control. Each week of exposure will be separated by a minimum one-week washout period.
Population:	24 HIV-infected men, half of whom will be uncircumcised.
Intervention:	Nightly application of 2 mL of BufferGel, PRO 2000/5 Gel (P), or placebo gel for a period of seven consecutive nights each. Gel will be applied to the shaft and glans of the penis at bedtime, left on for a minimum of six hours, and washed off the next morning.
Study Duration:	Accrual will require approximately three months. Each participant will take part in the study for a minimum of five weeks. Therefore the entire study should be completed within six months.
Primary Objective:	To assess the toxicity of BufferGel and PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa of HIV-infected men.
Primary Endpoints:	(1) Participant reports of urethral pain, urethral burning, penile itching, penile rash, or penile ulceration. (2) Erythema (with or without induration), vesiculation, bullous reaction, and ulceration, of the penile shaft, foreskin, or glans, as observed by visual exam. (3) Erythema or ulceration of the urethral meatus, as observed by visual exam. (4) Positive (i.e., greater than trace) urine leukocyte esterase test.
Secondary Objective:	To assess the acceptability of BufferGel and PRO 2000/5 Gel (P) among HIV-infected men.
Secondary Endpoints:	(1) Adverse events others than those listed as primary endpoints judged related to product use. (2) Reported positive attributes of the study products. (3) Reported negative attributes of the study products. (4) Reported willingness to use the study products for sexual intercourse.

SCHEMA



Notes: R = random assignment to product use sequence; C = crossover to next assigned product.
⊗ =post-use safety and acceptability assessment; ⊕ = re-screening eligibility assessment.

1 INTRODUCTION

1.1 Background and Prior Research

The Joint United Nations Programme on HIV/AIDS recently estimated that 36.1 million adults and children were living with HIV/AIDS at the end of 2000, and that about 15,000 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 male condom use has been shown to prevent HIV transmission [2], but women often are unable to negotiate the use of condoms by their male partners [3-5]. The female condom has been marketed as an alternative barrier method [4], but use of this device 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 prevention 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. Most notable among these is nonoxynol-9, which has been evaluated in several different doses and formulations. However, no clinical studies have yet demonstrated that these detergent-based products can prevent HIV infection, nonoxynol-9 products have been shown to cause mucosal erosion and ulceration in a dose-dependent manner [7-8], and the results of a large-scale clinical trial presented at the XIII International AIDS Conference indicated that use of nonoxynol-9 gel was associated with an increased risk of HIV infection, and afforded no protection against other STDs [9].

Particularly in light of the most recent findings with respect to the effects of nonoxynol-9 products, increasing attention has been given to developing non-detergent topical microbicides to prevent HIV infection. Two such products are BufferGel, developed by Reprotect, LLC, and PRO 2000/5 Gel (P), developed by Procept, Inc. and acquired recently by 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. PRO 2000/5 Gel (P) is designed to protect against HIV infection by inhibiting viral entry into susceptible cells.

BufferGel and PRO 2000/5 Gel (P) currently are not approved by the US Food and Drug Administration (FDA) for any use. However, both products have undergone extensive pre-clinical testing, both have been shown to inhibit/ inactivate HIV in vitro, and both are compatible with condoms. Both products also have undergone clinical testing in Phase I trials among healthy HIV-uninfected sexually abstinent and sexually active women. PRO 2000/5 Gel (P) also has been tested among HIV-infected women. In these studies, the products were shown to be safe and acceptable for vaginal use [10-13].

Phase I trials also have been conducted to assess the safety of BufferGel and PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa. In one trial, HIV-uninfected men applied either 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 three users of the active gel and one in four users of the inactive gel reported mild symptoms of genital itching, tingling, irritation, dryness, discoloration, or flaking of the dried gel. In a similar trial 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.

1.2 Rationale

Given the favorable pre-clinical and clinical results noted above, the HIV Prevention Trials Network (HPTN) currently is planning a large-scale Phase III trial of both BufferGel and PRO 2000/5 Gel (P). This study will enroll women at high risk for HIV infection who will be instructed to use a trial product — BufferGel, PRO 2000/5 Gel (P), or placebo gel — for all acts of sexual intercourse while they are in the study. Although participants also will be counseled to use condoms consistently and correctly throughout the study, they may not be able to negotiate condom use for all sex acts. As a result, at least some male partners of some participants will be exposed to an investigational product during the Phase III study.

Although the typical clinical development pathway for vaginal products (e.g., topical contraceptives) historically has not included safety evaluations among men — due to the more intense dose and exposure time for women who apply these products vaginally, and the greater vulnerability of the cervical and vaginal epithelium compared to the cornified squamous epithelium of the penis — recent efforts to articulate the most appropriate clinical development pathway for topical microbicides have specified that Phase I studies be conducted among men along with Phase I studies among women. The objective of the Phase I studies among men is to determine whether the frequency and severity of adverse events experienced by men is comparable to that observed among women. Provided the frequency and severity is comparable to (or less than that) observed among women, expanded safety and effectiveness trials would then be conducted among women without the direct involvement of their sexual partners as study participants.

This study serves the purpose of extending the Phase I safety profile of BufferGel and PRO 2000/5 Gel (P) to HIV-infected men. It is not known whether the safety of the products will differ for HIV-infected versus HIV-uninfected men. Although no differences are expected a priori, it is possible that other dermatologic conditions affecting the penis of HIV-infected men could affect the safety profile. As in the prior Phase I studies among HIV-uninfected men, this study will include both circumcised and uncircumcised men, since the thinner stratified epithelium on the glans of uncircumcised men, together with the potential for topical products to be "trapped" under the foreskin, could result in different safety profiles for circumcised and uncircumcised men.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

To assess the toxicity of BufferGel and PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa of HIV-infected men.

2.2 Secondary Objective

To assess the acceptability of BufferGel and PRO 2000/5 Gel (P) among HIV-infected men.

2.3 Study Design

This is a Phase I, randomized, blinded, crossover study to be conducted among 24 HIV-infected men residing in the Seattle, WA, area. Half of the 24 participants will be circumcised and half will be uncircumcised. The study design is summarized in the Schema above and the Schedule of Events in Appendix I. Participants will complete three weeks of nightly product application — one week each of BufferGel, PRO 2000/5 Gel (P), and placebo gel — with a one-week washout period between product use periods.

After providing written informed consent, potential study participants will undergo eligibility screening, including medical history, directed physical exam, genital exam, and urine testing. Eligible participants will be assigned at random to one of six possible sequences of product use (e.g., BufferGel followed by placebo gel followed by PRO 2000/5 Gel (P)). Two randomization schedules will be used to ensure balanced assignment among circumcised and uncircumcised men.

Following randomization, participants will be provided with

- seven days worth of the first product in their assigned sequence;
- study diaries on which to record the date and time of product application and removal, as well as any symptoms experienced and/or medications taken; and
- verbal and written instructions for product application and diary completion.

Participants also will receive verbal and written instructions to contact the site to report symptoms and/or discuss any concerns or questions they may have. Throughout the study, interim visits will be conducted as needed to evaluate reported symptoms.

Participants will apply the first assigned product to the penis once nightly. They then will complete a follow-up evaluation on study Day 7. The evaluation will consist of a medical history, review of the participant's study diary, genital exam, and urine testing. Adherence to the product application regimen will be assessed by reviewing participants' study diaries, observing the quantity of used and unused product supplies returned to the study site, and discussing participants' experiences. The occurrence of adverse events during the product use period will be ascertained by reviewing participants' study diaries and obtaining a clinical history since the last visit. Participants will complete a self-administered questionnaire to assess product acceptability.

Participants then will undergo a one-week washout period during which no study products will be applied. On study Day 14, participants will complete a re-screening evaluation to confirm their willingness to continue in the study as well as confirm the absence of exclusionary conditions (see Section 3.2). Participants who are free of such conditions will be provided with seven days worth of the second product in their assigned sequence, study diaries, and instructions. They then will apply the second assigned product once nightly and complete a follow-up evaluation identical to that described above on study Day 21. Participants who do not meet the eligibility criteria will be asked to extend the washout period until any exclusionary conditions resolve, and only then begin application of the second product.

After completing application and evaluation of the second product, participants will undergo another one-week washout period. On study Day 28, participants will complete a re-screening evaluation to confirm their willingness to continue in the study as well as confirm the absence of exclusionary conditions. Participants who are free of such conditions will be provided with seven days worth of the third product in their assigned sequence, study diaries, and instructions. They then will apply the third assigned product once nightly and complete a final follow-up evaluation on study Day 35. As was the case above, participants who do not meet the eligibility criteria on Day 28 will be asked to extend the washout period until any exclusionary conditions resolve, and only then begin application of the third product.

3 STUDY POPULATION

Twenty-four HIV-infected men — 12 circumcised and 12 uncircumcised — will be included in this study. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be recruited as described in Section 3.3 and assigned to a study product group as described in Section 7.3. Conditions for withdrawal from the study are described in Section 3.4.

3.1 Inclusion Criteria

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

- Age 18 years and older.
- HIV-infected, as documented by licensed ELISA/Western blot, HIV PCR, and/or bDNA test results recorded in medical records.

  Note: If an HIV diagnosis based on at least one of the above-listed tests cannot be documented with the participant's medical records, study staff will obtain written informed consent and perform HIV counseling and testing (licensed ELISA/Western blot) to confirm the diagnosis prior to enrolling the participant in the study.

- Most recent CD4 cell count greater than 200, as documented by medical records dated within the year prior to enrollment or, if medical records are not available, based on participant self-report.
- Able and willing to communicate in English.
- Able and willing to provide written informed consent to take part in the study.
- Able and willing to provide adequate information for locator purposes (as defined by local site standard operating procedures).

- Able and willing to abstain — during the three seven-day product use periods — from application of topical products other than the study products to the penis.

- Able and willing to abstain — during the three seven-day product use periods — from sexual intercourse, masturbation, and other activities that may cause penile irritation or injury.

3.2 Exclusion Criteria

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

- Ever (based on participant self-report):
    - History of allergy to any component of the study products (see Section 4.3).
    - History of recurrent or persistent non-gonococcal urethritis.
    - History of penile contact dermatitis, eczema, psoriasis, severe seborrheic dermatitis, other dermatological condition or medical problem that, in the opinion of the Investigator, would make participation in the study unsafe or complicate interpretation of study outcome data.
- In the last six months (based on participant self-report):
    - Occurrence of any non-HIV STD, including a genital herpes outbreak.
- In the last 30 days (based on participant self-report):
    - Modification of HIV treatment regimen.
    - Participation in any other study of an investigational product.
- At the time of study screening:
    - Penile piercing observed on genital exam.
    - Current signs or symptoms of an STD.
    - Current use of any medication that, in the opinion of the Investigator, would make participation in the study unsafe or complicate interpretation of study outcome data.

- Any abnormal physical or genital exam finding that, in the opinion of the Investigator, would make participation in the study unsafe or complicate interpretation of study outcome data.

- Positive (i.e., greater than trace) urine leukocyte esterase (LE) test.

3.3 Participant Recruitment

Study participants will be recruited primarily from the Harborview Medical Center Madison Clinic, where over 900 HIV-infected persons receive medical care. The study site partially funds the salary of a full-time research nurse who functions as a recruitment specialist and provides a consistent presence at the clinic. This nurse will approach potential study participants on a one-on-one basis at the clinic and use a screening form to help her describe study objectives and requirements, and to determine eligibility for the study. This approach has been extremely effective in triaging and screening HIV-infected participants patients from the Madison Clinic for participation in epidemiologic, prevention, therapeutic, and pathogenesis studies.

If needed, to augment the primary approach just described, participants may be recruited for this study through local health care providers with a large volume of HIV-infected patients. Participants excluded from other HPTN studies due to HIV infection also may be recruited. Participants also may be sought through advertising (posters, brochures, and postings on the site's HPTU website), announcements in newsletters distributed to participants in previous studies, and outreach at venues frequented by men who have sex with men.

Site staff will meet at least weekly to discuss current recruitment status, targets, and strategies. Staff also will follow-up with all persons who express an interest in the study to ensure that screening appointments are scheduled and carried out in a timely manner.

3.4 Participant Withdrawal

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain him for the entire five-week study period. Given the small study sample size, and the importance of ascertaining all safety outcomes among study participants, 100 percent retention of enrolled participants is targeted. Study site staff are responsible for developing and implementing local standard operating procedures to achieve complete follow-up.

However, participants may withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety (e.g., due to intolerance of the study products or development or exacerbation of a concomitant medical condition) and/or if they are unwilling or unable to comply with required study procedures. In particular, participants who experience vesiculation, bullous reaction, or ulceration, or are diagnosed with a confirmed STD, will be followed until the condition resolves and then will be withdrawn from the study (see Appendix III). Participants who voluntarily withdraw from the study, are withdrawn by the Investigator, or are not adherent to the study product application regimen, as defined in Section 4.5, will be replaced.

Participants also may be withdrawn if the study sponsor or regulatory authorities terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to Day 35, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4 STUDY TREATMENTS

4.1 Study Product Regimens, Administration, Duration, and Dispensation

4.1.1 Product Regimens

Study participants will be assigned at random to one of six possible sequences using each of the three study products: BufferGel, PRO 2000/5 Gel (P), and placebo gel.

Two randomization schedules will be used to ensure balanced assignment among circumcised and uncircumcised men (see also Section 7.3). Participants will apply each of the three study products for one week, with a minimum one-week washout period between product use periods. For each application of each product, participants will dispense 2 mL from a 5 mL amber-colored topical syringe pre-filled by the study site pharmacist. Participants will be given detailed verbal and written instructions for proper application of study products.

4.1.2 Product Administration and Duration

Participants will apply the first assigned study product to the penis once nightly for seven nights, beginning on Day 0. The pre-measured 2 mL dose will be applied onto the dorsal aspect of the penis and then spread manually to coat all surfaces except the scrotum. Uncircumcised men will retract the foreskin, coat the glans, and replace the foreskin. Participants will allow the product to air dry at least 5-10 minutes, or until they are comfortable coming into contact with clothing, pajamas, sheets, etc. Participants will leave the product in place overnight (6-10 hours) and then wash it off with water and their usual soap the next morning (e.g., during the participant's morning shower). Participants will undergo post-exposure evaluations after seven days of product use.

Participants then will undergo a minimum one-week washout period during which no study product will be applied. Participants will be instructed that during this period they may engage in masturbation and/or sexual intercourse, however they still are requested to contact the study site to ask questions about the study and/or report any symptoms they may have.

On study day 14, after participants are re-screened for continued eligibility, they will receive the second assigned study product, and begin application of that product, in the same manner as the first product, once nightly for seven nights. Participants will undergo post-exposure evaluations after seven nights of product use.

Participants then will undergo another minimum one-week washout period. On study day 28, after participants are again re-screened for continued eligibility, they will receive the third assigned study product, and begin application of that product, in the same manner as the first and second products, once nightly for seven nights. Participants will undergo post-exposure evaluations after seven nights of product use.

4.1.3 Product Dispensation

A new prescription will be required after each screening — on days 0, 14, and 28 — in order for the site pharmacist to dispense each assigned study product to participants.

4.2 Study Product Preparation for Topical Administration

The site pharmacist will pre-fill seven 5 mL amber-colored topical syringes with 2 mL of study product, and assemble them as a one-week supply for each participant. The syringes must be stored at room temperature, and will be given a 30-day expiration date.

4.3 Study Product Formulations

4.3.1 BufferGel

The active ingredient of BufferGel is the hydrogen ion. 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). Hydrogen ions are buffered (released or bound) by abundant carboxyl groups on the carbopol 974P polymer which constitutes the major nonaqueous component (4 percent polymer, 94 percent water) of BufferGel. 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. BufferGel is supplied in 100 gram tubes, and must be stored at room temperature.

4.3.2 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 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), 4%, is an aqueous gel formulation containing four percent (w/w) PRO 2000/5, Carbopol 1382, lactic acid, trolamine, methylparaben, propylparaben, and sodium benzoate. It is buffered to pH 4.5. PRO 2000/5 Gel (P) is supplied in 3.7 gram tubes, and must be stored below 35° C.

4.3.3 Placebo Gel

The placebo gel is K-Y Jelly, a licensed, commercially available water-based lubricant that contains chlorhexidine gluconate and methylparaben as preservatives as well as glucono delta lactone, glycerine, hydroxyethylcellulose, purified water, and sodium hydroxide. It should be stored at room temperature.

4.4 Study Product Supply, Acquisition, and Accountability

4.4.1 Product Supply

BufferGel will be provided by ReProtect, LLC. PRO 2000/5 Gel (P) will be provided by Interneuron Pharmaceuticals, Inc. The placebo gel must be purchased by the study site pharmacy from a commercial vendor.

4.4.2 Product Acquisition

BufferGel, PRO 2000/5 Gel (P), and syringes for topical administration will be made available to the study site through the NIAID Clinical Research Products Management Center. The site pharmacist will obtain these products from the Clinical Research Products Management Center according to the instructions in the manual "Pharmacy Guidelines and Instructions for AIDS Clinical Trials Group," in the section entitled "Investigational Agent Control." The study site will purchase the placebo gel from a commercial vendor.

4.4.3 Product Accountability

The site pharmacist must maintain complete records of all study products agents received from the NIAID Clinical Research Products Management Center and subsequently dispensed to study participants. Supplies of the placebo gel also must be accounted for in a similar manner. All unused BufferGel, PRO2000 Gel (P), and syringes must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated.

4.5 Adherence Assessment

Participants will record in their study diaries the date and time of each product application, as well as the date and time at which each application is washed off. The diaries also will collect information on participant compliance with other protocol requirements (e.g., abstinence from sexual intercourse). Participants will return all used and unused product syringes to the study site at their Day 7, 21, and 35 visits. At these visits, Study staff will assess adherence with the study product use regimen by reviewing the study diaries, counting the number of used and unused syringes, and discussing participants' experiences.

Application of all three study products on all seven consecutive assigned nights will be targeted, however lapses of product use on one or two assigned nights will be accommodated, as follows:

- Participants who miss one application will be instructed to complete the remaining application on the night following the seventh assigned night, and then to present for their post-use evaluation visit. In such cases, participants will have completed at least one consecutive nightly application immediately prior to the evaluation.

- Participants who miss two applications will be instructed to complete two applications on the two consecutive nights following the seventh assigned night, and then to present for their post-use evaluation visit. In such cases, participants will have completed at least two consecutive nightly applications immediately prior to the evaluation.

  Note: In some cases, this scenario may result in participants completing a total of eight product applications; additional product supplies will be provided to participants as needed.

Participants who complete seven applications of each product on seven consecutive nights, or adhere to the two scenarios just described, will be considered "adherent" to the product use regimen. In addition to the above, participants who experience an adverse event (AE) that requires product discontinuation (see Appendix III), but apply study products on all nights prior to experiencing the AE also will be considered "adherent" to the product use regimen.

Although all available outcome data from all enrolled study participants will be included in study data analyses, all "non-adherent" participants will be withdrawn from the study, and one additional participant will be enrolled in the study for each participant who either drops out of the study or is withdrawn due to "non-adherence." As such, all analyses will include at least 24 "adherent" participants.

Note: Participants will not routinely be withdrawn from the study due to intermittent non-compliance with other protocol requirements (e.g., abstinence from sexual intercourse), provided they are willing to try to become compliant for the remainder of the study.

4.6 Toxicity Management

Participants will be instructed to report all AEs to study staff at the time of AE onset. Participants who report AEs deemed by the study clinician — based on the participant's description — to be associated with use of study products will be instructed to wash off the product with plain warm water and to present to the study site for an in-person evaluation (except in potential emergency situations, in which participants will be instructed to present to an emergency room). Based on the results of this evaluation, the Investigator will recommend either continuation or discontinuation of product use, consistent with the criteria in Appendix III. The investigator also may prescribe or recommend the use of medications or other preparations to treat the AE.

Participants who discontinue use of one study product due to an AE — other than vesiculation, bullous reaction, ulceration, or confirmed STD — will not routinely be withdrawn from the study. In consultation with the Protocol Clarifications Team (see Section 10.1) the Investigator will judge whether the participant should continue product use and/or be "crossed over" and, following a washout period, begin use of the other study product(s). Participants who experience vesiculation, bullous reaction, or ulceration, or are diagnosed with a confirmed STD, will be followed until the condition resolves and then will be withdrawn from the study. All AEs will be followed and reported as described in Section 6.

4.7 Concomitant Medications

Enrolled participants may continue use of all concomitant medications — except exclusionary topical preparations applied to the penis — during this study. All concomitant medications will be recorded on applicable study case report forms. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable case report forms.

5 STUDY PROCEDURES

5.1 Pre-Screening

If desired, study staff may pre-screen potential study participants for the study by telephone or in-person at off-site locations. During these interactions, study staff may explain the study (including the requirements to abstain from masturbation and sexual intercourse during product use periods) to participants and ascertain presumptive eligibility, to be confirmed at a Screening and Enrollment Visit at the study site. Sensitive pre-screening data may be recorded and stored at the study site in the absence of written informed consent, provided that the information is collected in such a manner that it cannot be linked to participant identifiers.

5.2 Screening and Enrollment Visit (Day 0)

Note: If required, the procedures specified below may be completed over the course of two or more visits. Study documentation should specify the dates upon which each procedure is performed, and the final visit should be treated as "Day 0." The timeframes for eligibility determination specified in Section 3 are relative to Day 0.

- Confirm participant identity and assign Participant ID number.
- Explain the purpose of the visit and the informed consent and eligibility determination processes.
- Obtain written informed consent.

- Collect participant contact and locator information.
- Administer Demographics Form.
- Obtain medical history.
- Obtain written permission to obtain medical records documenting HIV status and most recent CD4 count.
- Assess vital signs and perform symptom-directed physical exam.
- Perform genital exam, including visual inspection of the penile shaft, foreskin, and glans; use hand held lens to examine any observed abnormalities. Take digital photograph of any observed abnormalities, and of normal area(s) if needed for clinical decision-making and/or documentation purposes.
- Collect urine and perform dipstick urine LE test.
- Determine eligibility based on medical history, exam findings, and urine test results.

  ⇒ If the participant **does not** meet the study eligibility criteria, he is ineligible; **discontinue** participation.

  ⇒ If the participant **does** meet the study eligibility criteria, **proceed** with the following:

  - Obtain the next sequential randomization envelope and determine the participant's random assignment.
  - Provide the participant with the first assigned study product, a study diary, and verbal and written instructions for their use.
  - Instruct the participant to abstain from sexual intercourse, masturbation, and other activities that may cause penile irritation or injury.
  - Provide contact information and instruct the participant to contact the study site to ask questions and/or report any symptoms they may have during the study period.
  - Schedule Day 7 Post-Use Evaluation Visit.
  - Complete and submit all required data collection forms.

5.3 Reminder Contacts (Days 5-6, 12-13, 19-20, 26-27, and 33-34)

- Contact the participant by telephone, fax, and/or e-mail to remind him of his next scheduled visit, and to bring all required materials to the visit (used and unused product syringes, study diary, concomitant medication bottles, etc).

5.4 Post-Use Evaluation Visits (Days 7, 21, and 35)

- Confirm participant identity and verify Participant ID number.
- Update locator information.
- Collect used and unused product syringes, review the participant's diary and obtain a medical history to assess adherence with all protocol requirements and determine whether any AEs were experienced during the product use period.
- Perform genital exam, including visual inspection of the penile shaft, foreskin, and glans; use hand held lens to examine any observed abnormalities. Take digital photograph of any observed abnormalities, and of normal area(s) if needed for clinical decision-making and/or documentation purposes.
- Collect urine and perform dipstick urine LE test.
- If any AEs are observed/reported, assess the reported events clinically and provide or refer the participant to appropriate medical care; follow and report on all AEs as described in Section 6.
- Administer Acceptability Assessment.
- Schedule next visit (i.e., Day 14 or Day 28 Post-Washout/Pre-Product Use Visit) and provide instructions for washout period *(not applicable on Day 35).*
- Complete and submit all required data collection forms.

5.5 Post-Washout/Pre-Product Use Visits (Days 14 and 28)

- Confirm participant identity and verify Participant ID number.
- Update locator information.
- Obtain medical history since last visit (i.e., since Day 7 or Day 21).

- Perform genital exam, including visual inspection of the penile shaft, foreskin, and glans; use hand held lens to examine any observed abnormalities. Take digital photograph of any observed abnormalities, and of normal area(s) if needed for clinical decision-making and/or documentation purposes.

- If any AEs are observed/reported, assess the reported events clinically and provide or refer the participant to appropriate medical care; follow and report on all AEs as described in Section 6.

- Collect urine and perform dipstick urine LE test.

- Determine eligibility to begin next product use period based on medical history, exam findings, and urine test results.

  ⇒ If the participant **does not** meet the eligibility criteria, extend washout period and schedule another Post-Washout/Pre-Product Use Visit.

  ⇒ If the participant **does** meet the eligibility criteria, **proceed** with the following:

  - Provide the participant with next assigned product, a study diary, and verbal and written instructions for their use.

  - Instruct the participant to abstain from sexual intercourse, masturbation, and other activities that may cause penile irritation or injury.

  - Reinforce contact information and instructions to contact the study site to ask questions and/or report symptoms.

  - Schedule next visit (i.e., Day 21 or Day 35 Post-Use Evaluation Visit).

  - Complete and submit all required data collection forms.

5.6 Unblinding Contact

After all participants have completed the study, and analyses of study data have been completed, the SDMC will provide the Investigator with information on the product use sequence assigned to each participant. If desired by individual participants, site staff may then contact participants (e.g., by phone, fax, e-mail, in-person visit) to inform them of the product use sequence to which they were assigned.

5.7 Interim Contacts and Visits

Interim contacts and visits may be performed at participant request at any time during the study. All interim contacts and visits must be documented in participants' study records and on applicable case report forms. When interim contacts or visits are conducted in follow-up to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care; all AEs will be followed and reported as described in Section 6.

6 ADVERSE EVENT REPORTING REQUIREMENTS

Study participants will be provided with 24-hour contact information and instructions to contact the study clinician to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Study clinicians will instruct participants who report AEs associated with the use of study product to wash off the product with warm water and — depending on the severity of the event — to present to the study site (for more mild events) or to an emergency room (for more serious events) for immediate evaluation. Based on the results of this evaluation, the Investigator will recommend either continuation or discontinuation of product use, consistent with the criteria specified in Appendix III. The Investigator also may prescribe or recommend the use of medications or other preparations to treat the AE.

Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document on study 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 defined according to the DAIDS SAE Reporting Manual for the HPTN (dated June 1, 2001). All AEs will be graded using the DAIDS Table for Grading Severity of Adverse Experiences (also referred to as the “Toxicity Table”). Both the DAIDS SAE Reporting Manual and the Toxicity Table are provided in the study-specific procedures manual.

Site staff also will report all AEs that meet serious adverse event (SAE) reporting requirements to the DAIDS Regulatory Operations Center (ROC), according to the procedures and time frames set forth in the DAIDS SAE Reporting Manual for the HPTN. The "intensive" reporting requirements specified in the DAIDS SAE Reporting Manual will be followed. ROC staff will forward SAE reports to the NIAID Medical Officer and the Safety Specialist at the DAIDS Regulatory Affairs Brach. Information on all AEs will be included in reports to the US Food and Drug Administration (FDA) and other applicable regulatory authorities. Site staff also will report information on all AEs and SAEs to their IRB in accordance with Federal regulations and local IRB requirements.

7 STATISTICAL CONSIDERATIONS

7.1 General Design

This is a Phase I, randomized, blinded, crossover study with one week of participant exposure to each of two investigational products — BufferGel and PRO 2000/5 Gel (P) — and a placebo control gel. Each week of exposure will be separated by a minimum one-week washout period. Participants will be assigned at random to one of six possible sequences of product use, balanced within circumcised and uncircumcised participants. Product safety and acceptability will be assessed after application of each product once nightly for a period of seven consecutive nights.

7.1.1 Primary Endpoints

Consistent with the primary study objective to assess the toxicity of BufferGel and PRO 2000/5 Gel (P) on the penile epithelium and urethral mucosa of HIV-infected men, the following primary endpoints will be assessed:

- Participant reports of urethral pain, urethral burning, penile itching, penile rash, or penile ulceration.
- Erythema (with or without induration), vesiculation, bullous reaction, and ulceration, of the penile shaft, foreskin, and glans, as observed by visual exam.
- Erythema or ulceration of the urethral meatus, as observed by visual exam.
- Positive (i.e., greater than trace) urine LE test.

7.1.2 Secondary Endpoints

Consistent with the secondary study objective to assess the acceptability of BufferGel and PRO 2000/5 Gel (P) among HIV-infected men, the following secondary endpoints will be assessed:

- AEs other than those listed as primary endpoints judged related to product use.
- Reported positive attributes of the study products.
- Reported negative attributes of the study products.
- Reported willingness to use the study products for sexual intercourse.

7.2 Sample Size and Accrual

A minimum of 24 "adherent" (as defined in Section 4.5) HIV-infected men — 12 circumcised and 12 uncircumcised — will be included in the study. Based on preliminary estimates, it is expected that 9-12 participants will be enrolled per month, and that 24 participants will be accrued within three months. Additional participants may be included in the study as needed to replace non-adherent participants, as described in Section 4.5.

The table below presents the probability of observing either zero or two or more safety outcomes among groups of 12 (circumcised or uncircumcised) or 24 (circumcised and uncircumcised) participants for various "true" event rates.

	P(0 events observed)		P(2+ events observed)	
Event Rate	**n=12**	**n=24**	**N=12**	**n=24**
1%	.89	.79	<.01	.02
5%	.54	.29	.12	.34
10%	.28	.08	.34	.71
20%	.07	.005	.73	.97
30%	.01	<.001	.91	>.99
40%	.002	<.001	.98	>.99
50%	<.001	<.001	>.99	>.99

Based on the above, if any safety outcome occurs at a rate of less than five percent, then the probability of observing at least two such events is 12 percent among 12 participants (e.g., the subset of uncircumcised men) and 34 percent among 24 participants. Alternatively, 12 participants provide 91 percent power to exclude event rates of 30 percent or more, and 24 participants provide 97 percent power to exclude event rates of 20 percent or more.

7.3 Random Assignment

Upon enrolling in the study, each participant will be assigned at random to one of six possible sequences of product use. Two randomization schedules will be used to ensure balanced sequence assignment among circumcised and uncircumcised men. Specifically, two circumcised men and two uncircumcised men will be assigned to each sequence.

The SDMC will provide the study site with two series of numbered, sealed, opaque envelopes containing the random assignments for circumcised and uncircumcised participants. Site staff will assign the envelopes to participants sequentially, in the order in which they are enrolled in the study. The envelopes and their contents will be maintained in participants' study records.

7.4 Blinding

Throughout the period of study implementation and data analysis, neither study staff nor participants will be informed of the identity of product applied each week by individual study participants. Study staff and participants will be unblinded after all study visits and data analyses are completed.

Exceptions may be considered by the Protocol Clarifications Team (see Section 10.1) in situations where product information may be needed to protect the safety of the participant. In emergency situations, if a participant experiences an SAE that, in the opinion of the Investigator requires immediate unblinding, the study site pharmacist may disclose the treatment assignment to the Investigator without obtaining prior concurrence of the Protocol Clarifications Team.

7.5 Data Monitoring

Close collaboration between the Investigator, NIAID Medical Officer, Protocol Coordinator, and SDMC Biostatistician will be necessary to evaluate study progress and respond to occurrences of toxicity in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the study team on a regular basis.

The Investigator will be responsible for continuous close monitoring of all AEs that occur among study participants, and for alerting the rest of the study team if unexpected concerns arise. All concerns then will be addressed according to DAIDS and HPTN standard operating procedures. In particular, for this study, accrual will be suspended if two or more grade 3 or higher AEs (as defined by the DAIDS Standard Toxicity Tables) judged possibly, probably, or definitely related to product use are observed across at least two study participants (i.e., the study will not be stopped if two more related grade 3 AEs are observed in a single participant). The study team then will review all pertinent safety data and determine whether to continue accrual and product use. A decision to stop the

trial may be made by the study team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

7.6 Data Analysis

Primary data analyses will tabulate the number of observed primary endpoints — listed in Section 7.1.1 — by product and circumcision status.

All participants who enroll in the study will be included in each tabulation. Individual participants will contribute once to the calculation of event rates for each product. Additional safety analyses will tabulate the number and type of AEs experienced during use of each product, overall and by severity and relationship to product. The temporal relationship of product application and AE onset, and the duration of symptoms, also will be evaluated.
Due to the modest study sample size, statistical comparisons across products will not be performed. However, analyses will be performed to assess the number and proportion of participants with subjective or objective findings across products, to determine whether individual participants had similar symptoms and/or exam findings across products.

Additional data analyses will tabulate the number and type of positive and negative product attributes reported by study participants on the Acceptability Assessment completed after use of each product. Also tabulated will be the number and percent of participants who report willingness to use each product for sexual intercourse on the Acceptability Assessment. As above, statistical analyses across products will not be performed, however data will be evaluated to determine whether individual participants' had similar perceptions across products.

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form contained in Appendix II — 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 all applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education, outreach, and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the IRB responsible for oversight of research conducted at the study site. Subsequent to initial review and approval, the local IRB will review the protocol at least annually. The Investigator will make safety and progress reports to the IRB at least annually, and within three months of 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.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. The study site is responsible for developing a study informed consent form for local use, based on the template in Appendix II, that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with applicable regulations. The DAIDS ROC will review all site-specific informed consent forms and approve them for use according to DAIDS policies; study site staff may not begin obtaining informed consent from study participants until after receiving ROC approval of the forms, in the form of confirmed "site registration" to begin study operations.

Participants will be provided with a copy of their informed consent forms if they are willing to receive them. Study staff will document the informed consent process as described in the study-specific procedures manual.

8.3 Risks

Based on the results of prior Phase I studies conducted among HIV-uninfected men, it is possible that the study gels could cause genital itching, tingling, irritation, dryness, discoloration, or flaking of the dried gel. It also is possible that the gels could cause burning, pain, blisters, ulcers, sores, or other irritation of the penis. These effects are sometimes seen when men apply other gels to the penis. Also, these effects were seen in some women who tested the gels in the vagina. Some women also experienced difficulty urinating, pain when urinating, vaginal bleeding, abdominal pain, nausea, and diarrhea. Other unknown effects and risks could occur.

Also, it is possible that participants could experience social harm as a result of taking part in this study. For example, others could learn of participants' involvement in this study and infer that they are HIV-infected. Because of this, participants could be treated unfairly or discriminated against. Participants could experience embarrassment if others were to see and recognize digital photographs of their penis.

8.4 Benefits

There are 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 microbicide that prevents sexual transmission of HIV.

8.5 Confidentiality

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. All laboratory specimens, reports, photographs, study data collection, process, and administrative forms 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 the written permission of the participant, except as necessary for monitoring by NIAID and/or its contractors (e.g., the DAIDS monitoring contractor), the manufacturers of the study products, representatives of the HPTN Coordinating and Operations Center (CORE) and/or SDMC, and the FDA and other regulatory authorities.

8.6 Incentives

Participants will be compensated for their time and effort in this study. Pending IRB approval, they will receive $25 for each scheduled study visit.

8.7 Communicable Disease Reporting Requirements

Study staff will report communicable diseases identified among study participants as required by law. Participants will be made aware of all applicable reporting requirements during the study informed consent process.

8.8 Study Discontinuation

As noted in Section 7.5, accrual into this study will be suspended if two or more grade 3 or higher AEs (as defined by the DAIDS Standard Toxicity Tables) judged possibly, probably, or definitely related to product use are observed across at least two study participants. The study team then will review all pertinent data and determine whether to continue accrual and product use. A decision to stop the trial may be made by the study team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

The study also may be discontinued at any time by NIAID, the HPTN, the manufacturers of the study products, and/or the FDA or other regulatory authorities.

9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US Centers for Disease Control and Prevention.

10 ADMINISTRATIVE PROCEDURES

10.1 Study Coordination

NIAID will hold the Investigational New Drug (IND) application for this study. Copies of all regulatory documents submitted to this IND by NIAID will be forwarded to ReProtect and Interneuron Pharmaceuticals, 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 Trial Agreement executed between NIAID and each company.

Study implementation will be directed by this protocol as well as a study-specific procedures (SSP) manual. The SSP manual will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations.

Study case report forms will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the SDMC DataFax data management system. Quality control reports and queries will be routinely sent back to the site for verification and resolution.

Close cooperation between the study Investigator, NIAID Medical Officer, Protocol Coordinator, Biostatistician, Data Managers, and other study team members will be necessary in order to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the study team. These rates also will be evaluated by representatives of the HPTN CORE and SDMC on a regular basis. A Protocol Clarification Team — comprised on the Protocol Chair, Medical Officer, and Biostatistician — will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information sharing.

10.2 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 and study-specific procedures manual, and confirm the quality and accuracy of information collected at the study site and entered into the study database. The Investigator 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, product accountability forms), as well as observe the performance of study procedures. The Investigator also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NIAID, ReProtect, Interneuron Pharmaceuticals, FDA, and other regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.3 Protocol Compliance

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

10.4 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 Federal 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 site 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.

10.5 Use of Information and Publications

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

11 REFERENCES

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12 PROTOCOL MODIFICATIONS

The table below describes the history of modifications to this protocol.

Date	Version	Modifications
9 March 2001	1.0	NA (original version of protocol)
11 July 2001	1.0	Clarification #1: • Add IND number. • Clarify SAE reporting requirements to correspond with updated DAIDS SAE Reporting Manual for the HPTN.
20 August 2001	2.0	Amendment #1: • Incorporate Clarification #1. • Clarify primary endpoints. • Update safety information. • Revise exclusion criteria to clarify that dermatologic conditions are exclusionary only if specific to the penis. • Add use of digital photography in conjunction with genital exams. • Add protocol Section 12, "Protocol Modifications." • Update protocol version number, date, and table of contents.

Appendix I

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

SCHEDULE OF EVENTS

Procedure	Screening & Enrollment Visit (Day 0)	Follow-Up Evaluation Visit (Days 7, 21, and 35)	Post-Washout/ Pre-Product Use Visits (Days 14 and 28)
Obtain informed consent	X		
Collect demographic information	X		
Collect/update locator information	X	X	X
Obtain medical history	X	X	X
Assess vital signs and perform directed physical exam	X		
Perform genital exam and urine leukocyte esterase test/take digital photograph of any observed abnormality and of normal area(s) if needed for clinical decision-making and/or documentation purposes	X	X	X
Determine eligibility	X		X
Obtain random assignment	X		
Provide study product, diary, and instructions	X		X
Administer acceptability assessment		X	
Complete and submit data collection forms	X	X	X

Appendix II

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

REMINDER TO CLINICAL SITES: DO NOT USE PREAMBLE IN LOCAL CONSENTS.

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

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

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)
Version 2.0
20 August 2001

Principal Investigator: [name]
Telephone Number: [xxx-xxx-xxxx]

INFORMED CONSENT

You are being asked to take part in the research study named above. This is a clinical study of two gels being developed as "vaginal microbicides." Vaginal microbicides are designed to be inserted into the female vagina to prevent HIV transmission during sex. One gel is called BufferGel. The other is called PRO 2000/5 Gel (P), or "PRO 2000 Gel" for short. HIV is the virus that causes AIDS. "Transmission" means passing the virus from one person to another. Before you can decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given 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 or to withdraw from the study at any time without losing the benefits of your routine medical care.

PURPOSE OF STUDY

The purpose of the study is to find out if there are any bad effects when BufferGel and PRO 2000 Gel are applied to the penis of HIV-positive men. Both BufferGel and PRO 2000 Gel are "experimental." This means we do not yet know all of the effects they may have on men and women, and we do not know if they work to prevent HIV transmission. Because of this, the US Food and Drug Administration (FDA) has not approved the gels for use in the general population. The FDA is the part of the US government that regulates medications. The FDA has approved this study.

Before research can be done to find out if the gels prevent HIV transmission when inserted in the vagina, the gels must be tested to make sure they are safe. So far, the safety of the gels has been tested among women and HIV-negative men. In these studies, the gels were shown to be safe and well-tolerated when inserted in the vagina or applied to the penis, although some side effects did occur (as described below). This study tests the safety of the gels among HIV-positive men, compared to a gel that has been approved for use as a lubricant during sex.

The University of Washington is conducting this study with funding from the National Institute of Allergy and Infectious Diseases (NIAID). About 24 HIV-positive men in the Seattle area will take part in the study. For each person in the study, the study will last about 5 weeks.

PROCEDURES

Screening: If you decide to take part in this study, your first study visit will continue today, after you read, discuss, and sign this form. The visit will take about 60 minutes. We will ask you some questions, review your medical records, and do a physical exam to find out if you are eligible for the study. If your medical records are not available during this visit, we will ask you to come back for another visit when they are available. If your medical records do not show that you are HIV-positive, we will do an HIV test to confirm your HIV status. You will be asked to sign a separate informed consent form for the HIV test.

The questions we ask at this visit will be about you, your health, and the medications you take. The exam we do will focus on health problems that you have now, or had in the past, and will include an exam of your penis. In order to look closely for possible signs of irritation, we will use a magnifying glass when examining your penis. If we see any abnormalities, we will take a picture of them with a digital camera. We also may take pictures of normal areas if needed, for example to compare with an abnormality or show that an abnormality has gone away. Any pictures will be identified by your study code number only. You will give a urine sample that we will test for evidence of infection.

During the Study: If you are eligible for the study, you will have about 5 more study visits. You will use each of the three study gels — BufferGel, PRO 2000 Gel, and the approved gel — once a day for one week. Each time, you will apply the gel at bedtime and leave it on overnight (6-10 hours). You will wash off the gel the next morning. You will write on a diary card the time you apply the gel and the time you wash it off. You will record any symptoms you have and any medications you take.

After each week of using a gel, you will have a study visit that will take about 30 minutes. At these visits, we will ask questions about your health, review your diary card, examine your penis, and test your urine for evidence of infection. If we see any abnormalities on your penis, we will take a digital picture of them. We also may take pictures of normal areas if needed. Any pictures will be identified by your study code number only. You will fill out a form asking for your thoughts and opinions about the gel you used that week.

After these visits, before you start using the next gel, you will have a week of using no gel at all. This a called a "washout period." After each washout period, you will have a 30-minute study visit in which we will ask questions about your health, examine your penis, and test your urine for evidence of infection. The purpose of this is to make sure that you are still eligible for the study and ready to begin using the next gel. If you are having health problems at these visits, we will ask you to wait until the problems resolve before you begin using the next gel. If we see any abnormalities on your penis, we will take a digital picture of them. We also may take pictures of normal areas if needed. Any pictures will be identified by your study code number only.

Neither you nor the study staff will know which gel you are using each week. After all participants finish the study, and we find out the results of the study, if you wish, you will be told which gel you used each week. We also will tell you the results of the study.

Different study participants will use the gels in different orders. The order in which you will use the gels will be chosen "at random" by a computer. "At random" means “by chance,” like flipping a coin. Because there are three different gels, there are six possible orderings that could be chosen for you. You have a one-out-of-six chance of getting each ordering.

Contact Procedures: Once you join the study and start using the gels, it is very important for us to stay in touch with you and find out how you are doing. *[Modify as needed to reflect local locator procedures:]* We will ask for your name, address, phone number, and other contact information at your first study visit. We also will ask for the names and contact information of

people we can contact if we cannot reach you. We will ask you to update this information at each study visit.

We will use your contact information to remind you of scheduled study visits. If you miss a visit, we may call or send letters or visit your home to find you. We also will try to reach you through the contact people that you list for us. If we talk to these people, we will not tell them why we are trying to reach you.

Other Requirements: During the weeks when you are using the gels, you are asked to not have sexual intercourse or masturbate. You also should avoid other activities that may cause penile irritation or injury. The reason for this is that when we examine your penis, we will want to know if any effects seen are due to the gels. This could be difficult to determine if you take part in other activities that could cause similar effects. You may have sex and/or masturbate during the washout periods.

You must return all gel to the study site (at the end of each week of gel use).

You are asked to tell the study staff about any medications you take while you are in the study. You are asked not to take part in other research studies while you are in this study, and to tell the study staff if you plan to join another study.

If you have any signs of irritation on your penis, or other health problems in between visits, study staff may ask you to come in for an extra study visit to check on these problems.

If you drop out of the study before using all three gels for seven days, study staff may ask you to complete a final study visit with an exam of your penis.

RISKS AND/OR DISCOMFORTS

We do not yet know all the effects of BufferGel and PRO 2000 Gel on the penis. We also do not know whether BufferGel and PRO 2000 Gel may have different effects for HIV-positive men compared to HIV-negative men, or for uncircumcised men compared to circumcised men. When circumcised and uncircumcised HIV-negative men applied the gels to the penis, some had mild itching, tingling, irritation, dryness, discoloration, or flaking of the dried gel on the penis. It also is possible that the gels could cause burning, pain, blisters, ulcers, sores, or other irritation of the penis. These effects are sometimes seen when men apply other gels to the penis. Also, these effects were seen in some women who tested the gels in the vagina. Some women also experienced difficulty urinating, pain when urinating, genital bleeding, abdominal pain, nausea, and diarrhea. Although we think that men who apply the gels to the penis may be less likely to have these kinds of symptoms, it is possible that they could occur. Other effects and risks that we do not yet know about also could occur.

Although we will make every effort to protect your privacy and confidentiality, it is possible that others could learn that you are in this study or that you are HIV-positive. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. Also, it could be embarrassing for you if someone outside of the study were to see and recognize any pictures taken of your penis. To help prevent this, any pictures taken will be labeled with your study code number only, not your name. (See also the "**CONFIDENTIALITY**" section below.)

BENEFITS

This study will be of no direct benefit to you. This study will not provide you with medical care or other services. We will, however, refer you for services you may need. Also, you or others may benefit in the future from information learned from this study.

NEW FINDINGS

You will be told any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when the study results 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 investigator decides that continuing in the study would be harmful to you;
- you are found to have a sexually transmitted disease (STD);
- you need a treatment not allowed on this study;
- you are unable to keep appointments or use the study gels as instructed;
- you have a bad effect to the study gels;
- the study is cancelled by the FDA, NIAID, or the companies that make the study gels; and/or
- other administrative reasons.

ALTERNATIVES TO PARTICIPATION

There are no microbicides known to prevent HIV transmission during sex. The only known way to prevent HIV transmission during sex is to use a latex or polyurethane condom every time you have sex.

There may be other research studies going on here or in the Seattle area for which you may be eligible. If you wish, we will tell you about other studies that we know about.

COSTS TO YOU

There is no cost to you for being in the study. You will receive $25 for your time and effort at each scheduled study visit.

CONFIDENTIALITY

Your research records, including any digital pictures, will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. If we take any digital pictures, they will be focused on your penis, and your face will not be shown. The pictures will be identified with your study code number only. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the FDA, NIAID, study monitors, and the companies that make the study gels.

RESEARCH-RELATED INJURY

We will monitor your health closely while you are in the study. You will have an exam before and after using each gel. If you notice any penile irritation, or have any other symptoms between visits, please contact us. Study staff are "on call" 24 hours a day at [xxx-xxxx-xxx]. When you call, we will either give you instructions over the phone or ask you to come in for an exam. If any of the gels irritate your penis, we may tell you to stop using that gel for the rest of the week, but ask you to stay in the study and test the other gels.

If you have a medical emergency that requires immediate care, you should contact your primary care provider or go to an emergency room right away.

[Sites to specify institutional policy:] Based on what we know now, it is unlikely that you will be injured as a result of being in this study. If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. The cost of this treatment [will/will not] be charged to you or your insurance company. You will be told where you may receive additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or in case of research-related injuries, you should contact [name of investigator] at [number], or if you have questions about your rights as a research participant, you can call [name and title of IRB member] at [number].

SIGNATURES

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

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

_____	_____	_____
Participant Name (printed)	Participant Signature	Date
_____	_____	_____
Witness Name (printed)	Witness Signature	Date

Appendix III

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

ASSESSMENT, FOLLOW-UP, AND TREATMENT OF SIGNS AND SYMPTOMS

Condition	Product Use	Further Evaluation	Follow-up
Irritative symptoms *(itching, burning, pain, etc.)*	If no signs are observed on exam or urine test, continue current product use; otherwise follow guidelines for observed signs.	None	Re-examine within 3 days if symptoms persist.
Questionable Erythema	Continue current product use.	None.	Re-examine at end of product use period (at next scheduled Post-Use Evaluation Visit). Consider for crossover to next product.
Definite Erythema	Discontinue current product use.	None.	Re-examine within 3 days. Consider for crossover to next product.
Erythema and Induration	Discontinue current product use.	None.	Re-examine within 3 days. Consider for crossover to next product.
Vesiculation	Discontinue product use.	None.	Re-examine within 3 days. Follow-up to resolution then discontinue from study.
Bullous Reaction	Discontinue product use.	None.	Re-examine within 3 days. Follow-up to resolution then discontinue from study.
Ulceration	Discontinue product use.	Culture and DFA for herpes simplex virus 2; evaluate for other causes (e.g., syphilis, chancroid) if suspected based on clinical judgement.	Re-examine within 3 days. Treat infection (if diagnosed) with appropriate antibiotic therapy. Follow-up to resolution then discontinue from study.
Other Epithelial Change	Continue or discontinue current product use based on clinical judgement.	None.	Re-examine within 3 days. Consider for crossover to next product.
Positive urine LE *(>trace)*	Discontinue current product use.	Urine culture and urine LCR for gonorrhea and chlamydia.	Re-evaluate in 5-7 days, when urine test results are available. Treat infection (if diagnosed) with appropriate antibiotic therapy. If STD is diagnosed, follow to resolution, then discontinue from study. Otherwise consider for crossover to next product.
Confirmed STD	Discontinue product use.	None.	Treat with appropriate antibiotic therapy. Follow to resolution, then discontinue from study.

Appendix III

HPTN 032
Male Tolerance Study of BufferGel and PRO 2000/5 Gel (P)

ASSESSMENT, FOLLOW-UP, AND TREATMENT OF SIGNS AND SYMPTOMS (continued)

The following guidelines will be applied when defining dermatologic signs for this study:

Questionable erythema:	Subtle, mild redness of the skin
Definite erythema:	Obvious redness of the skin
Erythema with induration:	Obvious redness with firmness or hardness of the skin
Vesiculation:	Circumscribed elevation of the skin, up to 5 mm in diameter, containing fluid
Bullous reaction:	Circumscribed elevation of the skin, greater than 5 mm in diameter, containing fluid
Ulceration:	Excavation that results from loss of dermis as well as epidermis.