

DATE: 23 October 2003

RE: LETTER OF AMENDMENT FOR: HPTN 049, Version 2.0, dated 11 January 2003.

Phase I Safety and Acceptability Study of the Vaginal Microbicide 6% Cellulose Sulfate Gel Among HIV-Infected Women

TO: _____, Principal Investigator, HPTU PTN XX-XXX

FROM: Antonia Kwiecien, CORE Protocol Specialist

THE FOLLOWING INFORMATION IMPACTS THE HPTN 049 STUDY (COHORT 4 ONLY) AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

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

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

Summary of Revisions

- For Cohort 4 only - The entry criteria have been revised to include women who have had a sexually transmitted disease in the six months prior to enrollment.
- For Cohort 4 only - The entry criteria have been revised to include male partners who have had a sexually transmitted disease in the six months prior to enrollment.

The changes described herein will be incorporated in the next version of Protocol HPTN 049 if it undergoes full protocol amendment at a later time.

Upon receipt of IRB approval, the following protocol modifications, indicated by ~~strike through~~ and **bold** text, will be implemented:

1. In the protocol Section 3.2.1, eighth bullet:

- ~~In the six months prior to Enrollment (including at the study Screening Visit), diagnosed with or treated for any STD or pelvic inflammatory disease.~~

~~Note: Women with a history of herpes simplex virus 1 or 2 who have been asymptomatic for at least six months will not be excluded.~~

~~Note: Women with a history of genital warts in the last six months that have resolved prior to enrollment will not be excluded unless the warts were surgically removed in the three months prior to Enrollment.~~

2. In the protocol Section 3.2.1, after the fourteenth bullet:

- **At enrollment is being treated for any STD.**

3. In the protocol Section 3.2.2, at the second bullet

- ~~In the six months prior to Enrollment, diagnosed with or treated for any STD.~~
- **At enrollment is being treated for any STD.**

DATE: 01 August 2003

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Summary of Revisions

- The number of participants in Cohort 3 has been reduced from 24 to 12, and the number of participants in Cohort 4 has been reduced from 24 to 20 due to the low number of HIV infected sero-concordant couples that meet entry criteria and are interested in participating in the study.
- The study duration has been extended to 19 months.
- Other administrative clarifications have been incorporated in the protocol as needed.

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

1. In the protocol Schema:

Study Size: Up to 96 ~~80~~ women and up to 48 ~~32~~ men.

Treatment Regimen: Female participants will apply 3.5 mL of either 6% cellulose sulfate gel or a control gel intravaginally once or twice daily for 14 intramenstrual days, as follows:

Study Cohort	n CS gel	n Control gel	Frequency of Use
1: Sexually Abstinent	12	12	Once Daily
2: Sexually Abstinent	12	12	Twice Daily
3: Sexually Active and their male sexual partners	12 6	12 6	Once Daily
4: Sexually Active and their male sexual partners	12 10	12 10	Twice Daily

Study Duration: Accrual will require up to ~~11~~ 18 months. Each female participant will be followed for 14 days of product use and the entire study should be completed within ~~13~~ 19 months.

2. In the protocol Section 2.4.1:

This is a multisite, phase I, double blind, randomized, controlled frequency escalation study of 6% CS gel to be conducted among up to ~~96~~ 80 sexually abstinent, and sexually active HIV-infected women from Birmingham, AL; New York, NY; Philadelphia, PA; and Providence, RI. Sexually active participants' male partners also will be included in the study.

Female study participants will complete once or twice daily intravaginal application of 6% CS gel or control gel for 14 consecutive days between menses. The control arms serve to provide information regarding signs, symptoms and/or morbidity that may be attributed to normal variation and/or the study procedures (e.g., speculum insertion) or use of applicator rather than the investigational product studied. The frequency of application will be escalated across "~~cohorts~~" of ~~24 study participants each — 12 assigned at random to apply CS gel and 12~~ Cohorts 1 and 2 consisting of 24 women each, Cohort 3 consisting of 12 women, and Cohort 4 consisting of 20 women assigned at random to apply the ~~control gel~~— as follows:

Study Cohort	n CS gel	n Control gel	Frequency of Use
1: Sexually Abstinent	12	12	Once Daily
2: Sexually Abstinent	12	12	Twice Daily
3: Sexually Active and their male sexual partners	12 6	12 6	Once Daily
4: Sexually Active and their male sexual partners	12 10	12 10	Twice Daily

Each study site will target enrollment of ~~six~~ **20** participants. ~~— three assigned to apply CS gel and three assigned to apply the control gel in each cohort.~~ **Within Cohorts 1 and 2, accrual of six participants at each of the four study sites is targeted. Within Cohort 3, accrual of three participants at each of the four study sites, and within Cohort 4, accrual of 5 participants at each of the four study sites is targeted. Ideally, at each site, three of the six participants enrolled in Cohorts 1 and 2, at most two of the three participants enrolled in Cohort 3, and at most three of the five participants enrolled in Cohort 4 will be assigned at random to apply CS gel at the assigned frequency (once or twice daily). The other women in each cohort will be assigned to apply the control gel.** However, with prior approval of the Protocol Chair, enrollment “slots” may be shifted across sites in the event that a site encounters unexpected difficulty in meeting its accrual targets.

3. In the protocol Section 2.4.3, second bullet:

- Within each cohort of **24** participants accrued across sites (**24 each in Cohorts 1 and 2, 12 in Cohort 3 and 20 in Cohort 4**), if two women experience a grade 3 AE judged possibly, probably, or definitely related to product use, accrual will be suspended at all sites and a safety data review will be undertaken to determine whether to continue the study, as described in Section 6.1. AEs will be defined as in Section 6 and graded according to the DAIDS Serious Adverse Experience (SAE) Reporting Manual for the HPTN and the DAIDS Toxicity Table.

4. In the protocol Section 3.0:

Up to ~~96~~ **80** HIV-infected women will be included in this study, as will up to ~~48~~ **32** HIV-infected male partners of sexually active female participants. Participants will be selected for the study according to the criteria in Section 3.1 and 3.2. They will be recruited as described in Sections 3.3 and 3.4 and assigned to a study product group as described in Section 7.4. Participant retention procedures are described in Section 3.6 and conditions for withdrawal from the study are described in Section 3.7.

5. In the protocol Section 3.4, third paragraph:

Women found to be presumptively eligible at the Screening Visit will be scheduled for an Enrollment Visit to take place 3-5 ~~2-6~~ days following **the end of** their next menstrual period, but within 42 days of the Screening Visit. (Women who are not enrolled within 42 days of screening must repeat all screening evaluations.) At this visit, female participants' eligibility will be confirmed according to the procedures described in Section 5.2; confirmed eligible participants will be randomized (see Section 7.4) and enrolled in the study.

6. In the protocol Section 7.3:

As noted in Section 2.4 up to 96 **80** female participants and up to 48 **32** male partners will be included in this study. Female participants will be enrolled into four cohorts, ~~of 24 women each~~, **Cohorts 1 and 2 consisting of 24 women each, Cohort 3 consisting of 12 women, and Cohort 4 consisting of 20 women.** Within ~~each cohort~~ **Cohorts 1 and 2**, accrual of six participants at each of the four study sites is targeted, **within Cohort 3, accrual of three participants at each of the four sites is targeted, and with Cohort 4, accrual of 5 participants at each of the four study sites is targeted.** If for some reason a site experiences difficulty reaching its accrual targets, consideration will be given to shifting enrollment “slots” to the other sites, with prior approval of the Protocol Chair.

Ideally, at ~~At~~ each site, three of the six participants enrolled in ~~each cohort~~, **Cohorts 1 and 2, at most two of the three participants enrolled in Cohort 3, and at most three of the five participants enrolled in Cohort 4** will be assigned at random to apply CS gel at the assigned frequency (once or twice daily). The other ~~three~~ **women in each cohort** will be assigned to apply the control gel. Also at each site, accrual of each cohort will proceed sequentially, after the completion of follow-up of all participants in the prior cohorts, provided accrual is not suspended per the provisions of Section 2.4.3.

As a means to characterize the statistical properties of ~~this study~~ **Cohorts 1 and 2**, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among groups of 12 women for various “true” event rates:

Event Rate	P (0 events n=12)	P (≥1 event n=12)	P (≥2 events n=12)
1%	0.89	0.11	0.01
5%	0.54	0.46	0.12
10%	0.28	0.72	0.34
15%	0.14	0.86	0.56
25%	0.03	0.97	0.84
35%	0.01	0.99	0.96
45%	<0.01	>0.99	0.99

For example, if the true rate of a given endpoint in **Cohorts 1 or 2** is five percent, the probability that the endpoint will be observed in at least one of 12 women is 0.46. In addition, with a true rate of five percent, 12 women provide 88 percent power to exclude endpoint rates greater than 35 percent (i.e., the probability of observing 0 or 1 endpoint is less than 0.05 when the true rate is 35 percent, while this probability is 0.88 when the true rate is five percent).

The statistical properties of ~~this study~~ **Cohorts 1 and 2** also may be characterized by the width of confidence intervals (CI) around observed event rates. The following table presents the exact 95 percent CIs around endpoint rates when zero, one, or two endpoints are observed among 12 women:

No. Endpoints Observed	Lower Bound of CI	Upper Bound of CI
0	0.0%	26.5%
1	0.2%	38.5%
2	2.1%	48.4%

The properties described above are fairly robust relative to possible non-adherence to the study treatment regimen (as defined in Section 4.4). For example, if two women per cohort **in Cohorts 1 and 2** were non-adherent to the regimen, a subgroup analysis of the 10 adherent participants in the cohort would provide 74 percent power to exclude event rates greater than 45 percent for a given toxic event rate of 10 percent, and a pooled group of 20 participants would provide 74 percent power to exclude event rates greater than 25 percent for a given toxic event rate of five percent.

As a means to characterize the statistical properties of Cohort 3, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among groups of 6 women for various “true” event rates:

Event Rate	P (0 events n=6)	P (≥ 1 event n=6)	P (≥ 2 events n=6)
1%	0.94	0.06	<0.01
5%	0.74	0.26	0.03
10%	0.53	0.47	0.11
15%	0.38	0.62	0.22
25%	0.18	0.82	0.47
35%	0.08	0.92	0.68
45%	0.03	0.97	0.84

For example, if the true rate of a given endpoint in Cohort 3 is five percent, the probability that the endpoint will be observed in at least one of 6 women is 0.26. In addition, with a true rate of five percent, 6 women provide 97 percent power to exclude endpoint rates greater than 59 percent (i.e., the probability of observing 0 or 1 endpoint is less than 0.05 when the true rate is 59 percent, while this probability is 0.97 when the true rate is five percent).

The statistical properties of Cohort 3 also may be characterized by the width of confidence intervals (CI) around observed event rates. The following table presents the exact 95 percent CIs around endpoint rates when zero, one, or two endpoints are observed among 6 women:

No. Endpoints Observed	Lower Bound of CI	Upper Bound of CI
0	0.0%	45.9%
1	0.4%	64.1%
2	4.3%	77.7%

As a means to characterize the statistical properties of Cohort 4, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among groups of 10 women for various “true” event rates:

Event Rate	P (0 events n=10)	P (≥ 1 event n=10)	P (≥ 2 events n=10)
1%	0.90	0.10	<0.01
5%	0.60	0.40	0.09
10%	0.35	0.65	0.26
15%	0.20	0.80	0.46
25%	0.06	0.94	0.76
35%	0.01	0.99	0.91
45%	<0.01	>0.99	0.98

For example, if the true rate of a given endpoint in Cohort 4 is five percent, the probability that the endpoint will be observed in at least one of 10 women is 0.40. In addition, with a true rate of five percent, 10 women provide 91 percent power to exclude endpoint rates greater than 40 percent (i.e., the probability of observing 0 or 1 endpoint is less than 0.05 when the true rate is 40 percent, while this probability is 0.91 when the true rate is five percent).

The statistical properties of Cohort 4 also may be characterized by the width of confidence intervals (CI) around observed event rates. The following table presents the exact 95 percent CIs around endpoint rates when zero, one, or two endpoints are observed among 10 women:

No. Endpoints Observed	Lower Bound of CI	Upper Bound of CI
0	0.0%	30.9%
1	0.3%	44.5%
2	2.5%	55.6%

7. In the protocol Section 7.4:

Upon enrolling in the study, female participants will be assigned at random to apply either 6% CS gel or the control gel. Randomization will be stratified by cohort and by site to **help** ensure equal balanced assignment to each product within each cohort at each site. ~~Specifically, provided each site meets its accrual target of six women per cohort, three women per cohort at each site will be assigned to apply CS gel, and three women per cohort at each site will be assigned to apply the control gel.~~

8. In the Cohort 1 and 2 Sample Informed Consent, Purpose of the study, last paragraph:

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About ~~96~~ **80** women and ~~48~~ **32** men from Birmingham, AL; Providence, RI; Philadelphia, PA, and New York, NY will take part in the study. The study will last about ~~13~~ **19** months. Your part will last about two months.

9. In the Cohort 3 and 4 Sample Informed Consent, Purpose of the study, last paragraph:

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About ~~96~~ **80** women and ~~48~~ **32** men from Birmingham, AL; Providence, RI; Philadelphia; PA, and New York, NY will take part in the study. The study will last about ~~43~~-**19** months. Your part will last about two months.

10. In the Male Partners Sample Informed Consent, Purpose of the study, last paragraph:

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About ~~96~~ **80** women and ~~48~~ **32** men from Birmingham, AL; Providence, RI; Philadelphia; PA, and New York, NY will take part in the study. The study will last about ~~43~~-**19** months. Your part will last about two months.

HPTN 049
Phase I Safety and Acceptability Study of
the Vaginal Microbicide 6% Cellulose Sulfate Gel
Among HIV-Infected 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 on Drug Abuse
US National Institute of Mental Health
US National Institutes of Health

Co-Sponsored by:

Contraceptive Research and Development Program (CONRAD)

IND # 57,833 held by CONRAD

Protocol Chair:

Wafaa El-Sadr, MD
Harlem Hospital and Columbia University
New York, NY

Final Version 2.0
11 January 2003

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Phase I Safety and Acceptability Study of
the Vaginal Microbicide 6% Cellulose Sulfate Gel
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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 Site 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 the pharmaceutical co-sponsor 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-sponsor for review prior to submission.

I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the product 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 Site Principal Investigator

Signature of Site Principal Investigator

Date

HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse experience
AGC	atypical granular cells
AIDS	Acquired Immunodeficiency Syndrome
AIS	endocervical adenocarcinoma in situ
ALP	alkaline phosphatase
ALT	alanine transaminase
APTT	activated partial prothrombin time
ASC	atypical squamous cell
ASC-H	atypical squamous cells, cannot exclude HSIL
ASC-US	atypical squamous cell of undetermined significance
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BV	bacterial vaginosis
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CL	(HPTN) Central Laboratory
CONRAD	Contraceptive Research and Development Program
CORE	(HPTN) Coordinating and Operations Center
CRPMC	Clinical Research Product Management Center
CS	cellulose sulfate
CVL	cervicovaginal lavage
DAIDS	Division of AIDS
EIA	enzyme immunoassay
FDA	(United States) Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody-absorption
GGT	gammaglutamyl transaminase
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSIL	high-grade squamous intraepithelial lesions
IND	investigational new drug
IRB	institutional review board
LDMS	Laboratory Data Management System
LE	leukocyte esterase
LSIL	low-grade squamous intraepithelial lesions
LL	local laboratory
MHA-TP	microhemagglutination- <i>Treponema pallidum</i>
mg	milligram
mL	milliliter
N-9	nonoxynol-9

LIST OF ABBREVIATIONS AND ACRONYMS - continued

NAT	nucleic acid amplification test
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
PCR	polymerase chain reaction
PT	prothrombin time
RNA	ribonucleic acid
ROC	Regulatory Operations Center
RPR	rapid plasma reagin
SAE	serious adverse experience
SDMC	(HPTN) Statistical and Data Management Center
STD	sexually transmitted disease
WB	Western blot

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PROTOCOL TEAM ROSTER

Roberta Black, PhD
NIAID Program Officer
Division of AIDS/NIAID/NIH
6700 B Rockledge Drive, Rm 4110
Bethesda, MD 20892
tel.: 301.496.8199
fax.: 301.402.3684
e-mail: rblack@niaid.nih.gov

Marianne Callahan
Sponsor Representative
Contraceptive Research and
Development Program
1611 North Kent Street, Suite 806
Arlington, VA 22209 USA
tel.: 703.276.3915
fax: 703.524.4770
e-mail: mcallahan@conrad.org

Missy Cianciola, MS
Protocol Operations Coordinator
SCHARP
1100 Fairview Avenue North
MP-1195
P.O. Box 19024
Seattle, WA 98109
tel.: 206.667.7290
fax: 206.667.4812
e-mail: missy@scharp.org

Wafaa El-Sadr, MD
Protocol Chair
Harlem Hospital
Division of Infections Diseases
Room 3101A
506 Lenox Avenue
New York, NY 10032
tel.: 212.939.2936
fax: 212.939.2968
e-mail: wme1@columbia.edu

Craig Hoesley, MD
Principal Investigator
University of Alabama at Birmingham
1530 3rd Avenue South BDB 467
(Box 20)
Birmingham, AB 35294-0012
tel.: 205.934.7090
fax: 205.975.2563
e-mail: choesley@uabid.dom.uab.edu

Cliff Kelly, MS
Statistical Research Associate
SCHARP
1100 Fairview Avenue North, MP-1195
P.O. Box 19024
Seattle, WA 98109
tel.: 206.667.2502
fax: 206.667.6888
email: cwkelly@scharp.org

Andrzej Kulczycki, Ph.D.
Subinvestigator
Asst. Prof., Dept. of Epidemiology &
International Health
University of Alabama at Birmingham
217 Ryals Public Health Bldg., 1665
University Blvd.
Birmingham, AL 35294-0022
tel.: 205.934.9875
fax: 205.975.3329
e-mail: andrzej@uab.edu

Antonia Kwiecien BSc (Pharm)
Protocol Specialist
Family Health International
2101 Wilson Blvd, Suite 700
Arlington VA 22201
tel.: 703.516.9779
fax: 703.516.0295
e-mail: akwiecien@fhi.org

Lisa A. Maslankowski, MD
Principal Investigator/Protocol Co-Chair
University of Pennsylvania
3535 Market Street, #4051
Philadelphia, PA 19104
tel.: 215.746.7348
fax: 215.746.7377
e-mail: lisamasl@mail.med.upenn.edu

Christine Mauck, MD, MPH, FACPM
Sponsor Representative
Contraceptive Research and Development
Program
1611 North Kent Street, Suite 806
Arlington, VA 22209 USA
tel.: 703.276.3912
fax: 703.524.4770
e-mail: cmauck@conrad.org

Kenneth Mayer, MD
Principal Investigator/Protocol Co-Chair
Infectious Disease Division
2nd Floor Koffler Research Building
The Miriam Hospital
164 Summit Ave.
Providence, RI 02906
tel.: 401.793.4711
fax: 401.793.4709
email: kenneth_mayer@brown.edu

Barbra Richardson, PhD
Protocol Biostatistician
SCHARP
1100 Fairview Ave. North
MP-1195
PO Box 19024
Seattle, WA 98109 USA
tel.: 206-667-7788
fax: 206-667-4812
e-mail: barbrar@u.washington.edu

Lydia Soto-Torres, MD, MPH
NIAID Medical Officer
Division of AIDS/NIAID/NIH
6700 B Rockledge Drive, Room 4112
Bethesda, MD 20892
tel.: 301.594.9705
fax: 301.402.3684
e-mail: LSoto-Torres@niaid.nih.gov

HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women

SCHEMA

- Purpose:** To assess the safety and acceptability of 6% cellulose sulfate (CS) gel for vaginal use versus a control gel among HIV-infected women; to assess the acceptability of CS gel among the HIV-infected male sexual partners of female participants.
- Design:** Multisite, Phase I, double blind, randomized, controlled, frequency escalation study with 14 days of product exposure and follow-up.
- Study Population:** Sexually abstinent and sexually active HIV-infected women; HIV-infected male partners of sexually active women.
- Study Size:** Up to 96 women and up to 48 men.
- Treatment Regimen:** Female participants will apply 3.5 mL of either 6% cellulose sulfate gel or a control gel intravaginally once or twice daily for 14 intramenstrual days, as follows:

Study Cohort	n CS gel	n Control gel	Frequency of Use
1: Sexually Abstinent	12	12	Once Daily
2: Sexually Abstinent	12	12	Twice Daily
3: Sexually Active and their male sexual partners	12	12	Once Daily
4: Sexually Active and their male sexual partners	12	12	Twice Daily

Study Duration: Accrual will require up to 11 months. Each female participant will be followed for 14 days of product use and the entire study should be completed within 13 months.

Primary Objectives:

- To assess the local toxicity of once and twice daily intravaginal application of 6% CS gel on the vulvar and cervicovaginal mucosa of HIV-infected women versus a control gel.
- To assess the systemic toxicity of once and twice daily intravaginal application of 6% CS gel among HIV-infected women.

Secondary Objective:

- To assess the acceptability of, and adherence to, a short-term regimen of 6% CS gel among HIV-infected women and their HIV-infected male sexual partners.

Exploratory Objectives:

- To measure the occurrence of cervicovaginal shedding of HIV before and after use of 6% CS gel or the control gel.
- To measure vaginal flora characteristics before and after use of 6% CS gel or the control gel.

Study Sites:

- Harlem Hospital Center and Bronx-Lebanon Hospital Center, New York, NY, USA
- Miriam Hospital and Women and Infants Hospital, Providence, RI, USA
- University of Alabama at Birmingham, Birmingham, AL, USA
- University of Pennsylvania, Philadelphia, PA, USA

1.0 INTRODUCTION

1.1 Background

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 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), which has been evaluated in several different doses and formulations. However, no clinical studies have yet demonstrated that N-9 products can prevent HIV infection; N-9 products have been shown to cause mucosal erosion and ulceration in a dose-dependent manner ^[7-8]; and preliminary results of a large-scale clinical trial presented at the XIII International AIDS Conference indicated that use of an N-9 gel may be associated with a higher rate of HIV infection when compared with an “over the counter” vaginal lubricant, and afforded no protection against STDs ^[9]. However, the potential protective properties of the comparator gel used in this study make the data difficult to interpret.

Particularly in light of the most recent findings with respect to the effects of nonoxynol-9 products, increasing attention has been given to developing other products as topical microbicides to prevent HIV infection. One such investigational product is sodium cellulose sulfate (CS) gel.

1.2 Prior Research

Sodium CS is a non-cytotoxic antifertility agent that exhibits antimicrobial activity *in vitro* against sexually transmitted pathogens. A gel containing 6% CS has been shown (in decreasing order of efficiency) to stimulate acrosomal loss, inhibit hyaluronidase, and impede sperm penetration into cervical mucus *in vitro*. The clinical formulation has been shown to be contraceptive in rabbits at 1 mg/mL, when the sperm and product are pre-mixed prior to vaginal inoculation, and at 50 mg/mL using vaginal application of the formulation prior to sperm introduction^[10].

The hyaluronidase inhibition and contraceptive properties of CS have been known for more than 40 years. Clinical trials performed before 1973 outside the United States with a suppository containing only CS, with a lower molecular weight than the current clinical formulation, showed a high degree of contraceptive efficacy^[11]. Presently, a vaginal contraceptive suppository that contains 100 mg CS and 230 mg N-9 is marketed in Germany under the name of A gen 53. Clinical studies with this product report a high degree of safety with a slight burning sensation being the only reported side effect^[12].

The antimicrobial activity of CS has been evaluated by exposing laboratory strains, and in some cases clinical isolates, of viruses, protozoa, bacteria, and yeast to increasing doses of the drug and attempting to culture them in appropriate media. Complete inhibition of infection was observed for HIV, HSV-1, HSV-2 and HPV at concentrations less than 200 micrograms per mL. Fifty percent inhibition of *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *G. vaginalis*, *T. vaginalis*, *C. albicans*, *S. aureus*, and *P. aeruginosa* was seen at concentrations below 12 mg/mL. In addition, *in vitro* studies have shown that CS does not inhibit the proliferation of lactobacillus strains^[10].

Animal and human studies suggest that CS gel is minimally irritating to the vaginal epithelium. Vaginal irritation studies showed mild irritation in rabbits and no irritation in rats after 14 days of exposure^[10].

In a recently completed Phase I study, healthy women who applied either 2.5 mL (150 mg) or 5.0 mL (300 mg) of 6% CS gel to the vagina on six consecutive days experienced less irritation than women who applied either a presumed inactive control gel (K-Y® Jelly) or an active control gel containing N-9 (Conceptrol®). For example, colposcopic findings were observed at follow-up among one of 12 women who applied 2.5 mL of CS gel and among two of 12 women who applied 5.0 mL of CS gel, whereas such findings were observed among three of 12 women who applied K-Y Jelly and among six of 12 women who applied Conceptrol. Further, colposcopic findings involving disruption of the epithelium or blood vessels were observed only among women who applied the control gels^[13].

Similar results were observed in a Phase I study conducted among healthy men who applied 6% CS gel to the penis on seven consecutive days: irritation was observed in one of 24 men who applied 6% CS gel and three of 12 men who applied an N-9 gel (unpublished data).

CS has been shown to have anticoagulant effects *in vitro* but not in human or animal studies. No changes in activated partial thromboplastin times or platelet counts were seen in the above-mentioned Phase I vaginal study ^[10, 13].

1.3 Rationale

There is an urgent need to develop a safe and effective vaginal microbicide to prevent heterosexual transmission of HIV. Based on available pre-clinical and clinical data, CS gel is a promising candidate microbicide. Building on the initial Phase I studies described above, CONRAD and the World Health Organization are implementing an expanded safety and acceptability study of CS gel among 90 sexually abstinent and 90 sexually active healthy women in Africa and India. In addition, the HPTN Microbicide Science Working Group and product review subgroup have approved HPTN collaboration with CONRAD in the further clinical development of CS gel, based on a review of all available pre-clinical and clinical data on the product. This HPTN study will complement other prior and ongoing studies of CS gel, in that it will assess the safety and acceptability of CS gel among HIV-infected women. Participants' male sexual partners (when relevant) also will be asked to assess the acceptability of the gel. As such, this study represents an important contribution to the clinical development of CS gel, thereby accelerating progress toward an eventual efficacy trial of this product.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objectives of this study are:

- To assess the local toxicity of once and twice daily intravaginal application of 6% CS gel on the vulvar and cervicovaginal mucosa of HIV-infected women versus a control gel.
- To assess the systemic toxicity of once and twice daily intravaginal application of 6% cellulose sulfate gel among HIV-infected women.

2.2 Secondary Objective

- To assess the acceptability of, and adherence to, a short-term regimen of 6% CS gel among HIV-infected women and their HIV-infected male sexual partners.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To measure the occurrence of cervicovaginal shedding of HIV before and after use of 6% CS gel or the control gel.
- To measure vaginal flora characteristics before and after use of 6% CS gel or the control gel.

2.4 Study Design

2.4.1 Overview

This is a multisite, phase I, double blind, randomized, controlled frequency escalation study of 6% CS gel to be conducted among up to 96 sexually abstinent, and sexually active HIV-infected women from Birmingham, AL; New York, NY; Philadelphia, PA; and Providence, RI. Sexually active participants' male partners also will be included in the study.

Female study participants will complete once or twice daily intravaginal application of 6% CS gel or control gel for 14 consecutive days between menses. The control arms serve to provide information regarding signs, symptoms and/or morbidity that may be attributed to normal variation and/or the study procedures (e.g., speculum insertion) or use of applicator rather than the investigational product studied. The frequency of application will be escalated across “cohorts” of 24 study participants each — 12 assigned at random to apply CS gel and 12 assigned at random to apply the control gel— as follows:

Study Cohort	n CS gel	n Control gel	Frequency of Use
1: Sexually Abstinent	12	12	Once Daily
2: Sexually Abstinent	12	12	Twice Daily
3: Sexually Active and their male sexual partners	12	12	Once Daily
4: Sexually Active and their male sexual partners	12	12	Twice Daily

Each study site will target enrollment of six participants— three assigned to apply CS gel and three assigned to apply the control gel — in each cohort. However, with prior approval of the Protocol Chair, enrollment “slots” may be shifted across sites in the event that a site encounters unexpected difficulty in meeting its accrual targets.

Participants in cohorts assigned to once daily dosing will apply the dose at bedtime. Participants assigned to twice daily dosing will apply one dose in the morning and the other at bedtime. Sexually active participants will have vaginal intercourse with their single HIV-infected male partner, using study-provided male condoms, at their usual frequency of at least twice per week during the 14 days of product application. On days when they have vaginal intercourse, these participants will substitute coital application(s) for the routine application(s), however the total number of daily applications will not exceed the assigned frequency. Additional information regarding the progression from Cohort 1 to Cohort 4 is provided in Section 2.4.2 below.

2.4.2 Study Visits and Procedures

After providing written informed consent, female participants will undergo eligibility screening, including medical history, symptom-directed physical exam, pelvic exam, urine testing for pregnancy and infection, STD counseling and testing, hematology and coagulation testing, and liver and renal function testing. For participants who are presumptively eligible at this visit, an Enrollment Visit will be scheduled to take place 2-6 days after the participant’s next menstrual period, but within 42 days of initial screening.

In addition for sexually active participants, the participant’s male sexual partner will be informed of the study and its requirements of him, and asked to provide written informed consent to take part. Sexually active participants whose male partners are not willing to provide written informed consent will not be eligible to take part in the study.

At their Enrollment Visits, participants will be provided their screening test results. Presumptively-eligible participants will undergo a pelvic exam with colposcopy, and urine pathogen and pregnancy testing to confirm their eligibility. Hematology, coagulation, and liver and renal function testing will be performed. Participants whose eligibility is confirmed at this visit then will be assigned at random to apply either 6% CS gel or the control gel once or twice daily for 14 consecutive days. Participants then will be provided with:

- Supplies of the assigned study product applicators, panty liners, and male condoms;

- Daily Study Records on which to record the date and time of product application and episodes of vaginal intercourse, as well as any symptoms experienced;
- Instructions for product application and Daily Study Record completion; and
- Instructions to contact the study site to ask questions about study procedures and/or report adverse experiences (AEs) between visits.

After completing five to nine consecutive days of product application, participants will complete a study Follow-up Visit (target Day 7) during which their Daily Study Records will be reviewed — to assess adherence to the product use regimen and ascertain whether any adverse experiences have occurred — and a pelvic exam with colposcopy will be performed. After completing 12 to 14 days of product application, participants will complete a study follow-up visit (target Day 14) during which their Daily Study Records again will be reviewed and a pelvic exam with colposcopy will be performed at both Days 7 and 14. Hematology, coagulation, and liver and renal function testing, urine pregnancy and pathogen testing also will be performed. At any of the study follow-up visits, or at any ad hoc visits initiated by participants between scheduled visits, abnormalities noted on pelvic exam will be evaluated and followed according to Appendix II; continued/discontinued product use also will be guided by Appendix II.

The acceptability of CS gel will be assessed via questionnaires administered to both female participants and male partners. At their study Enrollment Visits, female participants will complete a behavioral questionnaire regarding their past history of vaginal product use. At Day 14, female participants will complete a follow-up acceptability questionnaire regarding their specific perceptions of the gel they applied during the study. The male partners of sexually active participants will complete a follow-up questionnaire regarding their perceptions and experiences with the gel within four weeks after the female participant has completed product use.

2.4.3 Cohort Progression

The study will begin with accrual of sexually abstinent participants into Cohort 1. Thereafter, accrual and follow-up will proceed according to the following guidelines:

- Sequential accrual into Cohorts 2, 3, and 4 may begin upon completion of follow-up of all participants in the prior cohorts.

- Within each cohort of 24 participants accrued across sites, if two women experience a grade 3 AE judged possibly, probably, or definitely related to product use, accrual will be suspended at all sites and a safety data review will be undertaken to determine whether to continue the study, as described in Section 6.1. AEs will be defined as in Section 6 and graded according to the DAIDS Serious Adverse Experience (SAE) Reporting Manual for the HPTN and the DAIDS Toxicity Table.

3.0 STUDY POPULATION

Up to 96 HIV-infected women will be included in this study, as will up to 48 HIV-infected male partners of sexually active female participants. Participants will be selected for the study according to the criteria in Section 3.1 and 3.2. They will be recruited as described in Sections 3.3 and 3.4 and assigned to a study product group as described in Section 7.4. Participant retention procedures are described in Section 3.6 and conditions for withdrawal from the study are described in Section 3.7.

3.1 Inclusion Criteria

3.1.1 All Female Participants

Women who meet all of the following criteria (by self-report, unless otherwise specified) are eligible for inclusion in this study.

- Able and willing to provide written informed consent to take part in the study.
- Age 18-50 years, inclusive.
- HIV-infected by licensed enzyme immunoassay (EIA)/Western Blot (WB) or detectable HIV viral load, as documented in medical records or based on testing performed by study staff.
- Under the care of a medical professional for HIV management.
- Stable anti-retroviral therapy (if any) for at least one month prior to study screening, and regimen expected to remain unchanged for the duration of the study.
- CD4+ cell count of at least 200/mm³ at the time of study screening, based on testing performed by study staff, together with at least one documented CD4+ cell count of at least 200/mm³ in the six months prior to screening.

- HIV RNA plasma level less than 50,000 copies/mL at the time of study screening, based on testing performed by study staff.
- Have a regular menstrual cycle with a minimum of 21 days between menses, or have been amenorrheic for at least six months due to long acting progestin use.
- Willing to provide study staff with access to medical records.
- Willing and able to complete Daily Study Records (as determined by study staff).
- Agree, for the duration of the study, to apply 6% CS gel or control gel as required per protocol.
- Agree to abstain from non-therapeutic drug use while participating in the study.
- Agree to refrain from participating in other microbicide or contraceptive studies while participating in this study.
- Agree to abstain from the following activities during the period beginning 72 hours prior to the study Enrollment Visit and ending at the final study visit:
 - oral contact with her genitalia;
 - anal intercourse;
 - penetration of the vagina by fingers, sex toys, or any other objects;
 - use of any vaginal product other than the study gels, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps; and
 - douching.

3.1.2 Sexually Abstinent Female Participants

In addition to the criteria in Section 3.1.1, in order to be eligible for inclusion in study Cohorts 1 and 2, women must agree to abstain from vaginal intercourse during the period beginning 72 hours prior to the study Enrollment Visit and ending at the final study visit.

3.1.3 Sexually Active Female Participants

In addition to the criteria in Section 3.1.1, women must meet all of the following criteria in order to be eligible for inclusion in study Cohorts 3 and 4:

- Have been in a mutually monogamous relationship for at least three months with a male partner who is eligible for the study according to the criteria in Sections 3.1.4 and 3.2.2.
- Have a usual frequency of vaginal intercourse of at least two episodes per week with the male partner who meets the criteria in Sections 3.1.4 and 3.2.2.
- Agree, for the duration of the study, to:
 - have vaginal intercourse only with the male partner who meets the criteria in Section 3.1.4;
 - have vaginal intercourse at the usual frequency of at least two episodes per week with the male partner who meets the criteria in Section 3.1.4; and
 - use study-provided male condoms for each act of vaginal intercourse.
- Agree to abstain from vaginal intercourse during the 72 hours prior to the study Enrollment Visit.

3.1.4 Male Participants

Male sexual partners of sexually active female study participants who meet all of the following criteria (by self-report, unless otherwise specified) are eligible for inclusion in this study:

- Age 18 years and older.
- Able and willing to provide written informed consent to take part in the study.
- HIV-infected by licensed EIA/WB or detectable HIV viral load as documented in medical records or based on testing performed by study staff.
- Have been in a mutually monogamous relationship with the female study participant for at least three months.
- Agree, for the duration of the study, to:
 - have vaginal intercourse only with the female study participant;
 - have vaginal intercourse with the female study participant at the usual frequency of at least two episodes per week; and
 - use study-provided male condoms for each act of vaginal intercourse.

- Agree to abstain from the following activities with the female study participant during the period beginning 72 hours prior to the female participant's Enrollment and ending at the female participant's final study visit:
 - anal intercourse;
 - oral contact with the female study participant's genitalia; and
 - penetration of the vagina by fingers, sex toys, or any other objects.
- Agree to abstain from vaginal intercourse with the female participant during the 72 hours prior to her Enrollment Visit.

3.2 Exclusion Criteria

3.2.1 All Female Participants

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

Note: Women with observed abnormalities and/or signs of genital tract infection as described below will be referred for appropriate clinical follow-up and/or treatment.

- History of hysterectomy.
- History of sensitivity/allergy to any component of the study products, including latex for Cohorts 3 and 4.
- History of drug or alcohol use that in the opinion of the investigator contraindicates study participation.
- History of prior participation in this study, (i.e., in a prior cohort), as indicated by the study site's screening log and participant identification code list.
- Currently post-menopausal.
- Currently pregnant or breastfeeding, or within three months of last pregnancy outcome.
- Currently have or in the three months prior to Enrollment had an intrauterine device in place.

- In the six months prior to Enrollment (including at the study Screening Visit), diagnosed with or treated for any STD or pelvic inflammatory disease.

Note: Women with a history of herpes simplex virus 1 or 2 who have been asymptomatic for at least six months will not be excluded.

Note: Women with a history of genital warts in the last six months that have resolved prior to enrollment will not be excluded unless the warts were surgically removed in the three months prior to Enrollment.

- In the three months prior to Enrollment, had any of the following:
 - an abnormal Pap smear;
 - vaginal bleeding during or following sexual intercourse;
 - breakthrough menstrual bleeding, and/or;
 - gynecologic surgery.

Note: Abnormal Pap smear is defined by the following designations: all atypical squamous cell (ASC) interpretations (atypical squamous cell of undetermined significance (ASC-US), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (HSIL)(ASC-H)), low-grade squamous intraepithelial lesions (LSIL), HSIL, carcinoma in situ and squamous cell carcinoma as well as all atypical glandular cell (AGC) interpretations (atypical endocervical, endometrial, or glandular cells and AGC-favor neoplastic), endocervical adenocarcinoma in situ (AIS), and adenocarcinoma. Reactive Pap smear designations including reactive cellular changes associated with inflammation will be presumed normal in the absence of an ulcerative or non-ulcerative STD (including negative laboratory results for STDs) or deep epithelial disruption on speculum exam or colposcopy.

- Have been using a hormonal contraceptive method for fewer than three months prior to Enrollment.
- In the 30 days prior to Enrollment, participated in any other microbicide or contraceptive research study.
- In the 14 days prior to Enrollment, received a course of antibiotic therapy for gynecological care.
- In the seven days prior to Enrollment, used any spermicide or spermicidally lubricated condom.
- At Screening, have a Grade 3 or higher liver, renal, or hematology abnormality, according to the DAIDS Toxicity Tables.
- At Enrollment, have colposcopic findings involving deep disruption of the epithelium that are not iatrogenic in origin.

Note: If an observed epithelial disruption is iatrogenic in origin, the Screening and Enrollment Visits should be repeated at a later date following resolution of the finding(s), typically after the next menstrual cycle. The Screening and Enrollment Visits may be repeated only once for this reason.

- At Screening or Enrollment, have a clinically detectable genital abnormality.

Note: Women with genital warts located exterior to the labia minora (i.e., on the labia majora or mons) will not be excluded.

- At Screening or Enrollment, have any of the following signs of an STD or other genital tract infection — other than asymptomatic bacterial vaginosis (BV):
 - vaginitis;
 - cervicitis;
 - vulvar or cervicovaginal lesions (not iatrogenic in origin); or
 - laboratory signs of genital tract infection, other than asymptomatic BV.

Note: If observed vulvar or cervicovaginal lesions are iatrogenic in origin, the Screening and/or Enrollment Visits should be repeated at a later date following resolution of the finding(s), typically after the next menstrual cycle. The Screening and Enrollment Visits may be repeated only once for this reason.

Note: Cervicitis will be defined by the presence of mucopurulent discharge from the cervix or friability of the cervix. If there is any doubt as to whether discharge is mucopurulent, a swab test will be performed (i.e., a swab will be held to the cervix and if the swab colors yellow, the discharge will be considered mucopurulent).

Note: Signs of asymptomatic BV include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of KOH, pH>4.5, presence of clue cells, decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical or gram stain evidence of BV and symptoms (symptomatic discharge, odor, itching) will be excluded. Women without symptoms, but with clinical or gram stain evidence of BV, will not be excluded.

- At Screening or Enrollment, have any other condition that, in the opinion of the investigator, 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.

3.2.2 Male Participants

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

- History of sensitivity/allergy to latex or any component of the study products.

- In the six months prior to Enrollment, diagnosed with or treated for any STD.
- Self-reported STD symptoms within the two weeks prior to providing informed consent for the study that cannot be attributed to a non-STD cause upon genital exam.

Note: Men who report current STD symptoms will be offered a genital exam and, if indicated, referred for appropriate clinical follow-up and/or treatment.

- Have any other condition that, in the opinion of the investigator, 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 Recruitment Setting

Female study participants will be recruited primarily from infectious disease clinics associated with the four participating study sites, as follows:

- the Harlem Hospital Center and Bronx-Lebanon Hospital Center located in New York, NY;
- the Miriam Hospital and Women and Infants Hospital, located in Providence, RI.
- the 1917 Outpatient/Research Clinic at the Hospital of the University of Alabama at Birmingham, located in Birmingham, AL; and
- the Hospital of the University of Pennsylvania, located in Philadelphia, PA.

These hospitals all are located in urban areas and serve hundreds of HIV-infected women in each of the four study communities. Potentially-eligible participants also may be sought through a number of other mechanisms. For example, recruitment information may be distributed to medical staff and case managers at local HIV clinical practices to forward to potentially-eligible women. Women who have responded to previous research recruitment efforts or who have participated in previous research studies may be contacted by phone or by mail (with their prior permission). Participants also may be sought through newspaper ads, posting of flyers on public kiosks, and outreach at venues frequented by potentially-eligible women. Finally, this study will be listed with the US Department of Health and Human Services' AIDS Clinical Trials Information Service, which is accessible via phone (at 1-800-TRIALS-A) and on the Internet (at www.actis.org).

3.4 Recruitment, Screening, and Enrollment Process

Recruitment, screening, and enrollment for this study will proceed in a step-wise manner over the course of at least two study visits (i.e., the Screening and two) for female participants and at least one study visit for male sexual partners. For participants who do not meet the study eligibility criteria, the process will be discontinued when ineligibility is determined.

Potential female study participants will be recruited as described in Section 3.3, and scheduled for a study Screening Visit to take place on any non-menstrual day. After providing written informed consent for both study screening and on-study procedures, recruited women will undergo the screening medical history, exam, and laboratory procedures described in Section 5.1. For sexually active participants, the screening process also will include ascertainment of whether the participant currently has a monogamous HIV-infected male sexual partner whom she is willing to involve in the study.

Women found to be presumptively eligible at the Screening Visit will be scheduled for an Enrollment Visit to take place 3-5 days following their next menstrual period, but within 42 days of the Screening Visit. (Women who are not enrolled within 42 days of screening must repeat all screening evaluations.) At this visit, female participants' eligibility will be confirmed according to the procedures described in Section 5.2; confirmed eligible participants will be randomized (see Section 7.4) and enrolled in the study.

As an additional factor for eligibility determination, sexually active participants' monogamous HIV-infected male sexual partners also must provide written informed consent for the study and have their eligibility confirmed prior to randomization and enrollment of the female participant. This may occur at any time between the female participant's Screening and Enrollment Visits, or concurrent with the female participant's Enrollment Visit.

3.5 Co-Enrollment Guidelines

Female participants in this study may be co-enrolled in other clinical trials (e.g., of HIV treatment regimens) at the time of screening and/or enrollment into this study, provided they meet the eligibility criteria for this study listed in Section 3.1 and 3.2. Specifically, participants must have stable HIV treatment regimens and must not have participated in any other microbicide or contraceptive research study within the 30 days prior to enrollment in this study. Once enrolled in this study, however, participants will be counseled not to join any other new clinical trial while taking part in this study.

Male partners who take part in this study may be co-enrolled in any other clinical trials.

3.6 Participant Retention

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain him/her for the entire 14-day study period. One hundred percent retention of enrolled participants is targeted. Study sites are responsible for developing and implementing local standard operating procedures (SOPs) to achieve complete follow-up. Components of such SOPs include:

- Thorough explanation of the study schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of appropriate and timely visit reminder mechanisms (e.g., phone calls on the day prior to the visit).
- Immediate and multifaceted (e.g., by phone, mail, e-mail, in person) follow-up on missed visits.
- Mobilization of trained outreach workers to conduct in-person contact with participants at their homes and/or other community locations.

3.7 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.

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

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.5) of female participants who terminate from the study prior to Day 14. Male sexual partners will be asked to complete the follow-up acceptability assessment (as described in Section 5.6) if they or their partner withdraw from the study. Study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY PRODUCT

4.1 Product Formulation

4.1.1 CS Gel

Six percent CS gel contains 60 mg of the active ingredient, sodium cellulose sulfate, per milliliter of gel. Each 3.5 mL application of 6% CS gel therefore contains 210 mg of the active ingredient. The vehicle gel contains 20% glycerin as a humectant, 1.5% sodium carboxymethylcellulose as a thickener, 0.18% methylparaben and 0.02% propylparaben as preservatives, and water. The ingredients are United States Pharmacopeia/National Formulary grade materials. Addition of the active ingredient to the vehicle at a 6% concentration produces a thick gel that should be stored at room temperature. The pH of 6% CS gel is 7. The gel is slightly hazy in appearance with a light brown tint and is odorless.

Clinical supplies of CS 6% gel have been manufactured and packaged under good manufacturing practice conditions for this study by:

Personal Products Company
Women's Health Division of McNeil-PPC, Inc.
199 Grandview Road
Skillman, NJ 08558-9418

FDA Registration #2214133

4.1.2 Control Gel

The control 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 is a clear, odorless gel that is slightly less viscous than 6% CS gel. It should be stored at room temperature.

The gel has been packaged under good manufacturing practice conditions for this study into disposable, single-use applicators, and over-wrapped in pouches by:

Ortho Pharmaceutical
Division of OMJ, Inc.
P.O. Box 463
Manati, Puerto Rico 00701

FDA Registration #2650078

4.2 Product Application Regimen

Female participants will apply 3.5 mL of the assigned study product either once or twice daily for a period of 14 days, beginning on study Day 0 (i.e., the day of the Enrollment Visit). Participants will be instructed to remain recumbent for at least 15 minutes after each application and, if possible, to avoid emptying their bladder or bowel within the first hour after application.

- Participants in Cohorts 1 and 3 will apply the assigned product once daily, at bedtime.
- Participants in Cohorts 2 and 4 will apply the assigned product twice daily, in the morning and at bedtime, with an approximate 12-hour interval between applications. On study Day 7, participants in Cohorts 2 and 4 will be instructed to delay their morning application until after completion of their follow-up pelvic exam, unless the follow-up pelvic exam is scheduled in the afternoon.
- On days when participants in Cohorts 3 and 4 have vaginal intercourse, they will substitute coital application(s) — 5-15 minutes prior to intercourse if at all possible — for the routine daily application(s). However, the total number of daily applications will not exceed the assigned frequency. During these coital applications, it is understood that participants will not necessarily remain recumbent after application.

4.3 Product Supply and Accountability

CONRAD will provide both 6% CS gel and the control gel. Both products will be supplied in identical, single-use 3.5 mL applicators packaged in individual white wrappers. The packager prior to shipping the clinical supplies will verify the delivery volume of the pre-filled applicators.

Supplies of both products will be made available to the study sites through the NIAID Clinical Research Products Management Center (CRPMC). Site pharmacists will obtain supplies from the CRPMC according to the instructions in the manual “Pharmacy Guidelines and Instructions to DAIDS Clinical Trials Group,” in the section entitled “Investigational Agent Control.”

Site pharmacists must maintain complete records of all CS and control gel supplies received from the CRPMC and subsequently dispensed to study participants. All unused supplies must be returned to the CRPMC after the study is completed or terminated.

The HPTN Coordinating and Operations Center (CORE) will supply a single brand and type of lubricated latex male condom (not containing N-9) to each site for distribution to study participants. Sites will obtain unscented panty liners for distribution to participants.

4.4 Adherence Assessment

Participants will record on their Daily Study Records the date and time of each product application. The records also will collect information on the timing of sexual activity (if any), use (or non-use) of study and non-study condoms, use of other intravaginal products, and the emergence/resolution of any symptoms experienced. The investigator or designee will interview each participant and review her Daily Study Records at her Day 7 and Day 14 Follow-up Visits, along with the number of used and unused product applicators returned at these visits, to assess adherence to the study product use and sexual activity requirements.

Daily administration of the assigned study product at the assigned frequency on 14 consecutive study days is targeted, however lapses of consecutive day use will be accommodated, as follows:

- Participants in Cohorts 1 and 3 who miss an application on one day out of 14 will be instructed to complete one application on one additional day (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.
- Participants in Cohorts 1 and 3 who miss an application on two days out of 14 will be instructed to complete one application on two additional days (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.
- Participants in Cohorts 2 and 4 who miss one or two applications on one day out of 14 will be instructed to complete two applications on one additional day (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.

- Participants in Cohorts 2 and 4 who miss one or two applications on two days out of 14 will be instructed to complete two applications on two additional days (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.

Participants who complete twice daily administration of the assigned product on each study day between the Enrollment Visit (inclusive) and the Day 14 Follow-up Visit, as well as participants who adhere to one of the scenarios described above, will be considered adherent to the product use regimen. Participants who experience an AE that requires temporary suspension of product use at the instruction of the investigator for more than two days, but who are able to complete a total of 14 days of product use at the assigned frequency following resolution of the AE, prior to onset of the next menstrual period, also will be considered adherent. As well, participants who experience an AE that requires permanent product discontinuation, but completed daily administration at the assigned frequency on the days preceding the AE will be considered adherent.

For the sexually active cohorts (required to have vaginal intercourse at their usual weekly rate that must be at least twice per week), adherence is further defined as having at least two episodes of vaginal intercourse during the 14-day exposure period.

Non-adherent participants will be asked their reasons for non-adherence and this information will be recorded on study case report forms. If the participant is not willing to become adherent, the participant will be withdrawn from the study as described in Section 3.7. Non-adherent participants will not be replaced.

Note: Participants in the sexually active cohorts who have fewer than two episodes of vaginal intercourse between study Days 0 and 6 will be encouraged to resume their usual frequency of intercourse between Days 7 and 13.

4.5 Toxicity Management

In response to AEs reported by study participants and/or observed upon exam by study staff, the investigator or designee will recommend either continuation or discontinuation of product use consistent with the criteria in Appendix II. Product use also will be discontinued in the event of pregnancy.

Participants who discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete the safety evaluations scheduled to take place on study Days 7 and 14, and/or as specified in Appendix II.

4.6 Concomitant Medications

Enrolled study participants may continue use of all concomitant medications — except exclusionary antibiotics and preparations applied to the external genitalia or inserted into the vagina — during this study. All concomitant medications taken by participants throughout the course of the study — beginning with the Screening Visit — will be reported on applicable study case report forms. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable study case report forms.

4.7 Procedures to be Followed in the Event of Pregnancy

All participants will be instructed to report pregnancies to site investigator or to the study staff who will in turn report to the site investigator; the site investigator will inform the Protocol Team. The site investigator will counsel the participant and discuss possible risks if the pregnancy is continued. According to procedure included in the SSP Manual, the participant will be followed through the conclusion of her pregnancy, and live births will be followed for one year.

5.0 STUDY PROCEDURES

The study visit and procedures schedule is presented in Appendix I and described below. Detailed procedural instructions will be included in the Study-Specific Procedures Manual.

5.1 Screening Visit for Female Participants

(up to Day -42)

- Obtain written informed consent.
- Collect locator information, demographics, and medical history.
- Provide STD pre-test and HIV/STD risk reduction counseling; provide HIV pre-test counseling if medical records are not available to document HIV status.
- Collect urine and conduct pregnancy and leukocyte esterase (LE) test; if LE test is positive (greater than trace), perform culture and microscopy at the local laboratory (LL). Ship urine for chlamydia and gonorrhea nucleic acid amplification testing (NAT) at the HPTN Central Laboratory (CL).

- Perform symptom-directed physical exam.
- Perform pelvic exam, as follows:
 - naked eye exam of external genitalia,
 - speculum exam of vagina and cervix,
 - vaginal pH,
 - dried smear for Gram stain,
 - wet mount for trichomonas, candida, and BV,
 - sno-strip and cervicovaginal lavage (CVL) for HIV viral load at the HPTN CL,
 - Pap smear (unless medical records document a normal result in the past three months),
 - bimanual exam for adnexal or fundal masses or tenderness.

Note: Participants with abnormal Pap smear results will be referred for treatment

- Collect blood and perform the following at the LL:
 - complete blood count (CBC),
 - CD4+ cell count,
 - liver function testing (ALP, ALT, AST, GGT, total bilirubin),
 - renal function testing (BUN, creatinine) ,
 - coagulation testing (PT, APTT),
 - syphilis serology (RPR, with confirmation by FTA-ABS or MHA-TP),
 - HIV serology (EIA/WB), if HIV status is not adequately documented in available medical records,
 - process and ship plasma for HIV RNA polymerase chain reaction (PCR) at the CL.
- Provide the participant with:
 - instructions regarding the study behavioral requirements,
 - instructions to contact study staff to ask questions and report onset of menses,
 - instructions to inform her male sexual partner regarding her potential participation in the study and it's behavioral requirements (cohorts 3 and 4 only),
 - practice Daily Study Records and instructions for use, and
 - male condoms.
- Schedule next visit.
- Complete and submit required data collection forms.

5.2 Enrollment Visit for Female Participants

(Day 0)

- Update locator information.
- Verify that male sexual partner is eligible for the study and has provided written informed consent for study participation (cohorts 3 and 4 only).
- Provide results of all screening tests and post-test counseling.
- Administer baseline behavioral assessment .
- Review practice Daily Study Records.
- Collect urine and conduct pregnancy and LE test; if LE test is positive (greater than trace), perform culture and microscopy at the LL.
- Perform pelvic exam with colposcopy, as follows:
 - naked eye exam of external genitalia,
 - speculum exam of vagina and cervix,
 - colposcopic exam and imaging of vulva, vagina, and cervix,
 - vaginal pH,
 - dried smear for Gram stain,
 - wet mount for trichomonas, candida, and BV,
 - sno-strip and CVL for HIV viral load at the HPTN CL, and
 - bimanual exam for adnexal or fundal masses or tenderness.
- Collect blood and perform CBC, liver and renal function testing, coagulation testing, and plasma and serum archive at the LL; process plasma for HIV RNA PCR at the HPTN CL.
- Obtain and document random assignment.
- Provide the participant with:
 - supplies of the assigned study product,
 - instructions regarding the study behavioral requirements,
 - instructions to contact study staff to ask questions and/or report AEs,
 - Daily Study Records and instructions for use,
 - panty liners, and
 - male condoms.
- Schedule next visit.
- Complete and submit required data collection forms.

5.3 Enrollment Visit for Male Partners

(Day –42 to Day 0)

- Obtain written informed consent.
- Collect demographic and locator information.
- Collect information on STD history during the past six months and STD symptoms within the prior two weeks; perform genital exam if participant reports STD symptoms within the prior two weeks or if the participant requests an exam.
- If medical records are not available to document HIV status:
 - provide HIV pre-test counseling,
 - collect blood for HIV serology, and
 - deliver test results and post-test counseling when results are available.

Note: If HIV testing is required, enrollment of both the female participant and the male partner must be deferred until the HIV status of both partners is confirmed.

- Provide the participant with:
 - male condoms and HIV/STD risk reduction counseling,
 - instructions regarding the study behavioral requirements, and
 - instructions to contact study staff to ask questions and/or report AEs.
- Schedule acceptability interview
- Complete and submit required data collection forms.

5.4 Day 7 Follow-up Visit for Female Participants

(target Day 7, allowable Day 5-9)

- Update locator information.
- Collect used and unused product applicators, review the participant's Daily Study Records, and obtain interval medical history to assess adherence with protocol requirements and determine whether any AEs occurred since the last visit.
- Collect urine and conduct pregnancy and LE test; if LE test is positive (greater than trace), perform culture and microscopy at the LL.

- Perform pelvic exam with colposcopy, as follows:
 - naked eye exam of external genitalia,
 - speculum exam of vagina and cervix,
 - colposcopic exam and imaging of vulva, vagina, and cervix,
 - vaginal pH,
 - dried smear for Gram stain,
 - wet mount for trichomonas, candida, and BV,
 - sno-strip and CVL for HIV viral load at the HPTN CL, and
 - bimanual exam for adnexal or fundal masses or tenderness.
- Follow up on any abnormalities observed according to Appendix II.
- Collect blood and perform CBC, liver and renal function testing, and coagulation testing at the LL; process plasma for HIV RNA PCR at the HPTN CL.
- Provide the participant with:
 - supplies of the assigned study product,
 - instructions regarding the study behavioral requirements,
 - instructions to contact study staff to ask questions and/or report AEs,
 - Daily Study Records and instructions for use,
 - panty liners, and
 - male condoms.
- Schedule next visit.
- Complete and submit required data collection forms.

5.5 Day 14 Follow-up Visit for Female Participants

(target Day 14, allowable Day 12-16)

- Update locator information.
- Administer follow-up acceptability assessment and study burden assessment.
- Collect used and unused product applicators, review the participant's Daily Study Records, and obtain interval medical history to assess adherence with protocol requirements and determine whether any AEs occurred since the last visit.
- Collect urine and conduct pregnancy and LE test; if LE test is positive (greater than trace), perform culture and microscopy at the LL.

- Perform pelvic exam with colposcopy, as follows:
 - naked eye exam of external genitalia,
 - speculum exam of vagina and cervix,
 - colposcopic exam and imaging of vulva, vagina, and cervix,
 - vaginal pH,
 - dried smear for Gram stain,
 - wet mount for trichomonas, candida, and BV,
 - sno-strip and CVL for HIV viral load at the HPTN CL, and
 - bimanual exam for adnexal or fundal masses or tenderness.
- Follow up on any abnormalities observed according to Appendix II.
- Collect blood and perform CBC, liver and renal function testing, and coagulation testing at the LL; process plasma for HIV RNA PCR at the HPTN CL.
- Complete and submit required data collection forms.

5.6 Acceptability Interview for Male Partners

After female participants have completed product use, their male partners will complete a structured interviewer-administered acceptability assessment regarding their perceptions of the gel and of taking part in the study. Individual interviews will be conducted either in a face-to-face setting or by phone and will be carried out within four weeks following completion of product use.

5.7 Interim Contacts and Visits

Interim contacts and visits may be performed at participant request or as deemed necessary by the Investigator at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care; all AEs associated with genital symptoms will be evaluated according to the pelvic exam procedures described for the Day 7 and Day 14 Follow-up Visits, and diagnosis and follow-up of any observed abnormalities will proceed according to Appendix II.

5.8 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 each participant's product assignment. 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 to which they were assigned.

6.0 SAFETY MONITORING AND ADVERSE EXPERIENCE REPORTING

6.1 Safety Monitoring

Close cooperation between the study team members will be necessary in order to monitor participant safety and respond to occurrences of toxicity in a timely manner. The team will meet via conference call every two weeks during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site Investigators are responsible for continuous close monitoring of all AEs that occur among study participants, and for alerting the rest of the protocol team if unexpected concerns arise. In particular, Investigators will immediately report to the protocol team the occurrence of any grade 3 or higher AE (as defined by the DAIDS Toxicity Tables) judged possibly, probably, or definitely related to product use.

Accrual will be suspended if two or more participants in any cohort experience a grade 3 or higher AE judged possibly, probably, or definitely related to product use. An independent statistician then will review all data pertinent to these AEs – including the participants' random assignments. If the participants who experienced the AEs were assigned to different study products, the statistician will recommend to the study team that the study continue (without providing any further information that would unblind the team). If the participants who experienced the AEs were assigned to the same study product, the study team will be unblinded and the following actions will be undertaken:

- If the participants who experienced the AEs were assigned to the control gel, the protocol will be amended to eliminate application of the control gel.
- If the participants who experienced the AEs were assigned to CS gel, the study team will review all available safety data and determine whether to allow the study to proceed. A decision to stop the study may be made at this time or at any such time that the team agrees that an un acceptable type and/or frequency of AEs has been observed.

6.2 Adverse Experience 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.

Study participants will be provided a 24-hour telephone number and instructed 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. 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.

Site staff also will report all AEs that meet SAE reporting requirements according to the procedures set forth in the Study-Specific Procedures Manual and the time frames set forth in the DAIDS SAE Reporting Manual. Specifically, DAIDS-defined "intensive" reporting requirements will be followed for this study.

Active follow-up for safety outcomes (serious and non-serious AEs) in each study participant will end one day after the final application of study product, however all SAEs reported by participants during the study treatment period and/or during the eight-week period following the final application will be reported in accordance with the DAIDS manual. Information on all AEs will be included in reports to the US Food and Drug Administration (FDA), and other applicable government and regulatory authorities. Site staff will report information on all AEs and SAEs to their Institutional Review Board (IRB) in accordance with all applicable regulations and local IRB requirements.

Note: The above-stated reporting requirements apply to enrolled female study participants. Participants and their male sexual partners will be instructed to report AEs experienced by male partners to the study clinician, who will evaluate and document the experience, as well as provide follow-up care or a referral for such care. In the event that a male partner experiences an AE that meets SAE reporting requirements, the experience will be reported as an SAE according to the procedures set forth in the Study-Specific Procedures Manual and the time frames set forth in the DAIDS SAE Reporting Manual.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a multisite, Phase I, double blind, randomized, controlled comparison, frequency escalation study with 14 days of product exposure and follow-up.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objectives to assess the local and systemic toxicity of 6% CS gel versus the control gel on the vulvar and cervicovaginal mucosa of HIV-infected women, the following endpoints will be assessed among female study participants:

- Genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use.
- Pelvic exam findings, including colposcopic findings, judged by the Investigator to be possibly, probably, or definitely related to product use.
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) observed among female participants for hematology, liver or renal function, and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use;
- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective as listed in Section 2.2, the following secondary outcomes will be assessed:

- Participant “adherence” to the product use regimen, as defined in Section 4.4;
- Participant willingness to use the assigned study product during sexual intercourse in the future, as reported via the follow-up acceptability questionnaires.
- Reported positive aspects of using the assigned study product.
- Reported negative aspects of using the assigned study product.

7.2.3 Exploratory Endpoints

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

- The number of copies of HIV RNA isolated from vaginal fluids at Screening, Enrollment, and Follow-up.
- Nugent score ^[14] for BV at Screening, Enrollment, and Follow-up.

7.3 Accrual, Follow-up, and Sample Size

As noted in Section 2.4 up to 96 female participants and up to 48 male partners will be included in this study. Female participants will be enrolled into four cohorts of 24 women each. Within each cohort, accrual of six participants at each of the four study sites is targeted. If for some reason a site experiences difficulty reaching its accrual targets, consideration will be given to shifting enrollment “slots” to the other sites, with prior approval of the Protocol Chair.

At each site, three of the six participants enrolled in each cohort will be assigned at random to apply CS gel at the assigned frequency (once or twice daily). The other three women will be assigned to apply the control gel. Also at each site, accrual of each cohort will proceed sequentially, after the completion of follow-up of all participants in the prior cohorts, provided accrual is not suspended per the provisions of Section 2.4.3.

As a means to characterize the statistical properties of this study, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among groups of 12 women for various “true” event rates:

Event Rate	P (0 events n=12)	P (≥ 1 event n=12)	P (≥ 2 events n=12)
1%	0.89	0.11	0.01
5%	0.54	0.46	0.12
10%	0.28	0.72	0.34
15%	0.14	0.86	0.56
25%	0.03	0.97	0.84
35%	0.01	0.99	0.96
45%	<0.01	>0.99	0.99

For example, if the true rate of a given endpoint is five percent, the probability that the endpoint will be observed in at least one of 12 women is 0.46. In addition, with a true rate of five percent, 12 women provide 88 percent power to exclude endpoint rates greater than 35 percent (i.e., the probability of observing 0 or 1 endpoint is less than 0.05 when the true rate is 35 percent, while this probability is 0.88 when the true rate is five percent).

The statistical properties of this study also may be characterized by the width of confidence intervals (CI) around observed event rates. The following table presents the exact 95 percent CIs around endpoint rates when zero, one, or two endpoints are observed among 12 women:

No. Endpoints Observed	Lower Bound of CI	Upper Bound of CI
0	0.0%	26.5%
1	0.2%	38.5%
2	2.1%	48.4%

The properties described above are fairly robust relative to possible non-adherence to the study treatment regimen (as defined in Section 4.4). For example, if two women per cohort were non-adherent to the regimen, a subgroup analysis of the 10 adherent participants in the cohort would provide 74 percent power to exclude event rates greater than 45 percent for a given toxic event rate of 10 percent, and a pooled group of 20 participants would provide 74 percent power to exclude event rates greater than 25 percent for a given toxic event rate of five percent.

7.4 Random Assignment

Upon enrolling in the study, female participants will be assigned at random to apply either 6% CS gel or the control gel. Randomization will be stratified by cohort and by site to ensure equal balanced assignment to each product within each cohort at each site. Specifically, provided each site meets its accrual target of six women per cohort, three women per cohort at each site will be assigned to apply CS gel, and three women per cohort at each site will be assigned to apply the control gel.

The SDMC will provide each study site with four series of numbered, sealed, opaque envelopes containing the random assignments for each cohort. 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. Each participant will be assigned a product code number. Using an unblinded list of product codes and assigned products, the pharmacist at each site will supply either 6% CS gel or control gel.

7.5 Blinding

Throughout the period of study implementation and data analysis, neither study staff nor participants will be informed of the participants' random assignments (except as specified in section 6.1). Both study products will be supplied in identical, single-use applicators packaged in individual white wrappers. Study staff and participants will be unblinded after all study visits and data analyses are completed. Individual exceptions may be considered by the Protocol Chair and Medical Officer 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 Chair and Medical Officer.

7.6 Data Analysis

All descriptive and inferential statistical analyses will be performed using SAS and StatXact statistical software. All randomized participants will be included in all analyses. In the text below, the term "treatment group" refers to a given frequency of a particular product, for sexually abstinent and sexually active participants separately. Secondary analyses will be performed that combine cohorts.

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods are to be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to the final follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test (for continuous response variables). When the use of formal testing to assess differences between the control gel and CS gel arms is required, the following methods are to be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression.

Control gel and CS gel participants within each cohort will be compared for baseline characteristics including demographics, pelvic examination, colposcopy, and laboratory measurements using descriptive statistics. Due to the small size of each cohort, formal comparisons will not be performed.

7.6.1 Primary Analyses

The primary aims of the study are to assess the local and systemic toxicity of once and twice daily application of 6% CS gel versus a control gel among HIV-infected women. The control gel provides information regarding signs, symptoms and/or morbidity that may be attributed to normal variation and/or the study procedures or use of applicator rather than the investigational product being studied. Primary data analyses will tabulate the number of primary endpoints — listed in Section 7.2.1 — observed during the study, by study cohort and product assignment within cohorts. All participants who enroll in the study will be included in each tabulation. Individual participants will contribute once to the calculation of event rates.

Additional safety analyses will tabulate the number and type of AEs observed overall and by severity and relationship to product, by cohort and product assignment. AEs that lead to discontinuation of product use and/or study participation will be tabulated separately. The temporal relationship of product application and AE onset, and the duration of symptoms, also will be evaluated. Finally, baseline, Day 7, and Day 14 laboratory measures will be summarized and the change in function, defined as the difference between the baseline and Day 14 measurements, will be described.

7.6.2 Secondary Analyses

Participant adherence to the product use regimen will be assessed within treatment group and comparisons will be made between the control gel and CS gel groups combining the cohorts with covariates for frequency of use and sexual activity. Similar analyses will be performed on the endpoints assessing acceptability. These include male and female participants' willingness to use the assigned product during intercourse in the future (as reported via questionnaire on study Day 14), reported positive aspects of using the assigned product, and reported negative aspects of using the assigned product (as reported via questionnaire). In addition, participants' preferences at Enrollment will be compared with acceptability after having used the study gels.

To explore potential effects of product use on cervicovaginal shedding of HIV, change in the number of copies of HIV RNA from baseline to Day 7 and Day 14 will be analyzed within each treatment group. In addition, the change in the number of copies of HIV RNA will be compared between the control gel and CS gel users and for sexually active and sexually abstinent women.

Similarly, to explore potential effects of product use on vaginal flora, change in Nugent scores from baseline to Day 7 and Day 14 will be analyzed within each treatment group. In addition, change in score will be compared between the control gel and CS gel users and for sexually active and sexually abstinent women.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the sample informed consent forms 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 applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible local IRBs 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 prior to the initiation of any study procedures. Each study site is responsible for developing study informed consent forms for local use, based on the samples in Appendix II, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. Participants will be provided with a copy of their informed consent form if they are willing to receive it. Study staff will document the informed consent process as described in the Study-Specific Procedures Manual.

8.3 Risks

Female participants may experience discomfort when having pelvic exams and/or undergoing phlebotomy for this study. During phlebotomy, they also may feel dizzy or faint, or develop a bruise or swelling where the needle is inserted; there is a very small chance of the participant getting an infection at the site where the blood is drawn.

Male and female participants may become embarrassed, worried, or anxious when receiving HIV and STD counseling. They also may become worried or anxious while waiting for their HIV and STD test results. Study staff will assist participants in dealing with these feelings.

Based on the prior completed Phase I vaginal study of CS gel versus K-Y Jelly, potential risks to female participants associated with use of the study products include vulvar and/or vaginal redness, itching, burning, or pain; abnormal vaginal bleeding; and abdominal pain and tenderness. For male participants, although exposure to the study products should occur rarely, if at all, given instructions to use male condoms during each act of vaginal intercourse while in the study, the prior Phase I penile study of CS gel indicated that mild penile tingling or stinging may occur if men are exposed to CS gel.

CS gel has been shown to have anticoagulant effects *in vitro*. Although no such effects were observed in the prior Phase I study among HIV-uninfected women, it is possible, that such effect could be observed among participants in this study.

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). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

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. In addition, participants will receive HIV/STD counseling and testing as part of the study screening process, as well as CD4+ cell count and HIV viral load measurements, pelvic exams and Pap smears. Participants will be referred to available sources care if needed to follow up on any medical problems identified as part of the study screening and/or follow-up procedures (see also Section 8.5).

8.5 Access to HIV-Related Care

This study will include HIV-infected women who are under the care of a medical professional for HIV management. Such women will continue with their regular source of care while in this study. As part of the study screening and enrollment process, the study may identify HIV-infected men and women who lack HIV-related care. Study staff will refer such persons to available sources of medical and psychosocial care in their community, as well as to any other available research studies for HIV-infected women.

8.6 Incentives

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

8.7 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 study data collection, process, and administrative forms, colposcopic photographs, 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.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; CONRAD; representatives of the HPTN CORE, SDMC, and/or CL; the US Food and Drug Administration, and/or other government and regulatory authorities.

8.8 Communicable Disease Reporting Requirements

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

8.9 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, CONRAD, and/or the US Food and Drug Administration or other government or regulatory authorities.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

The following types of specimens will be collected for processing at the LL:

- urine,
- vaginal swabs for wet mount,
- ecto- and endocervical specimens for Pap smear,
- serum, and
- plasma.

Each study site will adhere to standards of good laboratory practice, the HPTN CL Manual, the Study Specific Procedures Manual, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented in accordance with the Study Specific Procedures Manual.

9.2 Central Laboratory Specimens

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

- urine,
- vaginal swabs for dried smear and Gram staining,
- plasma,
- sno-strips, and
- CVL.

Each study site will adhere to standards of good laboratory practice, the HPTN CL Manual, and the Study Specific Procedures Manual for proper collection, processing, labeling, and transport of specimens for the HPTN CL. All specimens will be shipped in accordance with IATA specimen shipping regulations. Specimen collection, testing, storage, and shipment of all specimens analyzed by the HPTN CL will be documented using the HPTN Laboratory Data Management System (LDMS).

9.3 Quality Control and Quality Assurance Procedures

The HPTN CL has established a proficiency testing program at each study site. HPTN CL 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. CL staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

9.4 Specimen Storage and Possible Future Research Testing

As noted in Section 5, study site staff will archive serum and plasma collected from female participants at their Enrollment Visits. The purpose of this is to provide a baseline sample for possible testing in response to AEs observed during the study follow-up period. Archived serum and plasma, as well as stored residual material from genital secretion samples may possibly be used for approved AIDS-related research in the future. Storage of specimens is limited to one year after the last participant has completed follow-up (across sites), at which time all archived specimens will be discarded.

9.5 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, genital fluids, 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 United States Centers for Disease Control and Prevention.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the Study-Specific Procedures Manual — to the HPTN CORE. CORE staff will work with study site staff and complete “protocol registration” in accordance with DAIDS procedures. Included in this step will be CORE and DAIDS review of each site-specific study informed consent form.

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

10.2 Study Coordination

This study will be submitted to an existing Investigational New Drug (IND) application held by CONRAD (Number 57,833). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement executed between NIAID and CONRAD.

Study implementation will be directed by this protocol as well as the Study-Specific Procedures Manual. The Study-Specific Procedures 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 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. Representatives of the HPTN CORE and SDMC also will evaluate these rates on a regular basis. The Protocol Chair and Medical Officer 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.

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 local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, CL, NIAID, CONRAD, and US 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 NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRBs and the DAIDS Regulatory Operations Center (ROC) 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 Federal regulations, the site 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 document.

10.6 Use of Information and Publications

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

11.0 REFERENCES

1. Joint United Nations Programme on HIV/AIDS and World Health Organization (2000). *AIDS Epidemic Update: December 2000*.
2. Centers for Disease Control (1993). Update: barrier protection against HIV infection and other sexually transmitted diseases. *MMWR* 42, 589-597.
3. Stone, A.B. & Hitchcock, P. J. (1994). Vaginal microbicides for preventing the sexual transmission of HIV. *AIDS* 8, S285-S293.
4. Elias, C. J. & Coggins, C. (1996). Female-controlled methods to prevent sexual transmission of HIV. *AIDS* 10, S43-51.
5. Elias, C. J. & Heise, L. L. (1994). Challenges for the development of female-controlled vaginal microbicides [editorial]. *AIDS* 8, 1-9.
6. The International Working Group for Vaginal Microbicides (1996). Recommendations for the development of vaginal microbicides. *AIDS* 10, UNAIDS1-UNAIDS6.
7. Niruthisard, S., Roddy, R. E. & Chutivongse, S. (1991). The effects of frequent nonoxynol-9 use on the vaginal and cervical mucosa. *Sex Transm Dis* 18, 176-179.
8. Roddy, R. E., Cordero, M., Cordero, C. & Fortney, J. A. (1993). A dosing study of nonoxynol-9 and genital irritation. *Int J STD AIDS* 4, 165-70.
9. VanDamme, L. Advances in Topical Microbicides. Presented at the XIII International AIDS Conference, Durban, South Africa, July 2000.
10. CONRAD. (2001). Investigator's brochure: sodium cellulose sulfate 6% vaginal gel.
11. Godts, P. (1973). Etude Clinique sur un Contraceptif Vaginal (natr cellulose trisulfur). *ARS Medici* 6:1055-1059.
12. Martinez Sausor V. and Royo A.P. (1984). Estudio de la Eficacia y Aceptabilidad de un Espermicida Espermostatico/Vaginal en Ovulos et Portadoras de un Dispositivo Intrauterine. *El Medico* 91:82.
13. CONRAD. (2000). Final report: single and multiple exposure tolerance study of cellulose sulfate gel.
14. Nugent, R.P., Krohn, M.A., Hillier, S.L. (1991). Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol* 29, 297-301.

Appendix I: Schedule of Study Visits and Procedures

Female Participants

Procedure	Screening (up to -42)	Enrollment (Day 0)	Follow-Up (Day 7)	Follow-Up (Day 14)
Obtain informed consent	X			
Obtain informed consent from, and confirm eligibility of and consent from, male partner*	X			
Collect/update demographic and locator information	X	X	X	X
Obtain medical history	X			
Obtain participant's authorization to receive HIV-related medical records from their HIV care provider	X			
Provide HIV/STD pre-test and risk reduction counseling	X			
Provide HIV/STD test results and post-test counseling		X		
Collect urine for: -pregnancy test -leukocyte esterase screen -culture and microscopy (<i>if indicated</i>) -chlamydia and gonorrhea NAT (<i>at Screening; at follow-up only if indicated</i>)	X	X	X	X
Collect blood for: -complete blood count -CD4+cell count (<i>at Screening only</i>) -syphilis serology (<i>at Screening only</i>) -HIV serology (<i>at Screening only, if required</i>) -liver function testing -renal function testing -coagulation testing -plasma HIV viral load -plasma and serum archive (<i>at Enrollment only</i>)	X	X	X	X
Perform symptom-directed physical exam	X			
Perform pelvic exam with: -naked eye exam of external genitalia -speculum exam of vagina and cervix -vaginal pH -dried smear for Gram staining -wet mount for T. vaginalis, C. albicans, BV -Pap smear (<i>at Screening only, if required</i>) -sno-strip and cervicovaginal lavage	X	X	X	X
Perform colposcopy		X	X	X
Administer acceptability assessment		X		X
Administer study burden assessment				X
Distribute supplies/instructions	X	X	X	
Review Daily Study Records		X	X	X
Count returned product applicators			X	X
Schedule next visit	X	X	X	
Complete and submit data collection forms	X	X	X	X

*For sexually-active participants only; male partner must provide informed consent and eligibility information prior to enrollment of the female participant.

Appendix I (continued): Schedule of Study Visits and Procedures

Male Participants

Procedure	Screening/ Enrollment Visit (up to Day - 42)	During Study (Day 0 to Day 14)	Post-Study (up to Day 28)
Obtain written informed consent	X		
Collect demographic and locator information	X		
Provide HIV pre-test counseling and collect blood specimens for HIV serology	if required		
Collect focused STD history	X		
Perform genital exam	if indicated/requested		
Provide results of HIV test and post-test counseling.	if required		
Distribute condoms	X		
Complete data collection forms.	X		
Collect AE data		if indicated	
Administer acceptability assessment			X

Appendix II: Outcomes, Diagnostics, and Follow-Up Procedures

Condition	Product Use	Evaluation	Follow-up and Treatment Action
Deep Epithelial Disruption (Ulceration)	Discontinue.	Swab for herpes simplex culture. Perform syphilis serology. (Herpes serology optional.)	Re-evaluate in 5-7 days. If the ulcer has become worse or not healed in 5-7 days perform a biopsy. Ask participant to return in 7- 0 days for follow-up syphilis serology.
Superficial Epithelial Disruption (Abrasion/Peeling)	Continue.	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 hours. If condition is significantly worse, discontinue product use. Otherwise continue product use.
Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface	Continue.	Naked eye evaluation and/or colposcopy.	If asymptomatic, re-evaluate at next regularly scheduled visit. If symptomatic, re-evaluate by speculum examination in 48-72 hours. If worsened significantly, discontinue product use. Otherwise, continue product use.
Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema	Discontinue.	Naked eye evaluation and/or colposcopy.	Re-evaluate in 5-7 days.
Vaginitis (findings on exam such as vaginal discharge)	Temporarily discontinue (except for asymptomatic candida vaginitis).	Perform wet mount for <i>candida vaginitis</i> , <i>trichomoniasis</i> , and bacterial vaginosis.	See below for conditions.
Bleeding/Spotting	Temporarily discontinue (until evaluated).	Naked eye evaluation and/or colposcopy.	If determined to be endometrial bleeding with no other source, continue product use. Re-evaluate in 72 hours if the participant reports the bleeding/spotting has not resolved.
Suspected cervicitis (findings on exam such as discharge from the cervical os)	Provisionally continue.	Evaluate for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> .	Re-evaluate in 48-72 hours. If condition is worse, discontinue product use.
Petechial hemorrhage	Continue.	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48-72 hours. If condition is significantly worse, discontinue product use. Otherwise continue product use.
Ecchymosis	Continue.	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48-72 hours. If the condition is significantly worse, discontinue product use. Otherwise continue product use.

- For trichomonas or symptomatic BV, treat or refer for treatment. Do not resume product use.
- For symptomatic Candida vaginitis: manage with oral medication and re-evaluate in 3-5 days. If resolved, restart product use. If observed at Day 14, treat and follow up to document resolution.
- For asymptomatic Candida vaginitis :
 - If a participant has asymptomatic Candida vaginitis at the Day 7 Visit she should continue product use and be re-evaluated at the Day 14 Visit
 - If at the Day 14 Visit there are signs and symptoms compatible with vaginitis, treat and follow-up to document resolution.

Appendix III: Sample Informed Consent Forms

**Sample Informed Consent Form
Division of AIDS, NIAID, NIH**

**HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women**

**Final Version 2.0
11 January 2003**

Sexually Abstinent Women (Cohorts 1 and 2)

PRINCIPAL INVESTIGATOR: _____ **PHONE:** _____

INFORMED CONSENT

You are being asked to take part in the research study named above. This is a research study of a gel called Cellulose Sulfate Gel (or “CS Gel” for short). CS Gel is being developed as a “vaginal microbicide.” Vaginal microbicides are designed to be used in the vagina to prevent HIV transmission during sex. HIV is the virus that causes AIDS. Transmission means passing the virus from one person to another. Before you decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks and benefits 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 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 or to withdraw from the study at any time without losing the benefits of your routine medical care.

PURPOSE OF STUDY

The main purpose of this study is to find out if there are any bad effects when HIV-infected women use CS Gel in the vagina. CS Gel is “experimental.” This means that we do not yet know all the effects it may have on people, and we do not know if it works to protect against HIV. Because of this, the US Food and Drug Administration (FDA) has not approved CS Gel 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 CS Gel protects against HIV, we must first make sure that it is safe. So far, the safety of the gel has been tested among 24 HIV-negative women who applied the gel in the vagina and among 24 men who applied the gel to the penis. In these studies, the gel was shown to be safe and well-tolerated by both the women and the men. This study tests the safety of the gel when used by HIV-infected women, compared to a gel (K-Y Jelly) that has been approved for use as a sexual lubricant.

There are two other purposes of this study. One is to find out if CS Gel affects the amount of HIV in vaginal fluids. The other is to find out women's and men's opinions of the gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About 96 women and 48 men from Birmingham, AL; Providence, RI; Philadelphia, PA, and New York, NY will take part in the study. The study will last about 13 months. Your part will last about two months.

PROCEDURES

If you decide to join this study, and you are eligible to take part, you will have a total of 4 study visits. Each visit is described below. You will insert 3.5 mL (3/4 teaspoon) of the study gel either once or twice a day (depending on which group you are in) for 2 weeks and have follow-up visits after each week of using the gel.

Screening Visit: If you decide to take part in the study, your first visit will continue today, after you read, discuss and sign this form. No study procedures will be started before the study has been fully explained to you and you have signed this form. The visit will take 1-2 hours. To find out if you are eligible for the study you will be asked some questions, have a physical exam and a pelvic exam, give a urine sample, and have about 65 mL (or 4½ tablespoons) of blood drawn. The questions we ask will be about you, your health, and your sexual practices. If you are found to not be eligible for the study, your visit will end at that time.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical records related to your HIV infection. If your medical records are not available, you will have an HIV test. You will have counseling about HIV and other sexually transmitted diseases (STDs). You will talk about HIV/AIDS and other STDs, HIV and STD tests, what it means to know your HIV and STD status, and whether you are prepared to receive your HIV and/or STD test results. You will talk about ways that HIV and other STDs are spread, and ways to protect against them getting them and giving them to other people.

If you are willing to have STD and HIV testing (if necessary), you will give blood and urine for the tests. Your urine will be tested for infections and pregnancy. If you are pregnant, you will not be eligible for the study. Your blood will be tested to check on your overall health, immune system, liver, kidneys, HIV level, and how well your blood clots. Then you will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs, HIV level, and other possible problems.

You also will have a cervical lavage. This means a small amount of sterile water will be poured over your cervix and then collected to test for HIV levels. If your exams and tests show that you have an STD, you will not be able to join the study. However, we will refer you for medical care and other services you may need. If your exams and tests show no problems, you will continue to be eligible for the study.

Enrollment Visit: This visit will take place within 5 days after your next menstrual period. It will take about 1 hour. We will tell you your test results, including your STD and HIV test results. We will talk with you about the meaning of the results and how you feel about them. If you have an HIV test, you must receive your HIV test results to be in this study.

If the test results show that you are not eligible for the study, we will tell you about other studies you may be eligible for. We also will refer you for medical care and other services that you may need.

If you are eligible for the study, you will be asked some questions about your sexual history, your past use of vaginal products, and your opinions about vaginal products. You will give urine and about 55 mL (3½ tablespoons) of blood for testing. You will have a pelvic exam and cervical lavage. Some of your blood will be saved for testing if you have medical problems later in the study, but all of your blood will be discarded after the study is over. During the pelvic exam, the clinician will look into your vagina through a lens called a colposcope. The lens is attached to a camera, and a picture will be taken of the inside of your vagina. If your exam shows no problems, you will be entered in the study.

During the Study: You will be given pre-filled applicators of either CS Gel or the approved gel (K-Y Jelly) and instructions on how to use them. A computer program will be used to determine which gel you will use. This will be done “at random,” which means “by chance,” like flipping a coin. You will have a one-out-of-two or “50-50” chance of using each gel. Neither you nor the staff here will be able to choose which gel you use, and neither you nor the staff will know which gel you are given. 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.

You will be given a Daily Study Record to use every day to record when you used the gel, and if you had any discomfort or medical problems. You are asked to contact the study clinician if you have any discomfort or medical problems. You will bring your Daily Study Record and used and unused applicators to your follow-up visits.

Day 7 and Day 14 Follow-Up Visits: After each week of using the gel, you will return here for a Follow-up Visit. These visits will take about 1 hour. You will review your Daily Study Record with the study clinician and answer questions about your use of the gel and whether you had any medical problems or discomfort. You will give urine and blood (about 45 mL or 3 tablespoons) for testing like at the Enrollment Visit, and have a pelvic exam with the colposcope and cervical lavage. A picture will be taken of the inside of your vagina. At the Day 14 visit, you will have an interview on your thoughts and opinions of the gel, and what it was like to be in the study.

Contact Procedures: Once you join the study, 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 you 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, or other people in your home, we will not tell them why we are trying to reach you.

Other Requirements:

You **must not** do the following starting 72 hours (3 days) before your Enrollment Visit and during the entire time while in this study:

- have vaginal or anal sex
- have oral contact with the vagina (oral sex)
- douche
- insert fingers, sex toys, or any other products into the vagina
- use drugs except for medical use

You **must not** use spermicides or condoms lubricated with spermicides starting 7 days before your Enrollment Visit and during the entire time while in the study.

You are asked to tell the study clinician about any medications you take while in the study. You are asked not to take part in studies of other vaginal products and to tell the study staff if you plan to join another study.

If you have any medical problems or discomfort from the gel, you are asked to report them to the study clinician right away. The clinician will let you know what to do in case of a medical emergency, and may ask you to come in for an extra study visit to check on these problems. If a problem like a sore is found during a pelvic exam, the clinician may take a picture of it with the colposcope. The clinician also will use a swab to take a sample to test for STDs. After 5-7 days, you will be asked to come back for another exam with the colposcope. If the sore has not healed, the clinician will remove small samples of the skin (about the size of a pencil tip) for more testing.

If you miss or skip an application on one or two days, the study staff may ask you to continue using the gel for one or two days to make up for the days that were missed.

If you stop using the gel before the end of 14 days, study staff may ask you to complete a final study visit with a pelvic exam. They also may ask you to have the interview about your thoughts and opinions of the gel and what it was like to be in the study.

You must return all applicators (used or unused) to the study site.

Some of your blood and vaginal fluid that is left over after all required study testing is done may be stored and used for HPTN (HIV Prevention Trials Network) – approved HIV-related research. To protect your privacy, these samples will be marked with a numbered code only, not your name. No testing will be done on this leftover blood or vaginal fluid without your permission. All of your stored blood and vaginal fluid will be destroyed one year from the date of the last participant's final study visit.

RISKS AND/OR DISCOMFORTS

You may feel discomfort when having pelvic exams for this study. You also may feel discomfort when blood is drawn. You may feel dizzy or faint. You may have a bruise or swelling where the needle goes into your arm. There is a very small chance of getting an infection at the site where the blood is drawn.

You may become embarrassed, worried, or anxious when discussing sexual behaviors, STDs, and HIV. You may become worried or anxious while waiting for your STD and/or HIV test results. If you have HIV and/or an STD, knowing this could make you worried or anxious. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

You may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

Women in this study will be the first HIV-infected women to use CS Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. Some of the HIV-negative women who used CS Gel or the approved gel (K-Y Jelly) in other studies had vaginal redness, itching, burning, and pain; abnormal bleeding; and abdominal pain and tenderness. You could experience these effects or other effects that we do not yet know about. It is not known whether CS Gel has any effect on the HIV virus or the disease condition of HIV-infected people.

Some lab tests have indicated that CS Gel could effect how long it takes for blood to clot. When HIV-negative women used CS Gel in other studies, tests were done to see if there were any changes in how long it took for their blood to clot, and no changes were seen. It is possible, however, that CS Gel could affect blood clotting in HIV-positive women.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your HIV infection or your participation here. 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.

PREGNANCY

It is not known whether CS Gel has any effect on pregnancy or on the fetus. Due to the unknown effects and safety concerns of the gel, pregnant women may not join this study. You must have a negative pregnancy test before you join this study.

You have agreed to not have vaginal sex while using the study gel. However, if for any reason you do have vaginal sex while using the study gel, you must use the condoms given to you by the study staff as birth control, and protection for your partner (even if you are already using another form of birth control).

If you become pregnant during the study you should tell the study clinician right away. You will stop using the study gel and the study clinician will discuss your choices with you. The study clinician will contact you every three months during pregnancy, and every three months for one year after the baby is born so that we can find out about your health and your baby's health.

Because it is not known whether CS Gel passes through breast-milk and produces undesirable effects in the infant, women who are breastfeeding may not be in the study.

BENEFITS

This study may be of no direct benefit to you. However, you or others may benefit in the future from information learned in this study.

You will receive pelvic exams and counseling and testing for HIV and STDs. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If we find that you are infected with an STD, or have other medical problems, we will refer you for medical care and other services you may need. We will tell you about other research studies that you may be eligible for (if any).

NEW FINDINGS

You will be told of 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 study doctor decides that continuing in the study would be harmful to you;
- you need a treatment not allowed on this study;
- you are unable to keep appointments or use the study gel as instructed;
- you have a bad reaction to the study gel;
- you become pregnant;
- the study is cancelled by the FDA, NIAID, or CONRAD; and/or
- other administrative reasons.

COSTS TO YOU

There is no cost to you for taking part in the study.

You will be reimbursed for your time and effort for this study. You will receive (insert site-specific amount of money) for each scheduled study visit.

CONFIDENTIALITY

Your research records, including the pictures of your vagina, will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the FDA, NIAID, CONRAD, and study monitors.

[Sites to include/amend the following if applicable: State laws require the study staff to report the names of people who test positive for HIV and STDs to the [local health authority.] If you have HIV or an STD, 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 tell them of their possible infection, according to the confidentiality guidelines of the [health authority].

RESEARCH-RELATED INJURY

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 for the treatment will be charged to you or your insurance. 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 your injuries.

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

PROBLEMS OR QUESTIONS

If you ever have questions about this study or in case of research related injuries, you should contact *(name of investigator or study clinician)* at *(telephone number)*. If you ever have questions about your rights as a research participant you can call *(name and title of IRB member)* at *(telephone number)*.

SIGNATURES

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

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

_____	_____	_____
Participant Name (printed)	Participant Signature	Date

_____	_____	_____
Witness Name (printed)	Witness Signature	Date

**Sample Informed Consent Form
Division of AIDS, NIAID, NIH**

**HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women**

**Final Version 2.0
11 January 2003**

Sexually Active Women (Cohorts 3 and 4)

PRINCIPAL INVESTIGATOR: _____ **PHONE:** _____

INFORMED CONSENT

You are being asked to take part in the research study named above. This is a research study of a gel called Cellulose Sulfate Gel (or “CS Gel” for short). CS Gel is being developed as a “vaginal microbicide.” Vaginal microbicides are designed to be used in the vagina to prevent HIV transmission during sex. HIV is the virus that causes AIDS. Transmission means passing the virus from one person to another. Before you decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks and benefits 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 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 or to withdraw from the study at any time without losing the benefits of your routine medical care.
- You cannot take part in the study unless your male sexual partner also agrees to take part.

PURPOSE OF THE STUDY

The main purpose of this study is to find out if there are any bad effects when HIV-infected women use CS Gel in the vagina. CS Gel is “experimental.” This means that we do not yet know all the effects it may have on people, and we do not know if it works to protect against HIV. Because of this, the US Food and Drug Administration (FDA) has not approved CS Gel 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 CS Gel protects against HIV, we must first make sure that it is safe. So far, the safety of the gel has been tested among 24 HIV-negative women who applied the gel in the vagina and among 24 men who applied the gel to the penis. In these studies, the gel was shown to be safe and well-tolerated by both the women and the men. This study tests the safety of the gel when used by HIV-infected women, compared to a gel (K-Y Jelly) that has been approved for use as a sexual lubricant.

There are two other purposes of this study. One is to find out if CS Gel affects the amount of HIV in vaginal fluids. The other is to find out women’s and men’s opinions of the gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About 96 women and 48 men from Birmingham, AL; Providence, RI; Philadelphia, PA; and New York, NY will take part in the study. The study will last about 13 months. Your part will last about two months.

PROCEDURES

If you decide to join this study, and you are eligible to take part, you will have a total of 4 study visits. Each visit is described below. You will insert 3.5 mL (3/4 teaspoon) of the study gel either once or twice a day (depending on which group you are in) for 2 weeks and have follow-up visits after each week of using the gel.

Screening Visit: If you decide to take part in the study, your first visit will continue today, after you read, discuss and sign this form. Your male sexual partner will also be asked to give his informed consent and sign a similar form before your next visit. No study procedures will be started before the study has been fully explained to you and you have signed this form. The visit will take 1-2 hours. To find out if you are eligible for the study you will be asked some questions, have a physical exam and a pelvic exam, give a urine sample, and have about 65mL (or 4½ tablespoons) of blood drawn. The questions we ask will be about you, your health, your male sexual partner and your sexual practices. If you are found to not eligible for the study, your visit will end at that time.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical records related to your HIV infection. If your medical records are not available, you will have an HIV test. You will have counseling about HIV and other sexually transmitted diseases (STDs). You will talk about HIV/AIDS and other STDs, HIV and STD tests, what means to know your HIV and STD status, and whether you are prepared to receive your HIV and/or STD test results. You will talk about ways that HIV and other STDs are spread, and ways to protect against getting them and giving them to other people.

If you are willing to have STD and HIV testing (if necessary), you will give blood and urine for the tests. Your urine will be tested for infections and pregnancy. If you are pregnant, you will not be eligible for the study. Your blood will be tested to check on your overall health, immune system, liver, kidneys, and HIV level and how well your blood clots. Then you will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs, HIV level, and other possible problems.

You also will have a cervical lavage. This means a small amount of sterile water will be poured over your cervix and then collected to test for HIV levels. If your exams and tests show that you have an STD, you will not be able to join the study. However, we will refer you for medical care and other services you may need. If your exams and tests show no problems, you will continue to be eligible for the study.

Your male sexual partner will be asked to give his informed consent for this study and be asked about his health and sexual practices. He will be counseled and tested for HIV if necessary. If he is not willing to give his written consent, or if he is not eligible for the study, both of you will not be eligible for the study.

Enrollment Visit: This visit will take place within 5 days after your next menstrual period. By the time of this visit, your male sexual partner must come to the study site to give his informed consent, and to answer some questions to confirm his eligibility. We will tell you your test results, including your STD and HIV test results. We will talk with you about the meaning for the results and how you feel about them. If you have an HIV test, you must receive your HIV test results to be in this study.

If the test results show that you are not eligible for the study, we will tell you about other studies you may be eligible for. We also will refer you for medical care and other services that you may need.

If you are eligible for the study, you will be asked some questions about your sexual history, your past use of vaginal products, and your opinions about vaginal products. You will give urine and about 55 mL (3½ tablespoons) of blood for testing. You will have a pelvic exam and cervical lavage. Some of your blood will be saved for testing if you have medical problems later in the study, but all of your blood will be discarded after the study is over. During the pelvic exam, the clinician will look into your vagina through a lens, called a colposcope. The lens is attached to a camera, and a picture will be taken of the inside of your vagina. If your exam shows no problems, you will be entered in the study.

During the Study: You will be given pre-filled applicators of either CS Gel or the approved gel (K-Y Jelly) and instructions on how to use them. A computer program will be used to determine which gel you will use. This will be done “at random,” which means “by chance,” like flipping a coin. You will have a one-out-of-two or “50-50” chance of using each gel. Neither you nor the staff here will be able to choose which gel you use, and neither you nor the staff will know which gel you are given. 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.

You are asked to have vaginal sex with your male partner who has consented to be in this study with you as often as you usually do (at least 2 times per week), and to use study-provided condoms each time you have sex. You are asked to have sex only with this partner.

You will be given a Daily Study Record to use every day to record when you used the gel, and if you had any discomfort or medical problems. You are asked to contact the study clinician if you have any discomfort or medical problems. You will bring your Daily Study Record and used and unused applicators to your follow-up visits.

Day 7 and Day 14 Follow-Up Visits: After each week of using the gel, you will return here for a Follow-up Visit. These visits will take about 1 hour. You will review your Daily Study Record with the study clinician and answer questions about your use of the gel and whether you had any medical problems or discomfort. You will give urine and blood (about 45 mL or 3 tablespoons) for testing like at the Enrollment Visit, and have a pelvic exam with the colposcope and cervical lavage. A picture will be taken of the inside of your vagina. At the Day 14 visit, you will have an interview on your thoughts and opinions of the gel, and what it was like to be in the study.

Contact Procedures: Once you join the study, 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 you 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, or other people at your home, we will not tell them why we are trying to reach you.

Other Requirements:

You **must not** have vaginal sex during the 72 hours (3 days) before your Enrollment Visit.

You **must not** do the following starting 72 hours (3 days) before your Enrollment Visit and during the entire time while in this study:

- have oral contact with the vagina (oral sex)
- have anal sex
- douche
- insert fingers, sex toys, or any other products into the vagina
- use drugs except for medical use

You **must not** use spermicides or condoms lubricated with spermicides starting 7 days before your Enrollment Visit and during the entire time while in the study.

You are asked to tell the study clinician about any medications you take while in the study. You are asked not to take part in studies of other vaginal products and to tell the study staff if you plan to join another study.

If you have any medical problems or discomfort from the gel, you are asked to report them to the study clinician right away. The clinician will let you know what to do in case of a medical emergency, and may ask you to come in for an extra study visit to check on these problems. If a problem like a sore is found during a pelvic exam, the clinician may take a picture of it with the colposcope. The clinician also will use a swab to take a sample to test for STDs. After 5-7 days, you will be asked to come back for another exam with the lens. If the sore has not healed, the clinician will remove small samples of the skin (about the size of a pencil tip) for more testing.

If you miss or skip an application on one or two days, the study staff may ask you to continue using the gel for one or two days to make up for the days that were missed.

If you stop using the gel before the end of 14 days, study staff may ask you to complete a final study visit with a pelvic exam. They also may ask you to have the interview about your thoughts and opinions of the gel and what it was like to be in the study.

You must return all applicators (used or unused) to the study site.

Some of your blood and vaginal fluid that is left over after all required study testing is done may be stored and used for HPTN (HIV Prevention Trials Network) – approved HIV-related research. To protect your privacy, these samples will be marked with a numbered code only, not your name. No testing will be done on this leftover blood or vaginal fluid without your permission. All of your stored blood and vaginal fluid will be destroyed one year from the date of the last participant's final study visit.

RISKS and/or DISCOMFORTS:

You may feel discomfort when having pelvic exams for this study. You also may feel discomfort when blood is drawn. You may feel dizzy or faint. You may have a bruise or swelling where the needle goes into your arm. There is a very small chance of getting an infection at the site where the blood is drawn.

You may become embarrassed, worried, or anxious when discussing sexual behaviors, STDs, and HIV. You may become worried or anxious while waiting for your STD and/or HIV test results. If you have HIV and/or an STD, knowing this could make you worried or anxious. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

You may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

Women in this study will be the first HIV-infected women to use CS Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. Some of the HIV-negative women who used CS Gel or the approved gel (K-Y Jelly) in other studies had vaginal redness, itching, burning, and pain; abnormal bleeding; and abdominal pain and tenderness. You could experience these effects or other effects that we do not yet know about. It is not known whether CS Gel has any effect on the HIV virus or the disease condition of HIV-infected people.

Since you will be having vaginal sex with an HIV infected partner, repeated exposure to HIV may increase your chances of becoming infected with a more active or resistant strain of HIV.

Some lab tests have indicated that CS Gel could effect how long it takes for blood to clot. When HIV-negative women used CS Gel in other studies, tests were done to see if there were any changes in how long it took for their blood to clot, and no changes were seen. It is possible, however, that CS Gel could affect blood clotting in HIV-positive women.

There is also a possibility that you could be allergic to the material (latex) used to make condoms. "Allergic" means that you have itching, swelling, or skin irritation where the condom touches your skin.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your HIV infection or your participation here. 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.

PREGNANCY

It is not known whether CS Gel has any effect on pregnancy, or effect on the fetus. Due to the unknown effects and safety concerns of the gel, pregnant women may not join this study. You must have a negative pregnancy test before you join this study. You also must use a study-provided condom each time you have sex while in the study as birth control, and protection for your partner (even if you are already using another form of birth control).

If you become pregnant during the study you should tell the study clinician right away. You will stop using the study gel and the clinician will discuss your choices with you. The study clinician will contact you every three months during pregnancy, and every three months for one year after the baby is born so that we can find out about your health and your baby's health.

Because it is not known whether CS Gel passes through breast-milk and produces undesirable effects in the infant, women who are breastfeeding may not be in the study.

BENEFITS

This study may be of no direct benefit to you. However, you or others may benefit in the future from information learned in this study.

You will receive pelvic exams and counseling and testing for HIV and STDs. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If we find that you are infected with an STD, or have other medical problems, we will refer you for medical care and other services you may need. We will tell you about other research studies that you may be eligible for (if any).

NEW FINDINGS

You will be told of 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 study doctor decides that continuing in the study would be harmful to you;
- you need a treatment not allowed on this study;
- you are unable to keep appointments or use the study gel as instructed;
- you have a bad reaction to the study gel;
- you become pregnant;
- your partner stops taking part in the study;
- the study is cancelled by the FDA, NIAID, CONRAD; and/or
- other administrative reasons.

COSTS TO YOU

There is no cost to you for taking part in the study.

You will be reimbursed for your time and effort for this study. You will receive (insert site-specific amount of money) for each scheduled study visit.

CONFIDENTIALITY

Your research records, including the pictures of your vagina, will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. Your information and test results will not be given to your male sexual partner without your permission, and your male sexual partner's information will not be given to you without his permission. Your records may be reviewed, under guidelines of the Federal Privacy Act, by the FDA, NIAID, CONRAD, and study monitors.

[Sites to include/amend the following if applicable: State laws require the study staff to report the names of people who test positive for HIV and STDs to the [local health authority.] If you have HIV or an STD, 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 tell them of their possible infection, according to the confidentiality guidelines of the [health authority].

RESEARCH-RELATED INJURY

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 for the treatment will be charged to or your insurance. 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 your injuries.

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

PROBLEMS OR QUESTIONS

If you ever have questions about this study or in case of research related injuries, you should contact (*name of investigator or study clinician*) at (*telephone number*). If you ever have questions about your rights as a research participant, you can call (*name and title of IRB member*) at (*telephone number*).

SIGNATURES

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

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

_____	_____	_____
Participant Name (printed)	Participant Signature	Date

_____	_____	_____
Witness Name (printed)	Witness Signature	Date

**Sample Informed Consent Form
Division of AIDS, NIAID, NIH**

**HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women**

**Final Version 2.0
11 January 2003**

Male Partners

PRINCIPAL INVESTIGATOR: _____ **PHONE:** _____

INFORMED CONSENT

You are being asked to take part in the research study named above. This is a research study of a gel called Cellulose Sulfate Gel (or “CS Gel” for short). CS Gel is being developed as a “vaginal microbicide.” Vaginal microbicides are designed to be used in the vagina to prevent HIV transmission during sex. HIV is the virus that causes AIDS. Transmission means passing the virus from one person to another. Before you decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks and benefits 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 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 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, your partner will not be able to take part.

PURPOSE OF THE STUDY

The main purpose of this study is to find out if there are any bad effects when HIV-infected women use CS Gel in the vagina. CS Gel is “experimental.” This means that we do not yet know all the effects it may have on people, and we do not know if it works to protect against HIV. Because of this, the US Food and Drug Administration (FDA) has not approved CS Gel 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 CS Gel protects against HIV, we must first make sure that it is safe. So far, the safety of the gel has been tested among 24 HIV-negative women who applied the gel in the vagina and among 24 men who applied the gel to the penis. In these studies, the gel was shown to be safe and well-tolerated by both the women and the men. This study tests the safety of the gel when used by HIV-infected women, compared to a gel (K-Y Jelly) that has been approved for use as a sexual lubricant.

There are two other purposes of this study. One is to find out if CS Gel affects the amount of HIV in vaginal fluids. The other is to find out men’s and women’s opinions of the gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About 96 women and 48 men from Birmingham, AL; Providence, RI; Philadelphia, PA; and New York, NY will take part in the study. The study will last about 13 months. Your part will last about six weeks.

PROCEDURES

Screening/Enrollment Visit: After you read this form, you will have as much time as you need to ask questions to make sure that you fully understand the study. No study procedures will be started before the study has been fully explained to you and you have signed this form.

If you decide to take part in the study, your visit will continue today and will last about 1 hour. You will be asked some questions about your health and about your sexual history, and you may have a genital exam to find out if you are eligible to be in this study. The genital exam is optional; you may chose not to have a genital exam. If you are not eligible for the study, visit will end, and you and your partner will not be able to join the study.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical records related to your HIV infection. If your medical records are not available, you will have an HIV test. You will have counseling about HIV and other sexually transmitted diseases (STDs). You will talk about HIV/AIDS and other STDs, HIV tests, what means to know your HIV and STD status, and whether you are prepared to receive your HIV test results. You will talk about ways that HIV and other STDs are spread, and ways to protect against getting and giving them to other people.

If you are willing to undergo HIV testing (if necessary) you will give about 10 mL (or 2 teaspoons of blood) for the test. Your test results will be available in about [X days/weeks; sites to specify]. You must receive your HIV test result to be in the study, and you may be asked to return to the clinic to receive your result. If you are not infected with HIV, you and your partner will not be eligible for the study.

During the Study: If you and your partner are eligible for the study, and agree to take part, your partner will be given pre-filled applicators of either CS Gel or the approved gel (K-Y Jelly) to apply in her vagina for 14 days. A computer program will be used to determine which gel your partner will be given. This will be done “at random,” which means “by chance,” like flipping a coin. You and your partner will have a one-out-of-two or “50-50” chance of using each gel. Neither you, your partner, nor the staff here will be able to choose which gel you use, and no one will know which gel you are given. 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 and your partner used.

You are asked to have vaginal sex with your partner as often as you usually do (at least two times per week) while your partner is using the study gel. You must use study-provided condoms each time you and your partner have sex. You are asked to have sex only with this partner.

You also are asked to tell the study clinician if your skin comes into contact with the study gel. If this happens, the clinician will ask you if you had any reactions to the gel. You also may be asked to come to the clinic for an exam.

After you and your partner use the gel for 14 days, you will have an interview about your experience with the gel and the study. The interview can be done in person or by phone and will take about 30 minutes.

Contact Procedures: Once you join the study, 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 you 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:

You **must not** have vaginal sex with your partner during the 72 hours (3 days) before her Enrollment Visit.

You **must not** do the following during the 72 hours (3 days) before your partner's Enrollment visit and during the entire time while in this study:

- have oral contact with your partner's vagina (oral sex)
- have anal sex with your partner
- insert fingers, sex toys, or any other products into your partner's vagina

You **must not** use spermicides or condoms lubricated with spermicides starting 7 days before your Enrollment Visit and during the entire time while in the study.

RISKS AND/OR DISCOMFORTS

Because you will have sex with your partner after she puts the gel in her vagina, it is possible that some of the gel will come into contact with your skin. CS gel or the approved gel (K-Y Jelly) may cause irritation to the skin on or around the penis. For example, some HIV-negative men who applied CS Gel to the penis in other studies felt some mild tingling or stinging. It is important to use the gel only as instructed by the study staff, and to use condoms every time you have sex with your partner.

There is a possibility you may be allergic to the material (latex) used to make condoms. "Allergic" means you have itching, swelling, or skin irritation where the condom touches your skin.

It is not known whether CS Gel has any effect on the HIV virus or the disease condition of HIV-infected people.

Since you will be having vaginal sex with an HIV infected partner, repeated exposure to HIV may increase your chances of becoming infected with a more active or resistant strain of HIV.

Some of the interview questions may cause you to be embarrassed. You may choose not to answer any of these questions if you wish.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your HIV infection or participation here. 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.

BENEFITS

This study may be of no direct benefit to you. However, you or others may benefit in the future from information learned in this study. If you have any symptoms of STDs, the clinician may examine you and/or refer you for counseling, tests, and treatment. This study cannot provide you with medical care, but study staff will refer you to other available sources of care.

NEW FINDINGS

You will be told of 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:

- your partner stops taking part in the study;
- the study doctor decides that continuing in the study would be harmful to you or your partner;
- the study is cancelled by the FDA, NIAID, CONRAD; and/or
- other administrative reasons.

COSTS TO YOU

There is no cost to you for taking part in the study.

You will be reimbursed for your time and effort in this study. You will receive (insert site-specific amount of money) for your Screening/Enrollment visit and (insert site-specific amount of money) for the interview at the end of the study.

CONFIDENTIALITY

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. Your information and test results will not be given to your partner without your permission, and your partner's information will not be given to you without her permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the National Privacy Act, by the FDA, NIAID, CONRAD, and study monitors.

[Sites to include/amend the following if applicable: State laws require the study staff to report the names of people who test positive for HIV and STDs to the [local health authority.] If you have HIV or an STD, 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 tell them of their possible infection, according to the confidentiality guidelines of the [health authority].

RESEARCH-RELATED INJURY

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 for the treatment will be charged to you or your insurance. 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 your injuries.

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

PROBLEMS OR QUESTIONS

If you ever have questions about this study or in case of research related injuries, you should contact (*name of investigator or study clinician*) at (*telephone number*). If you ever have questions about your rights as a research participant you can call (*name and title of IRB member*) at (*telephone number*).

SIGNATURES

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

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

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

Appendix IV: Sample Informed Consent For The Storage Of Specimens Obtained While Participating In A DAIDS-Sponsored Research Trial

**Sample Informed Consent Form Page
Division of AIDS, NIAID, NIH**

**HPTN 049
Phase I Safety and Acceptability Study of the Vaginal Microbicide
6% Cellulose Sulfate Gel Among HIV-Infected Women**

**Final Version 2.0
11 January 2003**

**INFORMED CONSENT FOR THE STORAGE OF SPECIMENS
OBTAINED WHILE PARTICIPATING IN A DAIDS-SPONSORED
RESEARCH TRIAL**

INTRODUCTION

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

HOW WILL YOU GET THE SAMPLES FROM ME?

There will be NO ADDITIONAL samples taken from you for storage. After all the tests are done for this research study, there may be some blood or genital fluids left over. If you agree, left over samples will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples 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 specimens 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 samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will 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 samples 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 SAMPLES?

Your samples will be stored for one year after the last participant has completed their part of the study. After that, your samples will be destroyed.

HOW WILL MY SAMPLES BE STORED?

Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples 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 SAMPLES BENEFIT ME?

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

WHAT ARE THE RISKS?

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

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

People who may review your records include: *(insert Name of Site)* IRB, National Institutes of Health (NIH), study staff, study monitors, and their designees.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study.

If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used.

WHAT DO I DO IF I HAVE QUESTIONS?

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

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

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 my left over samples of blood and genital fluids stored and tested for future research related to HIV infection.

_____Yes

_____No

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

Participant's Name

Participant's Signature

Date

Study Staff Conducting
Consent Discussion

Study Staff Signature

Date

Witness' Name
(As appropriate)

Witness's Signature

Date