

DATE: 14 May 2003

RE: LETTER OF AMENDMENT FOR: HPTN 050, Version 2.0, dated 29 May 2002.

Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

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

FROM: Antonia Kwecien, CORE Protocol Specialist

THE FOLLOWING INFORMATION IMPACTS THE HPTN 050 STUDY 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

- The entry criteria have been amended to exclude women being treated with systemic PMPA from the pharmacokinetic study.

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

1. In the protocol Section 2.5:

In addition to the study procedures described above, the first six participants in cohorts A₂, B, and C will take part in a PK study of PMPA gel. **(If one of the first six participants in the C cohort is being treated with systemic PMPA, the participant will be enrolled in the non-PK study, and then subsequent slots will be filled for the PK study. No more than six participants being treated with systemic PMPA can enroll in the C cohort.)** At their study Day 0 Enrollment Visit and on study Day 13, ~~these participants enrolled in the PK study~~ will apply the first daily dose of PMPA gel at the study site and undergo phlebotomy for serum collection and PK analysis immediately prior to dosing then again at 0.5, 1, 2, 4, 6, 8, 12 hours

on both visits. An additional draw will be taken at 24 hours post dosing on the Day 13 Visit. For participants in cohorts B and C, if the HPDF of product use is determined to be twice daily, the second daily dose will be omitted on Day 13. Participants either will either stay at the clinic and/or will have an IV line inserted and be allowed to leave the clinic and return in time for scheduled blood draws. This decision will be made by the site investigator on a participant by, participant basis.

All PK samples will be shipped to the Contract Lab [refer to SSP Manual for sample collection and shipping details] for batched assay. Samples from each subject on both PK days will be run together. PK data from cohort A₂ will be analyzed once all the required samples from this cohort are received and assayed. If this analysis indicates that the cohort A₂ participants absorbed PMPA systemically and there was detectable study drug in the 24 hour sample on Day 14, PK study participants in cohorts B and C will have additional PK samples drawn at 48 and 72 hours post dosing. If the analysis indicates that unanticipated absorption of PMPA is found in any of the cohorts and/or more adverse events such as mucosal inflammation are found than expected in any participant, PK testing as described above for cohorts B and C will be done in six (but not necessarily the first six) of the D cohort participants. **(Participants in the D cohort being treated with systemic PMPA will not be enrolled in the PK study.)**

The principal parameter of interest after intravaginal dosing will be the AUC.

2. In the protocol Section 3.5.1 (new section):

3.5.1 Exclusion Criteria – Women, PK Study

The PK study will exclude all women being treated with systemic PMPA.

DATE: 31 January 2003

RE: LETTER OF AMENDMENT FOR: HPTN 050, Version 2.0, dated 29 May 2002.

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Summary of Revisions

- The product application regimen has been revised to allow participants enrolled in twice daily dose frequency cohorts to apply the morning dose if the follow-up pelvic and/or colposcopy examination is scheduled in the afternoon.
- Other administrative clarifications have been incorporated in the protocol as needed.

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

1. In the protocol Section 2.4.2:

In addition, all female participants will take part in follow-up focus groups and the male sexual partners of the sexually active participants (B and D cohorts) will have in depth individual interviews within ~~four~~ **six** weeks of completing the 14-day dosing regimen.

2. In the protocol Section 4.2.4:

Participants will be instructed to delay any morning dose of product until after the **Day 2 or 3 Follow-up Visit**, Day 7 Follow-up Visit, and Interim Visits requiring pelvic and/or colposcopy examination, **unless the examination is scheduled in the afternoon**. The participant will be instructed to discontinue product use after the evening application on Day 13.

Cohort A participants enrolled in the PK study will be asked to administer the first dose in the clinic on Day 0 after the pelvic exam. Participants will be instructed not to administer the product the night prior to the Day 13 Visit. They will apply the product ~~after the pelvic exam~~ during the Day 13 Visit.

If the HPDF is determined to be twice daily, cohorts B and C (and cohort D if indicated as per Section 2.5) participants enrolled in the PK study will be instructed to administer the product on Day 0 after the pelvic exam and again after the 12 hour PK draw. For the Day 13 Visit, participants will be instructed to apply their morning dose ~~after the pelvic exam~~ **during the Day 13 Visit, and** then discontinue product use (i.e. omit the second final Day 13 dose).

HIV Prevention Trials Network

Protocol 050: Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

CLARIFICATION MEMO #2

09 December 2002
IND # 57,833

Summary of Revisions

- A definition for abnormal Pap smear has been added.

The following protocol modification, indicated **bold** text, is made to the HPTN 050 Protocol:

1. At the end of Section 3.5:

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 HSIL (ASC-H)), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (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.

5. In the protocol Section 5.1.3.1, sixth bullet, first sub bullet:
Collect urine specimen for ~~LCR~~ **NAT** for *N. gonorrhoeae* and *C. trachomatis*.
6. In the protocol Sections 5.1.3.2, and 5.1.6.3 sixth bullet, first and second sub bullets:
Conduct ~~LCR~~ **NAT** for *C. trachomatis*.
Conduct ~~LCR~~ **NAT** for *N. gonorrhoeae*
7. In the protocol Section 5.1.5.1, ninth bullet, first sub bullet:
Collect urine for ~~LCR~~ **NAT** for *N. gonorrhoeae* and *C. trachomatis*.
8. In the protocol Section 5.1.5.2, eighth bullet, first and second sub bullets:
Conduct ~~LCR~~ **NAT** for *C. trachomatis*.
Conduct ~~LCR~~ **NAT** for *N. gonorrhoeae*
9. In the protocol Section 5.1.6.2, fifth bullet, first sub bullet:
Collect urine for ~~LCR~~ **NAT** for *N. gonorrhoeae* and *C. trachomatis*.
10. In Appendix II, seventh row after the first title row:

LCR NAT ^e	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i>	Urine	15-20 mL	CL
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HPTN 050
Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

A Study of the HIV Prevention Trials Network

Sponsored by:

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

Co-Sponsored by:

Gilead Sciences

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(Held by DAIDS)

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Final Version 2.0
29 May 2002

HPTN 050
Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
AE	adverse experience
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration curve
BMD	bone mineral density
BV	bacterial vaginosis
CBC	complete blood count
CC ₅₀	concentration causing 50% cytotoxicity
CL	Central Lab
CK	creatin kinase
CORE	Coordinating and Operations Center
CRF	case report form
CRPMC	Clinical Research Products Management Center
CVL	cervico-vaginal lavage
d4T	stavudine
DAIDS	Division of AIDS
DAVG	time-weighted changes from baseline average
EIA	Enzyme Immuno Assay
FDA	Food and Drug Administration
FTA	fluorescent triponemal antibody
HCG	Human Chorionic Gonadotropin
HIV, HIV-1	human immunodeficiency virus, type 1
HPTN	HIV Prevention Trials Network
HPDF	highest practical dose frequency
HSV, HSV-2	herpes simplex virus, type 2
IC ₅₀	concentration that inhibits 50 percent
IRB	Institutional Review Board
IV	intravenous
MHA-TP	microhemagglutination- <i>Treponema pallidum</i>
mL	milliliter
N-9	nonoxynol-9
PBMC	peripheral blood mononuclear cells
PK	pharmacokinetic
PMPA	((R)-9-(2-Phosphonylmethoxypropyl)adenine)
po	by mouth
NIAID	National Institute of Allergy and Infectious Diseases
RNA	ribonucleic acid
ROC	Regulatory Operations Center
SAE	serious adverse experience
sc	subcutaneous
SDMC	Statistical and Data Management Center
SIV	simian immunodeficiency virus
STD	sexually transmitted disease
SSP	study specific procedures
WB	Western Blot
w/v	weight in volume
ZVD	zidovudine

HPTN 050

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HPTN 050
Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel

SCHEMA

- Purpose:** To determine the safety and acceptability of PMPA gel for vaginal use among sexually abstinent and sexually active HIV-uninfected, and HIV-infected women; and to determine the acceptability of PMPA gel among their male sexual partners (when relevant).
- Design:** Phase I multisite stepped parallel dose and frequency study with 14 days of product exposure and up to 21 days of follow-up for each female participant.
- Study Population:** Up to 72 HIV-uninfected women (up to 60 sexually abstinent and up to 12 sexually active), up to 24 HIV-infected women (up to 12 sexually abstinent and up to 12 sexually active) and up to 24 male sexual partners (12 HIV-uninfected and 12 HIV-infected)
- Treatment Regimen:** Participants in cohorts A - D will apply PMPA gel intravaginally for 14 intramenstrual days and participants in cohort V (if required) will apply the gel vehicle only as follows:

Cohort	Description	N	Dose	Frequency
A ₁	HIV-uninfected/abstinent	12	0.3%	once daily
A ₂	HIV-uninfected/abstinent	12	1.0%	once daily
A ₃	HIV-uninfected/abstinent	12	0.3%	twice daily
A ₄	HIV-uninfected/abstinent	12	1.0%	twice daily
B	HIV-uninfected/active and their male sexual partners	12	highest practical dose frequency	
C	HIV-infected/abstinent	12	highest practical dose frequency	
D	HIV-infected/active and male sexual partners	12	highest practical dose frequency	
V	HIV-uninfected/abstinent (if required)	12	vehicle only	once daily

Study Duration: Accrual will require 11 months. Each participant will be followed for up to 21 days. Acceptability interviews will be convened within four weeks after the completion of product use and follow-up. Therefore the entire study should be completed within 13 months.

Primary Objectives:

- To assess the safety and toxicity of PMPA gel for vaginal use in assigned doses and frequency on vulvar and cervico-vaginal mucosa in HIV-uninfected women at low risk for HIV infection and in HIV-infected women
- To assess the systemic safety and absorption of PMPA gel for vaginal use in low-risk, HIV-uninfected women and in HIV-infected women.

Secondary Objectives:

- To assess the acceptability of, and adherence to, a short-term regimen of PMPA gel for vaginal use in low-risk, HIV-uninfected women and in HIV-infected women and their male sexual partners (when relevant).
- To examine qualitative aspects of acceptability and adherence, as a pilot for substantive qualitative and quantitative assessments in future studies.

Exploratory Objectives:

- To measure the occurrence of cervico-vaginal shedding of HIV over the course of PMPA vaginal gel use.
- To assess the genotypic resistance patterns of HIV in genital secretions and blood samples from the HIV-infected female participants over the course of PMPA vaginal gel use.
- To measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of PMPA vaginal gel use.

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 Pennsylvania, Philadelphia, PA, USA

1.0 INTRODUCTION

1.1 Topical Microbicides and Human Immunodeficiency Virus (HIV) Prevention

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. Most 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 control 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 PMPA gel ((R)-9-(2-Phosphonylmethoxypropyl) adenine), otherwise known as Tenofovir.

1.2 PMPA gel

1.2.1 General

PMPA is an adenosine nucleoside monophosphate (nucleotide) belonging to the class of acyclic phosphonomethylether nucleotides. Currently approved anti-retroviral nucleoside therapies such as zidovudine (ZVD), stavudine (d4T) and lamivudine (3TC) require cellular enzymes for metabolism to their active triphosphate forms. Since expression of these cellular kinases responsible for the initial phosphorylation of nucleosides is cell-type and cell-cycle specific, the nucleoside analogs may have limited therapeutic activity in unactivated or resting cells, such as macrophages. Therefore, other strategies have emerged over the past decade for creating agents with enhanced potency in a broad range of cells with decreased potential for resistance^[10-11].

One such strategy is the development of nucleotide analogs instead of the unphosphorylated nucleosides, such as ZVD. In pursuing the development of nucleotide analogs, it is evident that simple phosphorylation of a nucleoside analog would not be adequate, since the phosphorus-oxygen bond is quite labile and *in vivo* administration of this type of compound would result in rapid metabolism back to the nucleoside form. In order to produce a stable nucleotide analog, the oxygen in the phosphoester bond was switched with the proximate carbon in the nucleotide to produce a class of compounds termed phosphonomethylethers^[12-14].

Because they bypass the initial phosphorylation step, nucleotide analogs may possess greater activity in a broader range of cell types (both activated and resting cells) than nucleoside analogs. In addition, their lack of requirement for virus specific activation may decrease the propensity for development of antiviral resistance. Activity of PMPA against drug-resistant HIV has been studied *in vitro*. Results from these studies have demonstrated that PMPA shows broad activity and limited cross-resistance for HIV expressing common forms of ZVD and 3TC resistance. The development of simian immunodeficiency virus (SIV) resistance to PMPA during long term treatment was evaluated in SIV-infected newborn rhesus macaques^[15]. It was shown that although SIV resistant to PMPA is fully virulent, viremia levels remained low, and there was no detectable viremia rebound in three of the four infected animals.

The cellular enzyme responsible for PMPA metabolism to the phosphorylated forms is adenylate kinase^[16] which is highly active and ubiquitous.

PMPA exhibits activity against retroviruses and hepadnaviruses^[17,18] *in vitro*. In animal efficacy and toxicity studies, PMPA was found to be well tolerated even at high doses administered parenterally (subcutaneously or via intravenous infusion) or orally over prolonged periods.

Because PMPA has very limited oral bioavailability, a prodrug (tenofovir disoproxil fumarate (Tenofovir DF)) was created which is orally bioavailable and has been used in the clinical development of an oral form of PMPA. Phase I through II studies have been completed. A new drug application (NDA) was filed in the U.S. for the use of Tenofovir DF in the treatment of HIV infection in adults.

1.2.2 Anti-HIV Activity

PMPA and PMPA prodrug (Tenofovir DF) were evaluated *in vitro* for antiviral activity using HIV-1 IIIb strains of MT-2 cells (a T-lymphocyte line) and peripheral blood mononuclear cells (PBMC), and a clinical strain 96-250 of a macrophage/dendritic cell co-culture. Activity was studied by measuring the IC₅₀ concentration that inhibits 50 percent organism growth (IC₅₀) and the concentration that is toxic to 50 percent of the organism tested (CC₅₀).

The results are shown in Table 1 below ^[17].

Table 1 – Anti-HIV Activity (IC₅₀)/Cytotoxicity (CC₅₀) of PMPA and PMPA Prodrug

	Cell Lines				
	MT-2/IIIb		PBMC/IIIb		Macrophage/Dendritic Cells/96-250
	IC ₅₀	CC ₅₀	IC ₅₀	CC ₅₀	IC ₅₀
PMPA (micromolar)	0.63	1250	0.18	1200	0.05
PMPA Prodrug (micromolar)	0.007	22	0.005	29	0.003

1.2.3 Anti -SIV Activity

Subcutaneous (sc) injection of PMPA daily for four weeks in macaques resulted in 100% protection against acute SIV infection in a total of 25 treated animals without toxicity whether administered 48 hours prior to intravenous inoculation (dose of PMPA, 20 mg/kg in five animals, 30 mg/kg in 10 animals), four hours after inoculation (dose of PMPA 30 mg/kg in five animals), or 24 hours post-inoculation (dose of PMPA, 30 mg/kg in five animals). Evidence of SIV infection was not present in any treated animal monitored for up to 52 weeks, including viral load in plasma and PBMCs, SIV deoxyribonucleic acid (DNA) in PBMCs, SIV-specific antibody, and lymph node biopsy. In contrast, each of 10 animals receiving placebo 48 hours prior to inoculation became infected ^[19].

In a second study, intravaginal application of 10% PMPA gel weight in weight (w/w) administered 24 hours before, 0 hours, 24 hours after and 48 hours after intravaginal inoculation of SIV infection at 0 and 24 hours resulted in 100% protection in four female rhesus macaques, compared with evidence of infection in each of the two animals receiving placebo (vehicle only)^[20]. In a third study, 1% PMPA gel (w/w) administered 24 hours before, 15 minutes before, and 24 hours after a single intravaginal inoculation of SIV resulted in 80% protection in 5 female rhesus macaques, comparable to that of the 10% PMPA gel (w/w) group. Sixty percent protection was achieved in a third group of macaques which only received a single application of 1% PMPA gel (w/w) 15 minutes before SIV challenge. Treated macaques were monitored for a total of 20 weeks, by virus isolation from PBMCs. Such *in vivo* activity of an antiviral compound makes PMPA a promising agent for prevention of HIV infection.

In a model of chronic SIV infection, long-term daily subcutaneous PMPA treatment starting three weeks after virus inoculation resulted in rapid, pronounced (100-1000 fold) and persistent reduction of viremia in 3 of 4 newborn macaques without side effects; all treated animals remained disease-free for more than 13 months^[15]. Four untreated SIV-infected animals in the same study had persistent high-level viremia. Comparison with analogous studies using ZVD demonstrates superiority of PMPA.

1.2.4 Pharmacokinetics

IN VITRO

The stability of PMPA has been evaluated in vitro in rat and dog plasma and liver homogenates, in control and induced rat liver microsomes, and in dog intestinal homogenate. PMPA was stable in all biological matrices tested and no metabolites or degradants were detected. Furthermore, analysis of incubates using a chiral high pressure liquid chromatography method indicated that chiral inversion had not occurred in any of the matrices tested^[21].

In vitro testing of PMPA in combination with ZVD, didanosine, zalcitabine, d4T, 3TC, saquinavir, ritonavir, indinavir and nelfinavir concluded that these combinations each resulted in additive or synergistic efficacy^[22]. No antagonistic effects were noted.

IN VIVO

The kinetics of intracellular PMPA anabolism were studied in monkeys that received a single dose of 15, 30, or 60 mg/kg ¹⁴C-labeled PMPA subcutaneously. At various times after dosing, PBMC or lymph node biopsies were obtained for high pressure liquid chromatography analysis of intracellular PMPA metabolites^[23]. PMPA was efficiently taken up by PMBCs and anabolized to the active diphosphate (PMPApp) with intracellular concentrations of the antivirally active anabolite reaching 1.6 micromolar (60 mg/kg dose group). The half-life of PMPApp in this experiment was greater than 50 hours. This long intracellular half-life of the active diphosphate form supports the proposed once daily clinical dosing regimen.

Axillary, inguinal, and mesenteric lymph nodes were obtained at 48 hours post-dosing. Significant intracellular concentrations of PMPA and its metabolites were observed in lymph nodes from all three sites. Considering the heterogeneity of the cells comprising lymph nodes (e.g. dendritic cells, T and B lymphocytes, endothelial cells) and the *in vivo* efficacy of PMPA, the data suggest PMPA may be achieving particularly high concentrations in a subset of cells infected by SIV.

Pharmacokinetic data from human studies are cited in Section 1.2.5 below.

1.2.5 Initial Clinical Data Summary

A Phase I study of the intravenous formulation (Study 701) and Phase I through III studies of the oral prodrug formulation (Studies 901, 902 and 907) have been completed. Several others are ongoing.

Study 701 is a randomized, double-blind, placebo-controlled, dose-escalation (1 and 3 mg/kg/day for eight doses) trial of PMPA administered via intravenous infusion to 46 HIV-infected participants with CD4+ cell counts above 200 cells/mm³ and HIV ribonucleic acid (RNA) levels above 10,000 copies/milliliter (mL). Participants were dosed on day 1 and then on days 8-14. All participants tolerated dosing without significant adverse experiences (AE) or dose-limiting toxicities. Clinically significant hematologic, hepatic, renal, pancreatic, metabolic, or coagulation laboratory abnormalities were not observed. The most frequent AEs were mild headache, dizziness, fatigue, and nausea. The only moderate (grade 2) AEs considered being possibly drug-related included one participant with transient abdominal pain and one participant with transient fatigue. Both events resolved prior to discontinuation of dosing. No grade 3 or 4 AEs were reported.

Pharmacokinetic (PK) data from the second dose cohort (3.0 mg/kg/day) demonstrated a maximum serum PMPA concentration of 10.0 ± 3.10 µg/mL at the end of the first infusion. Serum concentrations of PMPA followed a typical two compartment profile with a distribution phase and an elimination phase with a terminal half-life of 7.15 ± 1.27 hr. All participants dosed with PMPA displayed quantifiable serum levels out to 24 hours after the first dose. There was a significant decrease in the clearance and volume of distribution of PMPA following repeated infusion at the 3.0 mg/kg dose level. Clearance of PMPA on Day 14 (152 ± 57.0 mL/hr/kg) was less than on Day 1 of the study (199 ± 75.3 mL/hr/kg) ($p = 0.018$, Wilcoxon signed rank test). The mean decrease in PMPA clearance was 24% (range 8.4 to 38.1%). The volume of distribution of PMPA also appeared to decrease with repeated dosing ($p = 0.028$, Wilcoxon signed rank test). Assuming that PMPA was eliminated unchanged in urine (as demonstrated in animal studies), the total body clearance of PMPA would reflect the renal clearance of the drug. The baseline creatinine clearance in these participants was determined to be 81.2 ± 14.9 mL/hr/kg on Day 1 and 75.8 ± 18.2 mL/hr/kg on Day 14 ($p = 0.018$, Wilcoxon signed rank test). Therefore, renal clearance of PMPA greatly exceeded the glomerular filtration rate and probably indicates active tubular secretion of PMPA by the kidney.

Based on data available for the two dose cohorts of Study 701 (1.0 and 3.0 mg/kg), the pharmacokinetics of PMPA appear to be independent of dose following the first infusion. The maximum concentration of drug and area under the plasma concentration time curve (AUC) values for the first PMPA dose demonstrated approximate dose-proportionality. However, due to the decrease in clearance of PMPA following repeated dosing at 3.0 mg/kg, AUC values were not proportional to dose on Day 14.

Study 901 is a Phase I/II, randomized double-blind, placebo-controlled study of the safety, tolerance, pharmacokinetics, and anti-HIV activity of PMPA administered orally to 50 HIV-1 infected patients with CD4+ cell counts above 200 cells/mm³ and HIV RNA levels above 10,000 copies/mL. Participants received either 75mg of study drug daily, 150mg daily, 300mg daily, 600mg daily or 75mg daily plus hydroxyurea 500mg twice daily; matching placebo or matching placebo plus hydroxyurea 500mg twice daily as a single dose on Day 1 followed by a one-week observation period. Participants continuing in the study received daily study drug treatment for four weeks. The most common clinical AEs reported were headache, abdominal pain, diarrhea, flatulence, nausea, nausea and vomiting, and abnormal electrocardiogram (these abnormalities occurred in two patients and were 1) a borderline low voltage abnormality and 2) non-specific T-wave abnormality. Both EKGs were normal at follow-up one month later). Peripheral neuritis was the only Grade 3 clinical AE thought to be possibly related to PMPA and it occurred in one patient receiving the 300mg dose. Grade 3 or higher laboratory AEs considered causally related to study drug included creatine kinase (CK) elevation (14% active versus 9% placebo), aspartate aminotransferase (AST) elevation (7% versus 0%) and alanine aminotransferase (ALT) elevation (4% versus 0%). Four participants were reported to have experienced Serious Adverse Experiences (SAEs) in Study 901. One in the placebo group who had a long history of depression died from an overdose of multiple drugs (non-study) approximately three months after being discontinued from the study. The other three SAEs were drug overdose resulting in hospitalization in one patient, asthma and bronchitis in one patient, and pneumonia requiring hospitalization in one patient. None of these SAEs were related to the study drug.

The pharmacokinetics of the oral prodrug were examined at four dose levels (75, 150, 300 and 600mg). The time to reach maximum serum concentration was rapid (0.8 to 1.0 hours) indicating rapid absorption and conversion of prodrug to PMPA. The pharmacokinetics of the prodrug was dose-proportional. The AUC at steady state following 8 and 28 days of dosing was comparable to the AUC following the first dose, indicating a lack of time dependency in PMPA pharmacokinetics. The pharmacokinetics of PMPA were predictable, reproducible, and were not altered by long term dosing of oral prodrug over 12 to 24 weeks in HIV-infected patients (study 907).

Preliminary virology data from the two PMPA intravenous dose cohorts (Study 701) demonstrated significant and potent suppression of plasma HIV RNA after as little as one dose of PMPA. After completion of seven consecutive days of intravenous PMPA dosing (study day 14), the median change in HIV RNA from baseline was -1.1 log, -0.6 log, and +0.1 log in the 3.0 mg/kg/day, 1.0 mg/kg/day, and placebo dose groups, respectively (p= 0.03 for 3.0 mg/kg vs. placebo, p= 0.008 for 1.0 mg/kg vs. placebo; Wilcoxon rank-sum test). The reduction in HIV RNA levels was not significantly different between the two active dose groups (p= 0.37, Wilcoxon rank-sum test). However, in the 3.0 mg/kg/day dose group, the suppression of HIV RNA appeared to be sustained for 1 week after discontinuation of PMPA dosing.

Changes in plasma HIV-RNA from baseline to completion at Day 35 of oral dosing (Study 901) were evaluated. The greatest decrease in HIV-1 RNA was observed in the 300mg group (decrease of 1.22 log copies/mL). Results from the other cohorts are summarized below. No significant changes in CD4+ cell counts were seen during the study.

Table 2 – Change in Plasma HIV-1 RNA from Baseline at Completion of PMPA prodrug dosing (Day 35): Study 901

Dose Group	Baseline (log copies/mL)	Median Change (log copies/mL)
Placebo	4.53	-0.01
Placebo + Hydroxyurea	4.39	-0.01
75mg	4.70	-0.33
75mg + Hydroxyurea	4.86	-0.22
150 mg	4.51	-0.44
300mg	4.12	-1.22
600mg	4.64	-0.80

An ongoing study 902 is a randomized, double-blind, placebo-controlled, multicenter assessment of the safety and efficacy of PMPA oral prodrug administered orally to HIV-1-infected patients with plasma HIV-1 RNA levels between 400 copies/mL and 100,000 copies/mL. Patients on stable antiretroviral therapy containing not more than four active agents for 8 weeks or longer at study entry were randomly assigned in a 2:2:2:1 ratio to add either PMPA oral prodrug at one of three doses (75mg, 150mg, or 300mg once daily) or placebo to their existing regimen in a double-blinded manner.

The co-primary efficacy end points in this study were the time-weighted changes from baseline average in log₁₀ HIV-1 RNA levels at Weeks 4 (DAVG₄) and 24 (DAVG₂₄) following randomization.

Comparing the placebo group with the PMPA oral prodrug groups, a statistically significant change from baseline viral load was seen as early as Week 1 and was sustained through Week 24. The antiviral effect was dose dependent, with the greatest effect always seen in the 300mg study drug group.

Antiviral activity was durable and sustained through 48 weeks of treatment. For placebo rollover patients, who received 300mg of study drug daily from Weeks 24-48, the antiviral response observed was consistent with that observed in patients who received the 300mg dose for 48 weeks.

The decrease in plasma HIV-1 RNA among patients taking 300mg of study drug appeared independent of the baseline HIV-1 genotype. In addition, there were no differences in the incidence of new resistance of mutations across the different arms of the study.

1.2.6 Animal Absorption Studies

The pharmacokinetics of intravaginal PMPA were examined in female rabbits following administration of a single dose of 0.5 mL of PMPA gel containing 1% weight in volume (w/v) PMPA (5 mg PMPA per animal; 50 μ Ci/kg). Concentrations of radioactivity in plasma were highest (0.010 μ g-eq/mL) at the first sample time point (0.5 hours) and below quantifiable limits at 24 hours, indicating that systemic exposure to PMPA was very low following intravaginal administration of the gel. Due to the very low plasma concentrations, PK parameters could not be estimated. The low exposure to PMPA may have been the result of prompt leakage out of the vagina of the formulation, which was administered by a bare syringe without an attached tube.

In a second study, eighteen female rabbits received a single intravaginal dose of 0.5 mL of PMPA gel containing 1% w/v PMPA (5 mg PMPA per animal; 50 μ Ci/kg). A further eighteen rabbits received a single intravaginal dose of 0.5 mL of PMPA gel containing 3% w/v PMPA (15 mg PMPA per animal; 50 μ Ci/kg). In contrast to the first study, the formulation was administered by a syringe fitted with a gavage needle, by depressing the plunger as the needle was removed. Six animals from each group were sacrificed at each of 0.5, 4, and 24 hours post dose. Tissues were removed for analysis of total radioactivity by sample oxidation and liquid scintillation. Vaginal tissues were rinsed and treated in one of two ways: divided directly into four lateral sections or scraped to remove the surface epithelial layer and divided into two longitudinal sections.

The majority of the administered dose was recovered in urine (15 - 38%) or cagewash (28 - 36%), suggesting that the formulation leaked out of the vagina. Tissue concentrations of radioactivity were highest in vaginal tissue at 30 minutes post dose, but displayed wide variability (0.65 - 98.3 μ g-eq/g for 1% PMPA; 10.3 - 274 μ g-eq/g for 3% PMPA). There was no clear relationship between tissue concentration and dose. For those vaginal tissues subjected to lateral sectioning, there was no consistent pattern of distribution. For those vaginal tissues subjected to scraping, radioactivity removed in the scrape was negligible, indicating that PMPA had penetrated into the tissue, or leaked out of the vagina.

Very little radioactivity was recovered in non-vaginal tissues, with the exception of the kidney (0.05 - 1.03%) and intestinal tissues (0.17 - 3.49%). The maximum concentrations of radioactivity in kidney occurred at 4 hours post dose (5.59 and 10.2 μ g-eq/g for 1 and 3% gel, respectively). The relatively high concentrations of radioactivity in intestinal tissues were attributed to ingestion of the formulation during grooming. Poor total recovery in many animals was attributed to loss of formulation on fur and paws.

1.2.7 Possible Risks and Side Effects

Minimal local irritation and little or no systemic adverse effects are expected with the use of PMPA gel intravaginally at the concentrations proposed for this study (0.3% and 1.0%). However, PMPA gel has not been tested topically in humans previously. Therefore, risks of treatment are not known and careful monitoring for adverse effects is planned. A summary of AEs reported to date in clinical studies of intravenous PMPA and related compounds which may be relevant for the use of PMPA gel is provided below.

In a Phase I/II clinical study (Study 701), intravenous administration of PMPA for eight days resulted in no serious (grade 3 or 4) AEs. Symptoms of headache, fatigue, dizziness, nausea, abdominal pain, taste perversion and light sensitivity were observed in one or more participants. Minor laboratory abnormalities observed in some participants included elevations in hepatic transaminases, creatine phosphokinase, lipase, and urine protein and a decrease in neutrophils.

In a Phase I/II study of the oral prodrug formulation (Study 901) administered for at least 35 days the following AEs thought to be causally related were reported in one or more of the participants: headache, abdominal pain, diarrhea, flatulence, nausea, nausea and vomiting, and abnormal electrocardiogram. Electrocardiograms were normal at the time of the follow-up visits. Peripheral neuritis was the only serious (grade 3) clinical AE thought to be possibly related to study drug, it occurred in one patient on active study drug. Grade 3 or higher laboratory AEs that were considered to be possibly or probably related to the study drug included CK elevation, AST elevation, and ALT elevation.

In an ongoing Phase II study of the oral prodrug formulation given in combination with other antiretroviral therapy (Study 902) administered for at least 48 days, the following grade 3 or higher clinical AEs occurred regardless of relationship to the study drug: asthenia, headache, accidental injury, allergic reaction back pain, fever, pain abdominal pain, flu syndrome, suicide attempt, viral infection, diarrhea, gastroenteritis, hepatitis, pancreatitis, colitis, hepatic failure, hepatitis C virus, liver function tests abnormal, nausea, depression, anxiety, drug dependence, convulsions, and intracranial hemorrhage. Depression was the only event that occurred at Grade 3 or Grade 4 severity in more than 5% of patients in any of the originally randomized treatment groups. The overall pattern of Grade 3 or Grade 4 AEs did not indicate a dose-response relationship in the active drug groups.

The following Grade 3 or higher laboratory abnormalities were reported: triglyceride elevation, CK elevation, AST elevation, neutropenia, serum amylase elevation, serum lipase elevation, ALT elevation, serum glucose elevation, urine glucose, total bilirubin elevation, decreased platelets, and hypophosphatemia. There were no statistically significant differences among treatment groups with respect to the incidences of any specific Grade 3 or 4 AE.

Bone mineral density (BMD) was also measured. The median reductions in BMD through 48 weeks were two percent or less with the maximum reduction occurring in the placebo group.

Ongoing studies (Gilead Studies 902, 903, 907 and 908) are evaluating a 300mg daily dosage of the oral PMPA prodrug. In the ongoing and completed studies, few SAEs have been judged to be study drug related. The oral prodrug has been well tolerated compared to placebo, and there appears to be no evidence of clinically significant dose-related toxicity in treatment-experienced HIV-1 infected participants.

Adverse effects observed with other antiviral nucleoside medications (including various approved agents) in participants include neuropathy, inflammation of the pancreas, seizures, changes in mental status, sleep problems, headaches, alopecia, agitation, nausea, vomiting, diarrhea, nephrotoxicity, skin rashes, painful mouth sores, changes in liver function, liver failure, lactic acidosis, low blood cell counts, infections, cancer, and death.

It is possible that PMPA gel could cause any of the effects listed above or other adverse effects not reported previously, including effects leading to death or permanent disability.

NONCLINICAL TOXICOLOGY SUMMARY

In animal studies, PMPA topical gel (0.3-10.0% PMPA) caused minimal to mild local irritation following intravaginal administration. In rats, intravaginal administration of PMPA gel (1-10% for 14 days) produced no evidence for local irritation or systemic toxicity as evidenced by no gross alterations in tissues and organs within the thoracic and abdominal cavities, and no histological lesions in the reproductive tissues (cervix, ovaries, uterine horns, vagina, vulva) or kidneys. In contrast, rats receiving the positive control, Conceptrol (N-9) had microscopic decidual reaction and hydrometra in the uterine horns.

In a 10-day rabbit vaginal irritation study, irritation was minimal in animals treated with 0.3-1.0% PMPA. At higher doses (3-10%), PMPA caused mild local irritation (increased leucocytic infiltrates, congestion and, in some cases, slightly increased edema) and produced average irritation scores similar to the Conceptrol control. However, unlike Conceptrol, no animals treated with PMPA had epithelial erosion or ulceration.

In systemic toxicology studies in animals, the principal target organs for both PMPA prodrug (oral) and PMPA (intravenous (IV) or sc) were the kidney, bone and gastrointestinal tract.

In the kidney, microscopic alteration included renal tubular epithelial karyomegaly, individual cell necrosis, tubular dilatation, degeneration/regeneration, and pigment accumulation. Interstitial nephritis was observed in dogs at doses of 10 and/or 30 mg/kg/day of PMPA prodrug. (In phase I, II and III studies where the maximum daily dose given was approximately 10mg/kg/day no human developed interstitial nephritis.) Incidence, severity, and reversibility of hisopathological changes were related to the dose and duration of treatment. Related biochemical changes included minimal rise in serum creatinine, glycosuria, proteinuria, phosphaturia and/or calciuria, and increased urinary output.

Effects on bone occurred in newborn to adult rhesus macaques at doses of 30mg/kg/day (sc). PMPA related bone lesions were characterized variably as abnormal growth plates and trabecula of the ribs and femurs, bone deformities and displacements, bone fractures, decreased bone densities, joint swellings and bone loss in the spine or pelvis. Elevated alkaline phosphatase activity, decreased serum phosphorus concentration, glucouria and proteinuria were observed in the macaques with bone lesions; calcium values were normal. Improvements occurred with dose reduction from 30mg/kg/day to 10mg/kg/day or interruption. In an ongoing study in newborn rhesus macaques receiving 10 mg/kg/day (sc) for over two years, no adverse clinical, biochemical, or radiographic changes demonstrating bone demineralization have been observed.

Slight to mild histologic changes were observed in the gastrointestinal tract in rat studies. The microscopic alterations included inflammation of the stomach and intestines, epithelial cell hypertrophy of the duodenum and jejunum, and villous atrophy of the ileum. No gastrointestinal toxicity was observed in dogs. There was a rise in serum ALT (less than twofold, 100mg/kg/day by mouth (po) or higher) and AST (less than onefold, 100mg/kg/day po) in the rat with no concurrent microscopic alterations in the liver. In the dog studies there was a rise in serum bilirubin concentration (twofold, 30 mg/kg/day po) with only slight centrolobular congestion and pigment accumulation observed microscopically.

1.3 Carrier Vehicle

Information regarding application site reactions for a similar carrier vehicle is available from several clinical studies of cidofovir gel for the treatment of genital warts, molluscum contagiosum and acyclovir-resistant HSV. In the latter study the carrier vehicle was used as the placebo gel. The formulation used in the HSV study differs from the PMPA gel vehicle primarily in that it contained propylene glycol rather than glycerol and would be expected to have a greater potential for local irritation. Application site reactions (pain or pruritis) in the HSV study were noted by 2 of the 12 participants randomized to placebo. Neither of the reactions was dose-limiting.

We have no human data on the intravaginal use of this carrier vehicle. It was utilized as one of the arms in a rabbit vaginal irritation study. Irritation scores from that study for a sham treatment group, vehicle alone and for varying concentrations of PMPA gel are cited below.

	Sham	Vehicle	PMPA 0.3%	PMPA 1%	PMPA 3%	PMPA 10%
Score	0.8	1.0	1.6	1.0	3.6	5.4

1.4 Rationale

Potential approaches to the development of topical agents for the prevention of vaginal HIV transmission include products which block initial virus infection through broad-based microbicidal activity (e.g. detergents; acid pH buffering agents; and anti-microbial peptides) or through inhibition of virus-cell attachment. However, it is unlikely that any single product will be completely efficacious in preventing initial HIV infection. Thus, the development of a topical product which could block local virus replication once infection has occurred is needed. Topical PMPA gel was chosen for study because of (1) activity in potential target cells (Langerhans-dendritic cells; monocyte/macrophages, and T cells) of the vagina and cervix; (2) its effectiveness in preventing the establishment of systemic infection in the SIV-macaque model; (3) demonstrated inhibition of vaginal transmission of SIV in the macaque model; and (4) an expectation of low local and systemic toxicity.

Rapid and efficient testing of microbicides, using standardized methods, can be carried out and generalizable results achieved by conducting multi-center studies in populations with different characteristics. The goal of this multi-center Phase I study is to determine the safety of PMPA gel for use as a vaginal microbicide and to make a preliminary assessment of the product's acceptability. The product is to be applied before vaginal intercourse, rather than used routinely; however, the stepped parallel design allows intensive exposure to the product to improve the ability to detect potential toxicity.

In this study, PMPA gel will be evaluated among four types of women. The first four study cohorts will consist of sexually abstinent HIV uninfected women to evaluate how healthy women react to the product. The fifth cohort will consist of sexually active HIV uninfected women to evaluate how healthy women react to the product with the possible added microtrauma of sexual activity. The sixth and seventh cohorts will consist of sexual abstinent and sexually active HIV infected women respectively to evaluate how HIV infected women react to the product, and to gain information on the occurrence of cervico-vaginal of HIV while using the product. The women and their male partners (when relevant) will also be asked to assess the acceptability of the product.

Based on the following findings, two concentrations of PMPA gel (0.3 and 1%) will be evaluated in this study. The efficacy of PMPA gel 10%^[24,25] and 1%^[25] has been evaluated in an SIV prevention model. Both concentrations prevented SIV infection in these models. The tolerability of PMPA gel has been evaluated in rats^[26] and rabbits^[27] in 14 and 10-day vaginal irritation studies, respectively. In rats, 1, 3 and 10% concentrations produced no irritation. In rabbits, toxicities were limited to minimal and mild vaginal irritation in groups exposed to the 3 and 10% concentrations, respectively. Based on animal models described above, 0.3 and 1% concentrations were chosen to be tested in humans given that the 1% concentration prevented SIV infection, and was well tolerated in rabbit vaginal toxicity tests. Both concentrations are expected to be well tolerated in humans. The expectation of low systemic toxicity is based on extensive toxicology studies in monkeys, rats, and dogs as well as Phase I/II studies in humans.

Any information about a product's characteristics, packaging, and methods of administration that increase the likelihood that it will be used as recommended for effective protection is relevant to further studies. As part of this study, data regarding the use and acceptability of a product that might protect against HIV and other STDs will be collected. Information about sexual behavior, including previous vaginal product use, sexual relationships and negotiation, use of condoms, etc., within each site is important background information for proceeding to Phase II/III studies.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objectives of this study are:

- To assess the safety and toxicity of PMPA gel for vaginal use in assigned doses and frequency on vulvar and cervico-vaginal mucosa in HIV-uninfected women at low risk for HIV infection and in HIV-infected women. Low risk is defined as:
 - having had no STD in the last six months;
 - being sexually abstinent or having been in a stable, sexually active mutually monogamous relationship for at least three months with a partner of the opposite sex who is not known to be HIV-infected and is at low risk for HIV; and
 - having not injected non-therapeutic drugs in the last year.
- To assess the systemic safety and absorption of PMPA vaginal gel in low-risk, HIV-uninfected women and in HIV-infected women.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the acceptability of, and adherence to, a short-term regimen of PMPA gel for vaginal use in low-risk, HIV-uninfected women and in HIV-infected women, and their male sexual partners (when relevant).
- To examine qualitative aspects of acceptability and adherence as a pilot for substantive qualitative and quantitative assessments in future studies.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To measure the occurrence of cervico-vaginal shedding of HIV over the course of PMPA vaginal gel use.
- To assess the genotypic resistance patterns of HIV in genital secretions and blood samples from the HIV-infected female participants over the course of PMPA vaginal gel use.
- To measure vaginal flora characteristics, and to descriptively examine changes in these characteristics over the course of PMPA vaginal gel use.

2.4 Study Design

2.4.1 Overview

This is a multisite Phase I stepped parallel dose and frequency study of PMPA gel (and carrier vehicle if required) to be conducted among up to 96 women and their male sexual partners (when relevant) from three sites in the US (maximum 48 women at any one site): New York, NY; Philadelphia, PA; and Providence, RI. All participants will apply PMPA gel intravaginally for 14 consecutive intramenstrual days. The dose and frequency of application will be escalated across “cohorts” of up to 12 study participants each, as follows:

Cohort	Description	N	Dose	Frequency
A ₁	HIV-uninfected/abstinent	12	0.3%	once daily
A ₂	HIV-uninfected/abstinent	12	1.0%	once daily
A ₃	HIV-uninfected/abstinent	12	0.3%	twice daily
A ₄	HIV-uninfected/abstinent	12	1.0%	twice daily
B	HIV-uninfected/active and their male sexual partners	12	highest practical dose frequency	
C	HIV-infected/abstinent	12	highest practical dose frequency	
D	HIV-infected/active and male sexual partners	12	highest practical dose frequency	
V	HIV-uninfected/abstinent (if required)	12	vehicle only	once daily

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. Participants in cohorts B and D will substitute a coital dose at least two hours before vaginal sexual intercourse for either the morning or bedtime dose on at least two days per week during the study dosing period. Additional information regarding the progression from cohort A₁ to cohort D is provided in Section 2.4.2 below.

2.4.2 Study Visits and Procedures

The schedule of study visits and procedures is summarized in Appendix I. After providing written informed consent, participants will undergo eligibility screening, including medical history, general physical exam, pelvic exam, urine pregnancy testing, urinalysis, HIV and STD counseling and testing, a CD4+ cell count for the HIV infected cohorts, hematology, liver and renal function testing. For participants who are presumptively eligible at this visit, an Enrollment Visit will be scheduled to take place 3-5 days after the participant’s next menstrual period, but within 6 weeks of initial screening.

For cohorts B and D, the participant’s male sexual partner will be informed of the study and its requirements of him. He will be asked to provide written informed consent and undergo screening including STD history, HIV and STD counseling and testing, and an optional genital exam in order to take part. Participants with male sexual partners who are not willing to provide written informed consent, or are found to be ineligible, will not be eligible to take part in the study. If for any reason the male sexual partner is not eligible to take part in the study, the female participant will not be eligible to take part in the study.

At their Enrollment Visits, female participants will be provided their screening test results. HIV and STD test results and referral for treatment if necessary will be provided in the context of post-test counseling. Presumptively eligible participants will undergo a pelvic exam with colposcopy, urine pregnancy testing and urinalysis to confirm their eligibility. Hematology, liver and renal function testing will be performed. For HIV-infected participants, a CD4+ cell count will be performed and specimens will be collected for quantitation of HIV viral load in plasma and cervico-vaginal fluids. Once all assessments are completed and final eligibility has been confirmed, participants will be provided with:

- Supplies of PMPA gel with applicators and panty liners (and male condoms for participants and their male sexual partners in cohorts B and D);
- Daily Study Records on which to record the date and time of product applications and episodes of vaginal intercourse, any symptoms experienced, and comments about the gel, applicator, symptoms and reasons for non-compliance if applicable;
- Instructions for product application and Daily Study Record completion; and
- Instructions to contact the site to report AEs.

After completing 2 or 3 days of product application, and then again after the first seven consecutive days of product application at the assigned dose and frequency, participants will complete a study Follow-up Visit (at Day 2 or 3 and on Day 7). During these visits their Daily Study Records will be reviewed — to assess adherence to the product use regimen and ascertain whether any AEs have occurred — and a pelvic exam will be performed. Hematology, liver and renal function testing also will be performed. For HIV-infected participants, specimens will be collected for quantitation of HIV viral load in plasma and cervico-vaginal fluids, and a CD4+ cell count.

After completing another seven consecutive days of product application, participants will complete a study follow-up visit (at Day 14) during which their Daily Study Records again will be reviewed and a pelvic exam with colposcopy will be performed. Hematology, liver and renal function testing, urine pregnancy and pathogen testing also will be performed. For HIV-infected participants, specimens will be collected for quantitation of HIV viral load in plasma and cervico-vaginal fluids, and a CD4+ cell count.

Seven days after completing study treatment (Day 21) participants enrolled in cohorts A and B (HIV-uninfected participants) will be contacted by telephone. A brief interview will be conducted. If the participant reports that an AE has occurred since the last study visit, she will be instructed to return to the clinic for clinical and/or laboratory evaluations if indicated. Participants in cohorts C and D (HIV-infected participants) will be instructed to return to the clinic for a follow-up visit. A pelvic exam will be performed. Hematology, liver and renal function testing also will be performed. Specimens will be collected for quantitation of HIV viral load in plasma and cervico-vaginal fluids, and a CD4+ cell count.

At any of the study follow-up visits, or at any additional ad hoc visits initiated by participants between scheduled visits, abnormalities noted on pelvic exam will be evaluated and followed according to Appendix III; continued/discontinued use of PMPA gel also will be guided by Appendix III.

Once all participants in cohort A have completed their Day 14 Visit, the Protocol Chairs, Principal Investigator(s), Medical Officer, Biostatistician, and Protocol Specialist or their designee (Protocol Safety Review Team) will review all available safety data to determine if participants in the subsequent B, C and D cohorts will be required to continue the Day 2 or Day 3 and the Day 7 visit regimen. The Day 2 or 3 or the Day 7 Visit may be omitted if the data indicates that having a participant under go both visits will not be required for participant safety.

The acceptability of PMPA gel will be assessed via questionnaires and group or individual interviews. At their study Enrollment Visits, female participants will complete a Behavioral Assessment pertaining to their past use of vaginal products. At Day 14, female participants will complete a Follow-up Acceptability Assessment regarding their perceptions of PMPA gel including applicator, vehicle and use-associated factors, as well as a Study Burden Assessment, regarding their perceptions of study visits, procedures and incentives. The male sexual partners of participants in cohorts B and D also will complete a questionnaire regarding their perceptions and experiences with PMPA gel, as well as a Study Burden Assessment, regarding their perceptions of study visits, procedures and incentives.

In addition, all female participants will take part in follow-up focus groups and the male sexual partners of the sexually active participants (B and D cohorts) will have in depth individual interviews within four weeks of completing the 14-day dosing regimen. These qualitative interviews will explore microbicide acceptability beyond the data obtained with structure or semi-structured questionnaires, including acceptability of administration methods (e.g., applicator, tube and applicator filling techniques, portability), acceptability of the gel vehicle itself (e.g., color, odor, taste, consistency), acceptability and feasibility of use (e.g., administration, dosing schedules, general hygiene issues, issues related to sex with the product, stealth factor) and other culturally and contextually relevant issues related to product use.

2.4.3 Stepped Parallel Dose and Frequency / Cohort Progression

As indicated in the listing of study cohorts above, the dose and frequency of PMPA gel use will be escalated — from 0.3% to 1.0% and from once daily to twice daily, respectively — among HIV-uninfected sexually abstinent participants. Based on the experience among these participants, the highest practical dose frequency (HPDF) will be determined, and cohorts B, C and D will complete dosing at the HPDF. Details of the cohort progression plan are provided below and depicted in Figure 1.

The study will begin with screening and enrollment of six participants into cohort A₁. If these six women complete the 14-day dosing regimen without experiencing any SAEs as defined in the DAIDS SAE Reporting Manual for HPTN [refer to the Study Specific Procedures (SSP) Manual] judged possibly, probably or definitely related to product use, enrollment into cohort A₁ will continue and enrollment of cohorts A₂ and A₃ will begin.

If one of the 12 participants in cohort A₁ experiences an SAE that is judged to be definitely, probably or possibly related to product use, the participant will be instructed to stop using the study product. The Protocol Safety Review Team will review all available safety data within 24 hours to determine if the participant may resume product use. Dosing for currently enrolled participants will not be interrupted unless deemed necessary by the Protocol Safety Review Team.

If two or more of the 12 participants in cohort A₁ experience SAEs that are judged to be definitely, probably or possibly related to product use, all participants will stop product use, and enrollment in all cohorts will be suspended. A new cohort of 12 HIV-uninfected sexually abstinent women (Cohort V) will be enrolled to apply the carrier vehicle once a day for 14 days. Cohort V participants will follow all study visits and procedures as for Cohort A₁ except those for the pharmacokinetic study and acceptability assessments. After completion of follow-up of this cohort, the Protocol Safety Review Team will review the data, and determine whether to allow the study to proceed.

As the study proceeds and enrollment continues if the first six women in cohorts A₂ and A₃ complete their dosing regimens without experiencing any SAEs judged possibly, probably or definitely related to product use, enrollment into both of these cohorts will continue and enrollment of cohort A₄ will begin. As the study proceeds, if one participant in either cohort A₂, A₃ or A₄ experiences an SAE judged possibly, probably or definitely related to product use, the effected participant(s) will be instructed to stop using the study product. The Protocol Safety Review Team will review all available safety data within 24 hours to determine if the participant may resume product use. If two or more of the 12 women in either of the cohorts A₂, A₃, or A₄ experience an SAE judged possibly, probably or definitely related to product use, the effected participants will be instructed to stop product use and enrollment in all cohorts will be suspended. The Protocol Safety Review Team will review all available safety data within 24 hours before continuation of product use and enrollment is allowed. Dosing for currently enrolled participants will not be interrupted unless deemed necessary by the Protocol Safety Review Team.

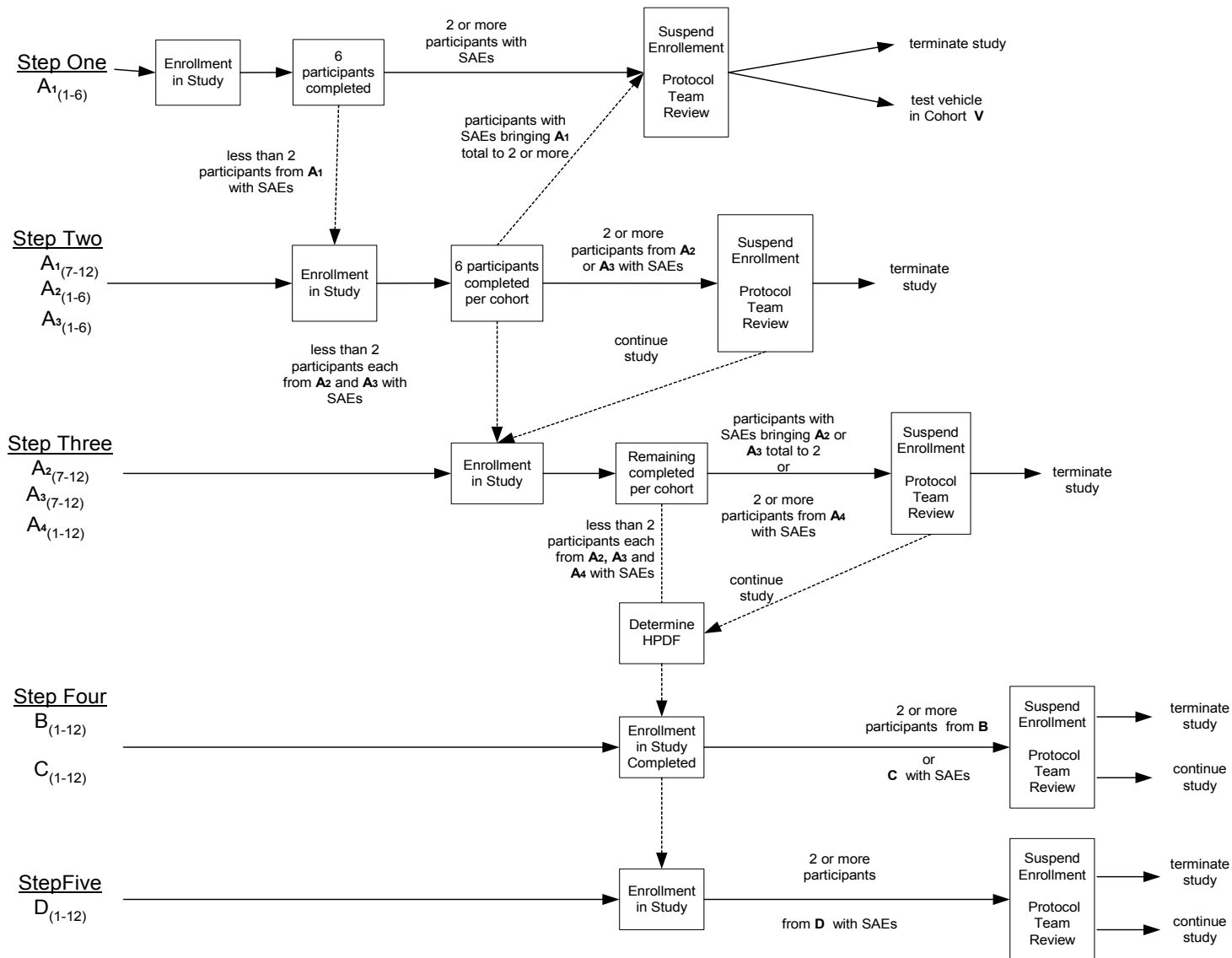
Upon completion of product use by cohort A₄, the Protocol Safety Review Team, and a Behavioral Scientist will determine the HPDF based on all available toxicity and acceptability data. The HPDF will be 1.0% PMPA gel used twice daily unless either the toxicity or acceptability data suggest the HPDF ought to be a lower dose and/or frequency.

After determination of the HPDF, screening and enrollment of both cohort B and cohort C will begin. Once enrollment of these cohorts has been completed, screening and enrollment of cohort D will begin. As the study proceeds, if one participant in cohort B, C or D experiences an SAE judged possibly, probably or definitely related to product use, the effected participant (s) will be instructed to stop using the study product. The Protocol Safety Review Team will review all available safety data within 24 hours to determine if the participant may resume product use. If two or more of the 12 women in cohorts B, C or D have SAEs judged possibly, probably or definitely related to product use, the effected participants will be instructed to stop product use and enrollment in all cohorts will be suspended. The Protocol Safety Review Team will review all available safety data within 24 hours before continuation of product use and enrollment is allowed. Dosing for currently enrolled participants will not be interrupted in either case unless deemed necessary by the Protocol Safety Review Team.

Additionally all data on all AEs judged to be possibly, probably or definitely related to product use will be communicated to the Protocol Safety Review Team within three working days after the site becomes aware of the AE. The Protocol Safety Review Team will hold regularly scheduled teleconferences to identify trends or emerging patterns in the AE data that may impact the continuation of enrollment and product use in all cohorts.

Note: If circumstance does not permit the entire Protocol Safety Review Team to be assembled within 24 hours, a preliminary review will be carried out by as many members as possible within 24 hours, and a review by the full team will be conducted within three working days.

Figure 1. Stepped Parallel Dose and Frequency / Cohort Progression



2.5 Pharmacokinetic Study

In addition to the study procedures described above, the first six participants in cohorts A₂, B, and C will take part in a PK study of PMPA gel. At their study Day 0 Enrollment Visit and on study Day 13, these participants will apply the first daily dose of PMPA gel at the study site and undergo phlebotomy for serum collection and PK analysis immediately prior to dosing then again at 0.5, 1, 2, 4, 6, 8, 12 hours on both visits. An additional draw will be taken at 24 hours post dosing on the Day 13 Visit. For participants in cohorts B and C, if the HPDF of product use is determined to be twice daily, the second daily dose will be omitted on Day 13. Participants either will either stay at the clinic and/or will have an IV line inserted and be allowed to leave the clinic and return in time for scheduled blood draws. This decision will be made by the site investigator on a participant by participant basis.

All PK samples will be shipped to the Contract Lab [refer to SSP Manual for sample collection and shipping details] for batched assay. Samples from each subject on both PK days will be run together. PK data from cohort A₂ will be analyzed once all the required samples from this cohort are received and assayed. If this analysis indicates that the cohort A₂ participants absorbed PMPA systemically and there was detectable study drug in the 24 hour sample on Day 14, PK study participants in cohorts B and C will have additional PK samples drawn at 48 and 72 hours post dosing. If the analysis indicates that unanticipated absorption of PMPA is found in any of the cohorts and/or more adverse events such as mucosal inflammation are found than expected in any participant, PK testing as described above for cohorts B and C will be done in six (but not necessarily the first six) of the D cohort participants.

The principal parameter of interest after intravaginal dosing will be the AUC.

3.0 STUDY POPULATION

Up to 96 women, 60 sexually abstinent HIV-uninfected, 12 sexually active HIV-uninfected with a mutually monogamous male sexual partner, 12 sexually abstinent HIV-infected, and 12 sexually active HIV-infected with a mutually monogamous seroconcordant male sexual partner will be enrolled in three sites. Participants will be testing a prescribed dose and frequency of administration of PMPA gel for 14 days, and will be followed for 21 days. A cohort of 12 sexually abstinent HIV-uninfected women will be enrolled should preliminary safety results indicate that a test of the carrier vehicle is warranted.

3.1 Inclusion Criteria - HIV Uninfected Abstinent Women, Cohorts A₁₋₄ and V

Women who meet the following criteria by self-report (unless otherwise specified) may be included in study cohorts A₁ – A₄ and V:

- are age 18 – 45 years,
- are HIV uninfected by licensed Enzyme Immuno Assay (EIA),
- are willing and able to provide written informed consent to take part in the study,
- are willing and able to complete a Daily Study Record as determined by study staff,
- are willing to undergo clinical evaluations, including colposcopy and biopsy (if clinically indicated) according to the protocol,
- are willing to participate in a group interview with other study participants (does not apply to cohort V),
- have a regular menstrual cycle with a minimum of 21 days between menses or have been amenorrheic for 6 months or more due to long acting progestins,
- agree from the time of the Screening Visit until the Day 14 Follow-up Visit to:
 - not use intravenous drugs (except for therapeutic use) and,
 - not participate in other microbicide or contraceptive studies,
- agree to abstain from the following activities for a minimum of 48 hours prior to the study enrollment visit (Day 0) until the Day 14 Follow-up Visit:
 - vaginal intercourse,
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps,
- agree for the duration of the study to insert PMPA gel as required by protocol.

3.2 Inclusion Criteria - HIV Uninfected Sexually Active Women, Cohort B

Women who meet the following criteria by self-report (unless otherwise specified) may be included in study Cohort B:

- are age 18 – 45 years,
- are HIV uninfected by licensed EIA,
- are willing and able to provide written informed consent to take part in the study,
- are willing and able to complete a Daily Study Record as determined by study staff,
- are willing to undergo clinical evaluations, including colposcopy and biopsy (if clinically indicated) according to the protocol,
- are willing to participate in a group interview with other study participants,
- have a regular menstrual cycle with a minimum of 21 days between menses or have been amenorrheic for 6 months or more due to long acting progestins,
- have currently (> 3 months) a single male sexual partner who is at low-risk for HIV infection (see section 2.1 for definition of low-risk) and who can be included according to the criteria in Sections 3.6 and 3.7,
- agree to inform her male sexual partner regarding her participation in a clinical trial and of the study requirement to have vaginal intercourse at their usual rate (at least twice weekly) from the time of the Enrollment Visit and for using study provided male latex condoms for every sexual episode (if any) from the time of the Enrollment Visit,
- agree from the time of the Screening Visit until the Day 14 Follow-up Visit to:
 - not use intravenous drugs (except for therapeutic use) and,
 - not participate in other microbicide or contraceptive studies,
 - agree to abstain from the following activities for a minimum of 48 hours prior to the study Enrollment Visit (Day 0):
 - vaginal intercourse,
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps,
- agree from the time of the Enrollment Visit (Day 0) until the Day 14 Follow-up Visit to:
 - have vaginal intercourse with her mutually monogamous consented male sexual partner at their usual weekly rate which must be at least two times per week,
 - use study provided male latex condoms for each act of vaginal intercourse,
 - insert PMPA gel as required by protocol,
 - agree from the time of the Enrollment Visit (Day 0) until the Day 14 Follow-up Visit to abstain from:
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps.

3.3 Inclusion Criteria - HIV-Infected Abstinent Women, Cohort C

Women who meet the following criteria by self-report (unless otherwise specified) may be included in study cohort C:

- are age 18 – 45 years,
- are HIV-infected by licensed EIA/Western Blot (WB) or detectable HIV viral load,
- have a 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,
- have an HIV RNA plasma level \leq 10,000 copies/mL if on anti-retroviral therapy OR have an HIV RNA plasma level $<$ 55,000 copies/mL if not on anti-retroviral therapy,
- are willing and able to provide written informed consent to take part in the study,
- are willing and able to complete a Daily Study Record as determined by study staff,
- are willing to undergo clinical evaluations, including colposcopy and biopsy (if clinically indicated) according to the protocol,
- are willing to participate in a group interview with other study participants,
- anti-retroviral therapy (if any) has been stable for one month prior to screening and is anticipated to remain unchanged for the duration of the study,
- are under the care of a medical professional for HIV management,
- are willing to provide study site staff with access to medical records related to their HIV infection,
- have a regular menstrual cycle with a minimum of 21 days between menses or have been amenorrheic for 6 months or more due to long acting progestins,
- agree from the time of the Screening Visit until the Day 14 Follow-up Visit to:
 - not use intravenous drugs (except for therapeutic use) and,
 - not participate in other microbicide or contraceptive studies,
- agree to abstain from the following activities for a minimum of 48 hours prior to the study Enrollment Visit (Day 0) until the second Follow-up Visit (Day 14):
 - vaginal intercourse,
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps,
- agree for the duration of the study to insert PMPA gel as required by protocol.

3.4 Inclusion Criteria - HIV-Infected Sexually Active Women, Cohort D

Women who meet the following criteria by self-report (unless otherwise specified) may be included in study cohort D:

- are age 18 – 45 years,
- are HIV-infected by licensed EIA/Western Blot (WB) or detectable HIV viral load ,
- have a 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,
- have an HIV RNA plasma level \leq 10,000 copies/mL if on anti-retroviral therapy OR have an HIV RNA plasma $<$ 55,000 copies/mL if not on anti-retroviral therapy,
- are willing and able to provide written informed consent to take part in the study,
- are willing and able to complete a Daily Study Record as determined by study staff,
- are willing to undergo clinical evaluations, including colposcopy and biopsy (if clinically indicated) according to the protocol,
- are willing to participate in a group interview with other study participants,
- anti-retroviral therapy (if any) has been stable for one month prior to screening and is anticipated to remain unchanged for the duration of the study,
- are under the care of a medical professional for HIV management,
- are willing to provide study site staff with access to medical records related to their HIV infection,
- have a regular menstrual cycle with a minimum of 21 days between menses or have been amenorrheic for 6 months or more due to long acting progestins,
- have currently ($>$ 3 months) a single male HIV-infected sexual partner who and who can be included according to the criteria in Sections 3.6 and 3.7,
- agree to inform her male sexual partner regarding her participation in a clinical trial and of the study requirement for having vaginal intercourse at their usual rate (at least twice weekly) from the time of the Enrollment Visit and for using study provided male latex condoms for every sexual episode (if any) from the time of the Enrollment Visit,
- agree from the time of the Screening Visit until the Day 14 Follow-up Visit to:
 - not use intravenous drugs (except for therapeutic use) and,
 - not participate in other microbicide or contraceptive studies,
- agree to abstain from the following activities for a minimum of 48 hours prior to the study Enrollment Visit (Day 0):
 - vaginal intercourse,
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps,
- agree from the time of the Enrollment Visit (Day 0) until the Day 14 Follow-up Visit:
 - have vaginal intercourse with her mutually monogamous consented male sexual partner at their regular weekly rate which must be at least two times per week,
 - use study provided male latex condoms for each act of vaginal intercourse ,

- insert PMPA gel as required by protocol,
- agree from the time of the Enrollment Visit (Day 0) until the Day 14 Follow-up Visit to abstain from:
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps.

3.5 Exclusion Criteria – Women, All Cohorts

This study will exclude women who meet any of the following criteria by self-report (unless otherwise specified) at Screening through to Enrollment:

- are post-menopausal,
- have had a hysterectomy,
- are currently breastfeeding,
- are currently using, or within the past year have used intravenous drugs (except for therapeutic use),
- are pregnant (based on a urine pregnancy test at Screening or Enrollment),
- have Grade 3 or higher liver, renal, or hematology abnormality [refer to SSP Manual] ,
- have received a course of antibiotic therapy in the 14 days prior to enrollment,
- have participated in other microbicide or contraceptive studies within one month of enrollment,
- has been previously enrolled in this study,
- currently have a clinically detectable genital abnormality (i.e. vulvar, vaginal, cervical and/or perineal ulcer and/or lesion or abnormal PAP smear)¹,
- have a history of sensitivity/allergy to any compound used in the study as described in section 4.1, including latex for cohorts B and D,
- are unwilling to use one of the following methods of contraception during the study unless surgically sterilized:
 - non N-9 condoms,
 - hormonal contraceptives,
 - abstinence,
- have used any spermicide or any spermicidally lubricated condom within one week prior to enrollment,
- have been using a hormonal contraceptive method for less than three months prior to enrollment,
- in the three months prior to enrollment have had any of the following:
 - vaginal bleeding during or following vaginal intercourse,
 - breakthrough menstrual bleeding,
 - an IUD,
 - an abnormal Pap smear,
 - a pregnancy,
 - an abortion,

¹ Women with human papilloma virus warts that are located exterior to the labia minora (i.e. labia majora, mons) will be allowed.

Women with genital warts in the six months prior to enrollment which have resolved prior to enrollment are eligible (unless they were removed by a surgical procedure in the previous three months.)

- gynecologic surgery.
- in the six months prior to enrollment have had any of the following:
- any STD or treatment for any STD 2
- signs, as seen on pelvic exam, consistent with an STD including:³
 - vaginitis,
 - cervicitis,
 - vulvar or cervico-vaginal ulcers ,
- signs of genital tract infection, other than asymptomatic bacterial vaginosis (BV) from laboratory evaluations⁴,
- Have any other condition that, in the opinion of the site 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.

3.6 Inclusion Criteria - Male Sexual Partners of Cohorts B and D

Male sexual partners of women in cohorts B and D who meet the following criteria by self-report (unless otherwise specified) may be included in the study:

- are age 18 years and older ,
- has been in a mutually monogamous relationship with the study participant for at least three months, and are willing to maintain this relationship for at least the duration of the study,
- are able and willing to provide written informed consent to take part in the study,
- are at low risk for HIV infection as defined in Section 2.1, and are HIV uninfected by licensed EIA (Cohort B Male sexual partners only),
- or are HIV-infected by licensed EIA/WB or detectable HIV viral load (Cohort D Male sexual partners only),
- are willing to undergo clinical evaluations, including HIV testing and a genital exam (if indicated) according to the protocol,
- are able and willing to have vaginal intercourse only with the study participant at their usual rate which must be at least two times per week, and to use study-provided lubricated male condoms each time during product use,
- are willing to abstain from vaginal intercourse for 48 hours before the Enrollment Visit (Day 0),
- are willing to abstain from the following from 48 hours before the Enrollment Visit (Day 0) until the end of study product use :
 - anal intercourse,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
- are willing to participate in an individual interview upon completing the study.

²Women with a history of HSV-2 are eligible if they have been asymptomatic for 6 months

³Women with signs or laboratory evidence of genital tract infection, other than asymptomatic BV, will be referred for treatment.

⁴Signs of asymptomatic BV may 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, a decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical criteria or gram stain evidence of BV and with symptoms (symptomatic discharge, odor, itching) will be excluded. Women without symptoms, but with clinical or gram stain evidence of BV, are still eligible.

3.7 Exclusion Criteria – Male Sexual Partners of Cohorts B and D

This study will exclude men and women in cohorts B and D if the male sexual partner:

- reports any treatment for STDs or presumed STDs within 6 months prior to enrollment,
- report any symptoms of STDs within 2 weeks of enrollment which cannot be evaluated by a focused physical exam,
- have a history of sensitivity/allergy to any compound used in the study as described in section 4.1, including latex for cohorts B and D,
- has any other condition that, in the opinion of the site 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.

3.8 Recruitment

Study participants will be recruited from clinics and the community at the following sites that are associated with the HPTN:

- NEW YORK, NY
 - Harlem Hospital Center and Bronx Lebanon Hospital Center
- PHILADELPHIA, PA
 - The Hospital of the University of Pennsylvania
- Providence, RI
 - Miriam Hospital, Women and Infants Hospital

The study sites are responsible for recruiting and enrolling study participants who meet the eligibility criteria specified in sections 3.1 to 3.7. The case report forms (CRF) will document this activity.

Study participants will be recruited from staff and consumers of community-based organizations, student populations from area Universities, colleges, clinics, and public gathering places that predominately serve women.

Recruitment will be conducted via outreach by project staff, flyers on public kiosks and newspaper ads if needed. Women who have responded to previous recruitment efforts or from previous studies who may meet eligibility requirements may be contacted by phone or by mail with their prior permission. HIV infected participants also will be recruited from area infectious disease clinics. Recruitment information may be sent to medical staff and case managers at local HIV clinical practices to give to possibly eligible women.

3.9 Participant Withdrawal

Given the relatively small study sample size, and the importance of ascertaining all safety outcomes among study participants, 100 percent retention of enrolled participants is targeted.

For each participant, clinic staff will obtain the names, addresses, and telephone numbers of contacts who would be expected to know the whereabouts of the subject enrolled in this study. The need to attend all scheduled follow-up visits must be emphasized to each study participant at every visit. In the event that a participant cannot be present for Day 14 evaluations, continuation of product use will be allowed for up to two days. If a participant misses a scheduled study visit, the study site staff will try to establish communication with the participant through all possible means (e.g., telephone, field contact, writing). Study site staff are responsible for developing and implementing local standard operating procedures to achieve complete follow-up.

However, participants may withdraw from the study for any reason at any time. The 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. The participant may also be withdrawn if she has excessive breakthrough uterine bleeding (which could hinder colposcopic examination).

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

Every reasonable effort will be made to have female participants who terminate from the study prior to Day 21 complete a final evaluation (as described in Section 5.1.5.) Female participants and their male sexual partners will be asked to complete the follow-up acceptability assessment (as described in Section 2.4.2) if they 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 CONSIDERATIONS

PMPA gel is an investigational drug and limited information is available on its mutagenic and carcinogenic potential. Measures should be taken to minimize contact during handling, preparation and disposal procedures.

4.1 Drug Formulation

PMPA gel is a clear, transparent, viscous gel packaged in epoxy inner-lined aluminum tubes with a white polyethylene screw cap equipped with a puncture tip. Each tube contains 6 grams of PMPA gel at concentrations of 0.3% or 1.0% (weight/weight) formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, hydroxyethylcellulose, and pH adjusted to 4-5. The gel is applied with a polyethylene applicator capable of administering a 4 gram (equal to 4mL) dose of gel.

In the event that a test of the carrier vehicle only is warranted (refer to Section 2.4.3) the carrier vehicle to be tested will be identical to PMPA gel but will not contain the active ingredient PMPA.

4.2 Usage Regimen

Study participants will receive supplies of PMPA gel from the study site for use during the study period. For participants in cohorts B and D, condoms will be supplied by the study site and will be used for all sexual encounters during the study period. All participants are expected to start using PMPA gel on Visit Day 0 and continue using PMPA gel daily, however instructions for application vary according to whether it is used in conjunction with vaginal intercourse (Cohorts B and D).

Staff will review and provide instruction for applicator use as needed. Detailed written instructions for the use of PMPA gel according to the protocol will be given to the participant [refer to the SSP Manual]

4.2.1 Cohort A

Each participant will be instructed to insert one applicatorful (4gm) of PMPA Gel intravaginally at bedtime. Twice daily use participants will be instructed to insert one applicatorful of product intravaginally in the morning and at bedtime.

4.2.2 Cohorts B and D

Each participant will be instructed to insert one applicatorful intravaginally at bedtime. If the HPDF is determined to be twice daily participants will be instructed to insert one applicatorful of product intravaginally in the morning and at bedtime. On days when participants have vaginal intercourse a pre-coital dose will be substituted for one of the routinely scheduled doses. If more than one coital act takes place per day, only one of the routinely scheduled doses will be substituted with a pre-coital dose, the participant must not exceed two doses per day. The coital dose may be inserted up to two hours before vaginal intercourse.

4.2.3 Cohort C

Each participant will be instructed to insert one applicatorful intravaginally at bedtime. If the HPDF is determined to be twice daily each participant will be instructed to insert one applicatorful intravaginally in the morning and at bedtime.

4.2.4 Delayed Product Use Prior to Follow-up Visit

Participants will be instructed to delay any morning dose of product until after the Day 7 Follow-up Visit, and Interim Visits requiring pelvic and/or colposcopy examination. The participant will be instructed to discontinue product use after the evening application on Day 13.

Cohort A participants enrolled in the PK study will be asked to administer the first dose in the clinic on Day 0 after the pelvic exam. Participants will be instructed not to administer the product the night prior to the Day 13 Visit. They will apply the product after the pelvic exam during the Day 13 Visit.

If the HPDF is determined to be twice daily, cohorts B and C (and cohort D if indicated as per Section 2.5) participants enrolled in the PK study will be instructed to administer the product on Day 0 after the pelvic exam and again after the 12 hour PK draw. For the Day 13 Visit, participants will be instructed to apply their morning dose after the pelvic exam then discontinue product use (i.e. omit the second final Day 13 dose).

4.3 Product Supply and Distribution

The PMPA gel, carrier vehicle and applicators for this protocol will be available through the NIAID Clinical Research Products Management Center (CRPMC). The study site pharmacist will order their product from the CRPMC according to the ordering instructions as provided in the SSP Manual. A weekly supply of product as described in Section 4.1 will be dispensed to study participants by the study staff on Visit Day 0 and Visit Day 7. An additional supply of product will be dispensed at interim visits if required.

The HPTN Coordinating and Operations Center (CORE) will supply a single brand and type of lubricated latex (not containing N-9) condoms to each site for distribution to study participants in Cohorts B and D.

Sites will be responsible for obtaining unscented panty liners for distribution to participants.

4.4 Product Accountability

The site pharmacist is required to maintain a complete record of all study products received from the CRPMC and subsequently dispensed. All unused study products must be held until the study is completed or terminated. At that time specific instructions will be provided for the return or destruction of the study products. Study product accountability will be maintained as outlined in the SSP Manual.

4.5 Adherence

Women will record information on the number of times PMPA gel was used, time it was administered, sexual behavior, use of study and non-study condoms, possible douching, and any specific symptoms experienced on the Daily Study Record forms. They will also have an opportunity to record narrative data about use of the product. These data will be summarized for all women for the duration of the study.

4.5.1 Definition of Non-adherence

Non-adherence is defined as three or more days (out of 14) of missed product use (defined as less than the scheduled dose frequency). If the participant has been instructed by study staff to miss 3 or more days of product use due to an AE, and the participant is able to achieve a full 14 days of product use without exceeding 3 consecutive days of non-use between menses the participant will be considered adherent.

For the sexually active cohort, adherence is further defined as having at least two episodes of vaginal intercourse during the 14-day exposure period.

Participants who miss less than three days will (if practical according to their expected date of menses onset) be asked to apply product for up to three additional days to attempt to achieve a full 14 days of product exposure. Participants may have their product use period extended for a maximum of three days. For participants who have their product use period extended, Day 14 pelvic and colposcopy exams will be deferred until a full 14 days of exposure is achieved. In cases where a participant's menstrual cycle is expected to begin prior to achieving 14 days of exposure, the exams will be performed prior to the onset of menses. 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.

Non-adherent participants will be asked their reasons for non-adherence and this information will be recorded on study case report forms.

4.6 Toxicity Management

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

Participants who discontinue product use will complete the safety evaluations scheduled to take place on study Days 7, 14 and 21.

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 Safety Review 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.

4.8 Concomitant Medications

Any concomitant medications will be permitted for the participant with the exception of those not permitted under criteria for inclusion and exclusion. All concomitant medications will be reported on the study participants' clinical records and recorded on the CRF for all medications received within 4 weeks prior to administration of study product, and throughout the study.

5.0 STUDY PROCEDURES

5.1 Clinical and Laboratory Evaluations

Refer to SSP for detailed instructions on specimen collection and laboratory procedures.

5.1.1 Screening Visit (up to Day – 42)

Potential participants will be screened for presumptive eligibility for the study according to the procedures described below. All procedures will be completed in a step-wise manner for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined. For potential participants who are found to be presumptively eligible at this visit, final eligibility will be confirmed at an Enrollment Visit scheduled to take place within 42 days of screening.

5.1.1.1 Clinical Procedures

- Obtain written informed consent.
- Assign Participant ID.
- Collect demographic and locator information.
- Collect medical history information.
- Provide HIV pre-test and risk reduction counseling to participants not known to be HIV infected.
- Collect urine specimen for pregnancy test and provide participant with results.
- Collect urine specimen for gonorrhea and chlamydia LCR at the Central Lab (CL).
- Collect urine specimen for urinalysis (microscopy and culture if indicated).
- Perform general physical exam.
- Perform pelvic examination including:
 - naked eye examination of vulva,
 - speculum examination of vagina and cervix,
 - collection of pH sample from the vaginal wall,
 - collection of swab specimen from the lateral vaginal wall for:
 - dried smear (smear specimen on two slides and allow to air dry);
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test),
 - collection of ecto- and endocervical specimen for Pap smear (first screening visit only, not to be done for participants having a record of a normal Pap in the last 3 months)
 - collection of sno-strip and Cervical Lavage (CVL) for HIV viral load (cohorts C and D only)

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

- bimanual examination for adnexal or fundal masses or tenderness
- Collect blood specimens for HIV1 (not to be done for HIV infected participants whose HIV status can be confirmed with medical records), syphilis serology, hematology, liver and renal function (all participants), and HIV RNA PCR at the CL and CD4+ (cohorts C and D only).
- Provide a practice Daily Study Record and instructions for completion.
- Schedule Enrollment Visit if no contraindications exist to study participation.
- Instruct the participant to call study staff when menses starts.
- Instruct the participant to abstain from the following activities for a minimum of 48 hours prior to the study enrollment visit:
 - vaginal intercourse,
 - anal intercourse,
 - douching,
 - oral contact with the vagina,
 - penetration of the vagina by fingers, sex toys or any other objects,
 - use of any vaginal product, including lubricants, drying agents, feminine hygiene products, diaphragms, and cervical caps,
- Complete and submit required data collection forms.

Note: Study condoms will be distributed to all participants during HIV pre-test and risk-reduction counseling.

5.1.1.2 Laboratory Procedures

- Perform human chorionic gonadotropin (HCG) pregnancy test.
- Record vaginal pH measurement.
- Record results of urinalysis (microscopy and culture if indicated).
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Send unstained dried smear to CL for later staining and analysis.
- Send sno-strip and CVL to the CL for analysis.
- Send urine to CL for LCR for gonorrhea and chlamydia.
- Prepare Pap smear (not to be done for participants having a record of a normal Pap three months prior to screening)
- Conduct EIA/WB test for HIV if indicated.
- Conduct complete blood count (CBC), blood chemistries (liver and renal function tests), RPR, RNA PCR, and CD4+ count (cohorts C and D only).

¹ HIV-infected participants will be instructed to bring confirmation of HIV status to the Screening Visit. (Copy of HIV Ab or VL testing), For HIV-infected participants who status cannot be confirmed by medical records, draw sample for HIV confirmatory testing.

5.1.2 Enrollment Visit – Baseline (Day 0 Non-Pharmacokinetic Participants; Day –1 and/or Day 0 Pharmacokinetic Participants Only)

Participants who are found to be presumptively eligible at their Screening Visit will complete Enrollment Visits 3 to 5 five days post-menses, and within 42 days after the Screening Visit. Participants who do not complete an Enrollment Visit within 42 days of screening must repeat the entire Screening Visit.

All participants will receive their screening test results at their Enrollment Visit. For those whose test results meet the study eligibility criteria, the procedures below will be undertaken in a step-wise manner to confirm eligibility. As was the case at the Screening Visit, procedures will be discontinued if ineligibility is determined at this visit.

Participants in the PK sub-cohorts may complete all Enrollment Visit procedures EXCEPT administering the first dose of PMPA gel and collecting PK blood samples on study Day –1 and/or study Day 0.

5.1.2.1 Clinical Procedures

- Update locator information.
- Provide results of HIV and STD tests and post test counseling.
- Review sample Daily Study Record for completeness and accuracy.
- Conduct Behavioral Assessment.
- Ensure participant still meets eligibility requirements.
- Collect urine specimen for pregnancy test and provide participant with results.
- Collect urine specimen for urinalysis (microscopy and culture if indicated).
- Perform pelvic examination including:
 - naked eye examination of vulva,
 - speculum examination of vagina and cervix,
 - colposcopic examination of the vulva, vaginal and cervical mucosa,
 - one colposcopic image, without filter, encompassing the cervix and fornices,
 - collection of pH sample from the vaginal wall,
 - collection of swab specimen from the lateral vaginal wall for:
 - dried smear (smear specimen on two slides and allow to air dry);
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test).
 - collection of sno-strip for HIV viral load (cohorts C and D only).
 - collection of CVL for HIV viral load and resistance testing (cohorts C and D only).
 - bimanual examination for adnexal or fundal masses or tenderness.
- Collect blood specimens for hematology, liver and renal function (all participants), HIV RNA PCR and resistance testing at CL (cohorts C and D only) and storage of plasma and serum.
- Review and provide instruction for applicator use as needed [refer to the SSP Manual].
- For Pharmacokinetic study participants collect blood specimens at baseline (Time 0). Have participant administer first dose of PMPA gel. Collect PK blood samples at 0.5, 1.0, 2, 4, 6, 8, and 12 hours post dosing (Day 0).

- For Non-Pharmacokinetic study participants observe participant apply first dose of study product (optional) or instruct participant to start using product on the day of the Enrollment Visit (Day 0).
- Instruct participants to distinguish between discolored or malodorous discharge and the discharge anticipated with use of PMPA gel.
- Provide Daily Study Record and instructions for completion.
- Distribute study product and panty liners.
- Distribute condoms.
- Schedule Day 7 follow-up visit.
- Label colposcopic image with coded number.
- Complete and submit required data collection forms.

5.1.2.2 Laboratory Procedures

- Perform HCG pregnancy test.
- Record vaginal pH measurement.
- Record results of urinalysis (microscopy and culture if indicated).
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct CBC, blood chemistries, liver and renal function tests (all participants) and RNA PCR and HIV resistance testing (cohorts C and D only).
- Send unstained dried smear to CL for later staining and analysis.
- Send plasma, sno-strip and CVL to the CL for analysis.
- Send serum to Contract Lab for PK analysis (8 samples per participant). See the SSP Manual for instructions.
- Archive serum and plasma.

Note: Plasma will be stored for HIV drug resistance genotyping. Resistance testing will be performed on selected samples as described in section 7.4.4.

Note: Serum and plasma for archive, and leftover CVL and sno-strip samples from all study visits will be destroyed one year after the last participant in the study (across sites) has completed follow-up.

5.1.3 Follow-up Visit(s) (Day 2 or 3 and / or Day 7)

This visit is scheduled to take place on Day 2 or 3 and on study Day 7. Every effort should be made to complete the Day 7 visit on Day 7, however the visit may take place — if necessary — between Days 5 and 9. As described below, the baseline evaluations completed at the study Screening and Enrollment Visits are repeated at this visit, with the exception that colposcopy is performed only if abnormalities are observed on speculum exam. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

Note: Once the participants in the A cohorts have completed their Day 14 Visits, the Protocol Safety Review Team may decide to omit the Day 2 or 3 Visit or the Day 7 visit for the participants in the B, C and D cohorts.

5.1.3.1 Clinical Procedures

- Update locator information.
- Review Daily Study Record, note the time of last product application, and conduct adherence interview.
- Count the number of used and unused tubes of PMPA gel returned.
- Perform pelvic examination including:
 - naked eye examination of vulva,
 - speculum examination of vagina and cervix,
 - collection of pH sample from the vaginal wall,
 - collection of swab specimen from the lateral vaginal wall for:
 - dried smear (smear specimen on two slides and allow to air dry);
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test),
 - collection of sno-strip and Cervical Lavage (CVL) for HIV viral load (cohorts C and D only)
 - bimanual examination for adnexal or fundal masses or tenderness.
- IF any abnormalities are noted on pelvic exam, refer to Appendix III for the procedures to be followed.
- IF abnormal vaginal discharge or purulent cervicitis is noted:
- Collect urine specimen for LCR for *N. gonorrhoeae* and *C. trachomatis*
- IF ulcerative lesions are noted:
 - Photograph lesions according to standard procedures in the SSP Manual.
 - Culture for herpes simplex
 - Collect blood specimen for syphilis serology.
 - If this is an AE re-evaluation visit 5-7 days after first detection of the ulcer and it has either become worse or not healed, perform a biopsy.
 - Label colposcopic image (noting photograph number) with coded number.
- Provide instruction for follow-up care and use of PMPA gel (or not) as appropriate. If appropriate and necessary provide additional supply of condoms, Daily Study Record, etc.
- Collect blood specimens for hematology, liver and renal function (all participants), HIV RNA PCR at CL (cohorts C and D only).

Note: Blood specimens will be collected at the Day 2 or 3 Visit only if the Day 7 visit for the participants in the B, C and D cohorts is omitted.

- Instruct participant to return if she experiences discomfort, or discolored or malodorous discharge.
- Provide Daily Study Record and review instructions for completion.
- Distribute study product and panty liners.
- Distribute condoms.
- Schedule Day 14 Follow-up Visit or Day 13 and Day 14 Follow-up Visit for PK participants.
- Complete all required data collection forms.

5.1.3.2 Laboratory Procedures

- Record pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and BV.
- Conduct CBC, blood chemistries, liver and renal function tests (all participants) and HIV RNA PCR (cohorts C and D only).
- Send unstained dried smear to CL for later staining and analysis.
- Send plasma, sno-strip and CVL to the CL for analysis.
- If indicated:
 - Conduct LCR for *C. trachomatis*.
 - Conduct LCR for *N. gonorrhoeae*.
 - Prepare culture for herpes simplex.
 - Conduct serologic test (RPR, confirmed by fluorescent triponemal antibody (FTA), may also elect to conduct microhemagglutination-*Treponema pallidum* (MHA-TP)) for syphilis.
 - Conduct CBC, blood chemistry analysis

5.1.4 Pharmacokinetic Study Participant Visit (Day 13 – PK Study participants only)

This visit is scheduled to take on study Day 13. Every effort should be made to complete this visit on Day 13, however the visit it may take place — if necessary — between Days 11 and 15. The PK study procedures are described below.

5.1.4.1 Clinical Procedures

- Update locator information.
- Collect blood specimen at baseline (Time 0). Have participant administer first daily dose of PMPA gel. Collect PK serum samples at 0.5, 1.0, 2, 4, 6, 8, 12 and 24 hours post dosing.

Note: if the HPDF is determined to be twice daily the participant will discontinue product use after the morning dose and will not apply and evening dose.

- Complete and submit required data collection forms.

5.1.4.2 Laboratory Procedures

- Send serum to Contract Lab for PK analysis (nine samples per participant). Refer to the SSP Manual for specific instructions.

5.1.5 Follow-up Visit (Day 14)

This visit is scheduled to take on study Day 14. Every effort should be made to complete this visit on Day 14, however the visit may take place — if necessary — between Days 12 and 16. As described below, the baseline evaluations completed at the study Screening and Enrollment Visits, including routine colposcopy, are repeated at this visit. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

5.1.5.1 Clinical Procedures

- Update locator information.
- Administer Follow-up Acceptability Assessment.
- Review Daily Study Record, note the time of last product application, and conduct adherence interview.
- Count the number of used and unused tubes of PMPA gel returned and return the unused tubes to the site pharmacy.
- Collect urine specimen for pregnancy test and provide participant with results.
- Collect urine specimen for microscopy and culture.
- Perform pelvic examination including:
 - naked eye examination of vulva.
 - speculum examination of vagina and cervix,
 - colposcopic examination of the vaginal and cervical mucosa for lesions,
 - one colposcopic photograph, without filter, encompassing the cervix and fornices,
 - collection of pH sample from vaginal wall,
 - collection of swab specimen from the lateral vaginal wall for:
 - dried smear (smear specimen on two slides and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test); and
 - collection of sno-strip for HIV viral load (cohorts C and D only).
 - collection of CVL for HIV viral load and resistance testing (cohorts C and D only).
 - bimanual examination for adnexal or fundal masses or tenderness.
- IF any abnormalities are noted on pelvic exam, refer to Appendix III for the procedures to be followed.
- IF abnormal vaginal discharge or purulent cervicitis is noted:
 - Collect urine for LCR for *N. gonorrhoeae* and *C. trachomatis*.
- IF ulcerative lesions are noted:
 - Photograph lesions according to standard procedures in the SSP Manual.
 - Culture for herpes simplex.
 - Collect blood specimen for syphilis serology.
 - If this is an AE re-evaluation visit 5-7 days after first detection of the ulcer and it has either become worse or not healed, perform a biopsy.
 - Label colposcopic image (noting photograph number) with coded number.
- Provide instruction for follow-up care.
- Collect blood specimens for hematology, liver and renal function (all participants), HIV RNA PCR and resistance testing at CL (cohorts C and D only).
- Instruct participant to return if she experiences discomfort, or discolored or malodorous discharge within the next week.

- Schedule Day 21 follow-up visit for cohorts C and D (and A and B participants if they choose to have a clinic visit) or telephone contact for cohort A and B participants.
- Administer Study Burden Assessment (Cohorts A and B only).
- Complete all required data collection forms.

5.1.5.2 Laboratory Procedures

- Perform HCG pregnancy test.
- Record results of urine microscopy and culture
- Record vaginal pH measurement .
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and BV.
- Send unstained dried smear to CL for later staining and analysis.
- Send plasma, sno-strip and CVL to the CL for analysis.
- Conduct CBC, blood chemistries, liver and renal function tests (all participants) and RNA PCR and HIV resistance testing (cohorts C and D only).
- If indicated:
 - Conduct LCR for *C. trachomatis*.
 - Conduct LCR for *N. gonorrhoeae*.
 - Prepare culture for herpes simplex.
 - Conduct serologic test (RPR, confirmed by FTA, may also elect to conduct MHA-TP) for syphilis.

Note: Plasma will be stored for HIV drug resistance genotyping. Resistance testing will be performed on selected samples as described in section 7.4.4.

5.1.6 Follow-up Contact (Day 21)

This contact is scheduled to take on study Day 21. Every effort should be made to complete this contact on Day 21, however it may take place — if necessary — between Days 19 and 23. Procedures for the Day 21 Contact are described below. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

If a participant in Cohorts A ⁽¹⁻⁴⁾ or B has not had any AEs since her last visit, a clinical/laboratory examination will not be necessary and the Day 21 contact may be conducted by telephone (see Section 5.1.6.1). Otherwise the participant return to the clinic for clinical and /or laboratory evaluation as described in Section 5.1.6.2. All participants in cohorts C and D will be required to return to the clinic for evaluation as described in Section 5.1.6.2.

5.1.6.1 Telephone Contact

- Update locator information.
- Conduct telephone interview and determine if the participant has taken any concomitant medications or experienced any AEs. If the participant requests a clinic visit and/or if AEs are identified, instruct participant to return to the clinic for evaluation.
- Complete and submit required data collection forms.

5.1.6.2 Clinical Procedures

- Update locator information.
- Collect urine specimen for microscopy and culture.
- Perform pelvic examination including:
 - naked eye examination of vulva
 - speculum examination of vagina and cervix,
 - collection of pH sample from the vaginal wall,
 - collection of swab specimen from the lateral vaginal wall for:
 - dried smear (smear specimen on two slides and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test)
 - collection of sno-strip and Cervical Lavage (CVL) for HIV viral load (cohorts C and D only)
 - bimanual examination for adnexal or fundal masses or tenderness.
- IF any abnormalities are noted on pelvic exam, refer to Appendix III for the procedures to be followed.
- IF abnormal vaginal discharge or purulent cervicitis is noted:
 - Collect urine for LCR for *N. gonorrhoeae* and *C. trachomatis*.
- IF ulcerative lesions are noted:
 - Photograph lesions according to procedures in the SSP Manual.
 - Culture for herpes simplex
 - Collect blood specimen for syphilis serology.
 - If this is an AE re-evaluation visit 5-7 days after first detection of the ulcer and it has either become worse or not healed, perform a biopsy.
 - Label colposcopic image (noting photograph number) with coded number.
- Provide instruction for follow-up care.
- Collect blood specimens for hematology, liver and renal function (all participants), HIV RNA PCR at CL (cohorts C and D only).
- Administer Study Burden Assessment (cohorts C and D only).
- Complete and submit required data collection forms.

5.1.6.3 Laboratory Procedures

- Record pH measurement .
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and BV.
- Send unstained dried smear to CL for later staining and analysis.
- Send sno-strip, CVL and serum sample to the CL for analysis
- Conduct CBC, blood chemistries, liver and renal function (all participants) and RNA PCR (cohorts C and D only).
- If indicated:
 - Conduct LCR for *C. trachomatis*.
 - Conduct LCR for *N. gonorrhoeae*.
 - Prepare culture for herpes simplex.

- Conduct serologic test (RPR, confirmed by FTA, may also elect to conduct MHA-TP) for syphilis.

5.1.7 Interim Contacts and Visits (ad hoc)

Interim contacts and visits may be performed at participant request or as deemed necessary by the site Investigator at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable data collection 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 experience 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 2 or 3 and/or Day 7 Follow-up Visit in Section 5.1.3. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

Participants will be encouraged to report any medical problems or discomfort and will be instructed to return to the clinic for clinical and/or laboratory evaluation if they experience any of the following symptoms:

- non-menstrual vaginal bleeding;
- discolored or malodorous vaginal discharge;
- genital discomfort including vaginal pain;
- burning sensation in the vagina and/or the vulva;
- vaginal dryness;
- dyspareunia;
- dysuria.

5.1.8 Cohort B and D Male Sexual Partner Screening / Enrollment Visit (Day -42 to Day 0)

Potential participants will be screened for presumptive eligibility for the study according to the procedures described below. All procedures will be completed in a step-wise manner for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined. For potential participants who are found to be presumptively eligible at this visit, final eligibility will be confirmed at their partner's Enrollment Visit scheduled to take place within 42 days of screening of their partner's Screening visit. Note that if the male sexual partner is ineligible, the female partner also is ineligible.

5.1.8.1 Clinical Procedures

- Obtain written informed consent.

- Collect demographic and locator information.
- Provide HIV pre-test and risk reduction counseling to participants not known to be HIV infected.
- Collect focused STD history.
- Collect blood specimens for HIV (not to be done for HIV infected participants whose HIV status can be confirmed with medical records)¹.
- Perform optional genital exam if participant reports symptoms consistent with an STD within 2 weeks of screening and/or enrollment or if the participant requests an exam.
- Distribute condoms.
- Instruct the participant to abstain from the following activities for a minimum of 48 hours before the Enrollment Visit Day 0:
 - vaginal intercourse with their sexual partner,
 - anal intercourse with their sexual partner,
 - oral contact with their sexual partner's vagina,
 - penetration of their sexual partner's vagina with fingers, sex toys, drying agents or any other objects.
- Provide results of HIV tests (if carried out) and post test counseling.
- Provide the participant with:
 - instructions regarding the study behavioral requirements, and
 - instructions to contact study staff to ask questions and/or to report AEs.
- Complete and submit required data collection forms.

5.1.8.2 Laboratory Procedures

- Conduct EIA/WB for HIV if indicated.

5.1.9 Post-Intervention Acceptability Assessment Group Interviews

Female participants in all cohorts will be asked to take part in group interviews.

Group interviews will be conducted according to the following principles:

- use of an interview guide [refer to SSP Manual] with a set of relevant questions;
- a trained facilitator who will permit broad and equitable discussion; and
- audio-taping of the session with transcription and content analyses.

Group interviews will be conducted with at least two and as many as eight study participants and will take place approximately two to six weeks following completion of a study regimen. Group discussion will be analyzed to assess acceptability, discomfort and perceived costs of microbicide use.

5.1.10 Post-Intervention Acceptability Assessment Individual Interviews

Male sexual partners of the sexually active (B and D) participants will be asked to take part in individual interviews.

¹ HIV-infected participants will be instructed to bring confirmation of HIV status to the Screening Visit. (Copy of HIV Ab or VL testing), For HIV-infected participants who status cannot be confirmed by medical records, draw sample for HIV confirmatory testing.

Individual interviews will be conducted according to the following principles:

- use of an interview guide [refer to SSP Manual] with a set of relevant questions;
- a trained interviewer who will conduct a semi-structured interview
- audio-taping of the session with transcription and content analyses.

Male sexual partners will be given a staff-administered questionnaire within six weeks following completion of a study regimen to collect quantitative follow-up acceptability and study burden data in addition to the individual interview.

Individual interviews will be conducted either in a face to face setting or by phone and also will be carried out within six weeks following completion of a study regimen. Responses will be analyzed to gain in depth information on microbicide acceptability beyond that obtained with the structural questionnaires.

6.0 SAFETY MONITORING AND ADVERSE EXPERIENCE REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chair(s), study site Investigator(s), NIAID Medical/Program Officer, CORE Protocol Coordinator, SDMC Biostatistician, and other 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. (Refer to Section 2.4.3 for details).

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. Accrual will be suspended if two or more study participants per cohort experience an SAE judged possibly, probably, or definitely related to product use. The Protocol Safety Review Team then will review all pertinent safety data and determine whether to continue accrual and product use. A decision to stop the trial may be made by the protocol team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed. (Refer to Section 2.4.3 for details).

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 CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. All AEs will be defined and graded as described in the DAIDS SAE Reporting Manual and the DAIDS Standard Toxicity Tables [Refer to the SSP Manual]. The investigator or designee will assess the relationship of all AEs to the study product based on the DAIDS SAE Reporting Manual, the Investigator's Brochure, and his/her clinical judgment.

Site staff also will report all AEs that meet serious adverse event (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 week 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 sexual partners to the study clinician, who will evaluate and document the experience, as well as provide follow-up care or refer the sexual partner for such care. In the event that a male sexual 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, DATA MANAGEMENT, AND ANALYSIS

7.1 General Design Issues

The primary aims of the Phase I study are to determine vulvar and cervico-vaginal mucosal toxicity, and to assess systemic toxicity and absorption of the product. A cohort of up to 96 women will be evaluated to assess the effect of daily PMPA gel use for 14 days on the emergence of genital ulcerations and symptoms of irritation and systemic safety and absorption of the product.

7.2 Study Endpoints

7.2.1 Primary Endpoints: Safety/Toxicity

The safety/toxicity endpoints of this study are as follows:

- macroscopic evidence of damage (judged not to be due to pathogen) to the vulvar and/or vaginal epithelium including ulceration and other lesions, severe erythema, and/or severe edema;
-
- macroscopic evidence of damage (judged not to be due to pathogen) to the cervical mucosa including ulceration and other lesions, severe erythema, and/or severe edema;
-
- laboratory evidence of Grade 3 or higher toxicity for hematology, liver or renal function as defined by the DAIDS Toxicity Table [refer to the SSP and DAIDS SAE Reporting Manuals] which cannot be directly attributed to another cause after consultation with the protocol chairs and the study site investigator.

7.2.2 Secondary Endpoints: Acceptability and Exploratory Endpoints

The acceptability of PMPA gel by study participants and when relevant their male sexual partners, will be assessed using measures of participant attitudes toward the product, use of the product, adherence with the study protocol, and their opinions on participating in the study. The following endpoint will be assessed:

- The proportion of participants who at their Day 14 Follow-up Visit indicate they would be "unlikely" to use PMPA gel in the future.

The following acceptability endpoints for both female participants and their male sexual partners will be assessed:

- likes/dislikes of the gel (vehicle, applicator, and use associated factors),
- occurrence and type of problems experienced with the gel itself,
- occurrence and type of problems experienced with the applicator,
- perceived occurrence in which the participant/partner had to interrupt sex to apply the gel,
- acceptability of use of the product during sexual intercourse,
- perceived occurrence of intercourse occasions in which the gel leaked out or dried out before, during, or after sex, and the implications of these results for a woman to use the product without partner knowledge as necessary/appropriate,
- attitudes about gel use during sexual intercourse
- willingness to use gel in the future

The qualitative and quantitative data will be used to facilitate a greater understanding of both the role of the gel itself in sexual risk prevention and the factors of gel use which either facilitate or impede the sexual relationship and hence prevention of HIV transmission via sexual behaviors.

The following exploratory endpoints will be assessed:

- number of copies of HIV RNA isolated from HIV-infected female participant's genital secretions over the course of PMPA vaginal gel use.
- change in the genotypic resistance patterns of HIV in genital secretions and blood samples from the HIV-infected female participants over the course of PMPA vaginal gel use.
- change in the presence of vaginal bacteria in all female participants over the course of PMPA vaginal gel use using the Nugent Scoring System.

7.3 Sample Size, Accrual, and Treatment-Dose Allocation

Recruitment will target:

- up to 48 abstinent, HIV uninfected women (cohorts A1-A4)
- up to 12 sexually active HIV uninfected women (cohort B) and their male sexual partners
- up to 12 sexually abstinent HIV-infected women (cohort C)
- up to 12 sexually active HIV-infected women and their male sexual partners (cohort D)
- (if required) up to 12 sexually abstinent, HIV uninfected women (cohort V)
-

Up to 32 women will be recruited per site. In step one, two women from each of the three sites will be recruited in A1. If two or more of these six women experience SAEs judged to be related to product use, four women from each of the three sites will be recruited in cohort V in order to test the vehicle. If fewer than two participants from these six experience SAEs related to product use, in step two, six women from each of the three sites will be recruited and will be sequentially allocated in one block of size six according to a 2:2:2 allocation i.e., the first two available women at each site will be enrolled in A1, the next two available women at each site will be enrolled in A2, and the next two available woman at each site will be enrolled in A3. In step three, if fewer than two participants within each of the first three cohorts (i.e. A1, A2, and A3) experience SAEs related to product use, eight women from each of the three sites will be recruited and will be sequentially allocated in one block of size eight according to a 2:2:4 allocation i.e., the first two available women at each site will be enrolled in A2, the next two available women at each site will be enrolled in A3, and the next four available women at each site will be enrolled in A4. Finally in step four, if fewer than two participants within each of the last three cohorts (i.e., A2, A3, and A4) experience SAEs related to product use, eight women, four for cohort B and 4 for cohort C, from each of the three sites will be recruited. After enrollment for B and C is completed, four women from each of the three sites will be recruited in cohort D.

This allocation provides an equal number of participants per site (up to 32 women) and per cohort and site (up to 4 women). If one or more sites experience difficulty reaching their enrollment targets in a timely manner, with prior approval from the protocol chair consideration will be given to allowing other site(s) to enroll up to 48 women (instead of 32), depending on the site's overall enrollment capacity.

7.3.1 Sample Size Justification

For a given level of dose and frequency, suppose the frequency of a given toxic event is 5%. The probability that such an event will occur in at least one of 12 independent women is 46%. In addition, with the true frequency of 5%, a cohort of 12 women will provide 88% power to exclude toxicity rates greater than 35% (i.e., the probability of observing 0 or 1 toxic event is less than 0.05 when the true rate is 35%, while this probability is 0.88 when the true rate is 5%).

event rate	P (No events n=12)	P (1 or more events n=12)	P (2 or more events n=12)
1%	0.886	0.114	0.006
5%	0.540	0.460	0.118
10%	0.282	0.718	0.341
15%	0.142	0.858	0.557
25%	0.032	0.968	0.842
35%	0.006	0.994	0.956
45%	0.001	0.999	0.992

In addition, the probability of an early stopping (i.e. observing 2 or more related SAEs in the first 6 participants) is 3.3% when the true toxic event rate is 5% (11.4% when the true toxic event rate is 10%).

In secondary analysis of HIV- uninfected abstinent women for a given level of dose (0.3% or 1.0%), suppose the true frequency of a given toxic event is 5% at either daily frequency of application. The probability that such an event would occur in at least one of 24 independent women is 71%. In addition, with this true frequency of 5%, a pooled cohort of 24 such women would provide 66% power to exclude toxicity rates greater than 20% (i.e., the probability of observing 0 or 1 toxic event is less than 0.033 when the true rate is 20%, while the probability is 0.66 when the true rate is 5%).

event rate	P (No events n=24)	P (1 or more events n=24)	P (2 or more events n=24)
1%	0.796	0.214	0.024
5%	0.292	0.708	0.339
10%	0.080	0.920	0.708
15%	0.020	0.980	0.894
20%	0.005	0.995	0.967

The following shows what the resulting 95% exact confidence intervals for the toxic event rate would be if no events, 1 event, or 2 events are observed. For example, if for a cohort of 12 women we observe no event then the exact 95% confidence interval for the toxic event rate is [0.0%; 26.5%].

Sample Size	No event	One event	Two events
N=12	[0.0% ; 26.5%]	[0.2% ; 38.5%]	[2.1% ; 48.4%]
N=24	[0.0% ; 14.2%]	[0.1% ; 21.1%]	[1.0% ; 27.0%]

The power considerations described above are fairly robust to address possible non-adherence to the study treatment regimen (as described in Section 4.5.1). For example, if two women per cohort were non-adherent to the regimen, a subgroup analysis of the 10 adherent women in the cohort would provide 74% power to exclude toxicity rates greater than 45% for a given toxic event rate of 10%. Furthermore, a pooled cohort of 20 women would provide 74% power to exclude toxicity greater than 25% for a given toxic event rate of 5%.

7.4 Data Monitoring and Analysis

Close collaboration among protocol team members will be necessary to evaluate study progress and respond to occurrences of toxicity in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the protocol team on a regular basis. 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.

7.4.1 Statistical Analyses

All descriptive and inferential statistical analyses will be performed using SAS and StatXact statistical software. All participants who receive treatment will be included in all analyses. A treatment group refers to a given level of dose and frequency, for HIV uninfected and HIV infected participants separately. Analyses will be performed that combine the HIV uninfected, abstinent participants with a common level of dose (0.3% or 1.0%).

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).

Due to the small sample size within each treatment group, comparison among the frequency groups will not be performed. However, cohorts will be compared for baseline characteristics including demographics, pelvic examination, colposcopy, and laboratory measurements using descriptive statistics.

Within-treatment 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).

7.4.2 Safety Analysis

The primary aim of the study is to assess the toxicity of PMPA gel on vulvar and cervico-vaginal mucosa. The number and the percentages of participants experiencing at least one AE, and the number and percentage experiencing each specific AE will be tabulated. Each subject will contribute once in each category (i.e. only for the first occurrence) for the calculation of event rates.

The number and percentage of participants experiencing each type of AE (including AEs leading to study discontinuation) is to be tabulated by severity and relationship to treatment for each treatment group. AEs that lead to study discontinuation will be listed in a separate data listing.

Overall summaries by treatment group include the number and percentage of participants experiencing: (1) any experience; (2) any moderate, severe, or life-threatening experience; and (3) any severe, or life threatening experience. The number and percentage of participants with an AE judged possibly, probably or definitely related to study treatment will be summarized for each treatment group.

Grade 3 or higher toxicity for hematology, liver or renal function is also a primary endpoint. Baseline and Day 14 laboratory measures will be summarized and the change in function, defined by the difference between Day 14 and baseline measurements, will be evaluated.

7.4.3 Analysis of Pharmacokinetic Data

Pharmacokinetics of PMPA will be evaluated after vaginal administration. This will include PMPA PK profile of the initial dose (Day 0) and PMPA PK profile at steady-state (Day 13) following the regimen described in Section 2.5. The analysis will be performed in an exploratory way by investigating plasma concentrations of PMPA and determining the AUC. PMPA accumulation will be determined by comparing the median PMPA AUC on Day 13 to the median AUC on Day 0. In addition PMPA AUC in sexually active versus sexually inactive cohorts will be compared.

Maximum concentration of drug (C_{max}) and time to reach maximum concentration of drug (T_{max}) will be calculated as part of the analysis as stated above.

7.4.4 Analysis of Exploratory Data

To assess the effect of product use on cervico-vaginal of HIV, change in the number of copies of HIV RNA from the Baseline visit to the Day 14 visit will be analyzed in the two HIV-infected groups. In addition the change in the number of copies of HIV RNA will be compared between the sexually active and the sexually abstinent women.

To assess the effect of product use on genotypic resistance on HIV, detectable HIV in cervico-vaginal secretions and plasma from the baseline and Day 14 Visits will be analyzed for the presence of drug resistance mutations in the two HIV-infected groups from baseline and Day 14 Visits. Genotyping will be performed retrospectively. Results from individual patients will not be used in clinical management.

To assess the effect of product use on vaginal flora, change in the presence of vaginal bacteria will be measured using the Nugent Scoring System. Vaginal flora pattern gram stains from the Baseline visit to the Day 14 visit in HIV-uninfected participants, and Baseline visit to the Day 21 visit in HIV-infected participants will be analyzed for each cohort. In addition, the change in presence of vaginal bacteria will be compared across cohorts.

7.4.5 Analysis of Acceptability Data

The secondary objective of the study is to determine through qualitative and quantitative analyses the acceptability of PMPA gel, applicator, and use for female participants; and the acceptability of PMPA gel for their male sexual partners. The number and percentage of participants who at their Day 14 Follow-up Visit who have not indicated they would be "unlikely" to use PMPA gel in the future will be calculated. Descriptive summaries of factors relating to acceptability will be performed for: applicator associated factors; vehicle-associated factors; and use-associated factors.

7.4.5.1 Quantitative Analysis

The number and percentage of participants' responses from the acceptability questionnaire will be calculated. Descriptive summaries of factors relating to acceptability will be performed for: vehicle associated factors, applicator associated factors, and use associated factors.

Questionnaire data will be tabulated to summarize group data regarding the acceptability of PMPA gel. Comparisons will be made examining acceptability data obtained on abstinent and sexually active women. Open-ended response data will be summarized for each site and across sites.

7.4.5.2 Qualitative Analysis

The focus groups and individual interviews will be audio-taped, transcribed and imported into Nvivo software to be coded.

Qualitative data coding schemes will be developed a priori for known protocol-driven factors related to acceptability. In addition, additional coding will be developed as data is processed, based on the content, themes and patterns that emerge from the data. Content analysis of the qualitative data will be done for each focus group and/or interview and a thematic summary report for each site and cohort will be completed. Cross-site comparisons will be done and a summary report produced. Categories, themes and patterns will emerge as a function of the analysis. The qualitative findings will be used to illustrate, facilitate and add to our understanding of the quantitative findings and the sociocultural context of acceptability in this sample.

The focus groups and in depth individual interviews will be audio-taped using high-fidelity tape recorders. The tapes will be immediately sent for transcription. After the transcripts are prepared, the discussion facilitators will verify the transcripts with the tapes to insure accuracy and completeness. Subsequently, each transcript will be imported into Nvivo software. This software package can handle rich data as text – with full ability to edit, visually code, and link documents as they are created, coded, filtered, managed and searched. Using the capabilities of the program, the interviewer will create memos attached to each transcript, recording personal observations and impressions that occurred during the interview.

Subsequently the investigators involved in qualitative data analysis will process the transcripts. In the initial stage, a coding scheme will be devised by two of the research investigators who will develop major coding categories and sub-categories as well as a preliminary code book that will be discussed with the rest of the qualitative investigators. Other team members will read several additional transcripts to identify new themes. Once consensus is reached about the final coding scheme, the investigators will code the rest of the transcripts.

The analysis of coded material will lead to the progressive identification of categories, themes, and patterns. This involves noting regularities in the behavior, attitudes, and opinions of people under study which are then organized under a conceptual label. Categories should be internally consistent but distinct from one another. The qualitative findings will be integrated into the quantitative data collected through the structured and semistructured acceptability surveys, helping to understand the latter and expand their meaning.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

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

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

Subsequent to initial review and approval, the local IRB will review the protocol at least annually. The site 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 female study participant before she is screened for and/or enrolled in the study. Written informed consent also will be obtained from sexually active female participants' male sexual partners. (Refer to Appendix IV for copies of informed consents). Participants will be provided with a copy of their informed consent forms if they are willing to receive them. Study staff will document the informed consent process as described in the Study-Specific Procedures Manual.

The study site is responsible for developing study informed consent forms for local use, based on the templates in Appendix IV, in accordance with all applicable US regulations and local guidelines. The DAIDS Regulatory Operations Center (ROC) will review all site-specific informed consent forms and approve them for use according to DAIDS policies. The study cannot be initiated at any site until the site is fully registered with the DAIDS ROC (through CORE) and has received written notification of protocol activation by CORE. Following ROC approval, CORE staff will “activate” the site to begin study operations, according to procedures specified in the SSP Manual.

8.3 Participant Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, colposcopic photographs, reports, study data collection, process, and administrative forms will be identified by coded number only to maintain participant confidentiality. All computer entry and networking programs also will be done by coded number only, and all local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participants' study information will not be released without the written permission of the participant, except as necessary for monitoring by NIAID and/or its contractors (e.g., the DAIDS monitoring contractor), Gilead Sciences, representatives of the HPTN CORE, the CL and/or Statistical and Data Management Center (SDMC), the FDA, and other regulatory authorities.

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 microbicide that prevents sexual transmission of HIV.

In addition, participants will receive HIV counseling and testing as part of the study screening process. Participants will also have pelvic exams, Pap smears, and be screened for a number of STDs. Participants will be referred for treatment if applicable. (Refer to Appendix III, see also Section 8.7)

8.5 Risks

Female study 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. Female participants also 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. Trained counselors will be available to help participants deal with these feelings.

Minimal local irritation and little or no systemic adverse effects are expected with the use of PMPA gel intravaginally at the concentrations proposed for this study (0.3% and 1.0%). However, PMPA gel has not been tested topically in humans previously. Therefore, risks of treatment are not known and careful monitoring for adverse effects is planned. A summary of AEs reported to date in clinical studies of intravenous PMPA and related compounds which may be relevant for the use of PMPA gel is provided in Section 1.2.7.

It is not known what effect PMPA Gel will have on the HIV virus or HIV disease progression in HIV infected participants.

Although the study site will make every effort to protect the privacy and confidentiality of all study participants, it is possible that participants' involvement in the study, including the focus groups, could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

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 Access to HIV-Related Care

HIV pre-test, risk reduction, and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Counseling will be provided in accordance with the Centers for Disease Control and Prevention guidelines. [refer to the SSP Manual] The study site will document its counseling policies and procedures prior to study implementation for purposes of staff training and study monitoring.

As part of the eligibility screening process, this study may identify persons who are infected with HIV. Study staff will provide participants with their HIV test results in the context of post-test counseling. They also will refer persons found to be HIV-infected to available sources of medical and psychosocial care, if any, and to any available research studies for HIV-infected persons. Women and men recruited for the C and D cohorts known to be HIV infected will continue with their regular source of care.

8.8 Study Discontinuation

As noted in Section 2.4.3, enrollment into this study will be suspended if two or more participants in any study cohort experience an SAE judged possibly, probably, or definitely related to product use. The protocol team then will review all pertinent data and determine whether to continue accrual and product use. The protocol team may decide to stop the study at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

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

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

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

10.0 TRAINING PROCEDURES

10.1 Colposcopy

Clinicians will participate in a colposcopy training program designed to establish and maintain consistent methods of distinguishing changes in cervico-vaginal mucosa. Training will focus on standardized identification of normal variation within the vaginal environment and abnormalities as defined in the protocol. Procedural guidelines and definitions for this purpose are included in the SSP Manual.

10.2 Data Collection

Training for Study Site staff responsible for collection of protocol data and transfer of those data to the SDMC will be conducted by staff from HPTN CORE and the SDMC.

10.3 Acceptability Assessment

The social scientist or other trained team member who is responsible for the acceptability data, the site Investigators and clinical study staff will participate in a training meeting at the same time/location as the clinician colposcopy training. Training will focus on standardizing the quantitative acceptability assessments, including instrument objectives, interview styles and techniques, data collection, management and entry, and data analysis/report writing.

In addition a training will be conducted for all qualitative focus group / interview facilitators. Training will focus on standardizing the quantitative acceptability assessments, including instrument objectives, interview styles and techniques, data collection, management, entry, coding and analysis, and report writing.

A process for achieving on-going communication between the social scientist (or other trained team member) at each site and the cross-site coordinator of the acceptability studies will be established.

11.0 ADMINISTRATIVE PROCEDURES

11.1 Study Coordination

This study will be submitted to an existing Investigational New Drug (IND) application held by DAIDS.

Implementation of this study will be directed by the protocol as well as a Study-Specific Procedures Manual. This 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 CRFs will be developed by the protocol 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 site Investigator, NIAID Medical Officer, Protocol Specialist, Biostatistician, Data Managers, and other protocol 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 team, and discussed routinely during conference called scheduled to take place at least every two weeks during the study implementation period.

11.2 Study Site Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to verify compliance with human subjects and other research regulations and guidelines, assess adherence to the study protocol and study-specific procedures manual, and confirm the quality and accuracy of information collected at the study site and entered into the study database. The Investigator will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs, product accountability forms), as well as observe the performance of study procedures. The Investigator also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NIAID, Gilead Sciences, FDA, and other regulatory authorities. A site visit log will be maintained at the study site to document all visits.

11.3 Protocol Compliance

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

11.4 Investigator Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with US regulations, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including site registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, CRFs, notations of all contacts with the participant, and all other source documents. All records must be retained on-site throughout the study's period of performance. The HPTN CORE will provide the study site with written instructions for long-term record storage at the completion of the period of performance.

11.5 Use of Information and Publications

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

12.0 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. Balzarini J, Hao Z, Herdewijn P, Johns D, De Clercq E. Intracellular Metabolism and Mechanism of Anti-Retrovirus Action of 9-(2-Phosphonylmethoxy)Adenine, a Potent Anti-Human Immunodeficiency Virus Compound. *Proc Natl Acad Sci, USA* 1991;88:1499-1503.
11. Martin J and Hitchcock M. Phosphonomethylether Compounds as Antiviral Agents. *Trans Proc* 1991;23:156-158.
12. Bronson J, Kim C, Ghazzouli I, Hitchcock M, Kern E, and Martin J. Synthesis and Antiviral Activity of Phosphonylmethoxyethyl Derivatives of Purine and Pyrimidine Bases. *Amer Chem Soc Symp* 1989;401:72-87.
13. De Clercq E, Sakuma T, Baba M, Pauwels R, Balzarini J, Rosenberg I, and Holy A. Antiviral Activity of Phosphonylmethoxyalkyl Derivatives of Purines and Pyrimidines. *Antiviral Res* 1987;8:261-272.
14. Pauwels R, Balzarini J, Schols D, Baba M, Desmyter J, Rosenberg I, Holy A, and De Clercq E. Phosphonylmethoxyethyl Purine Derivatives, A New Class of Anti-Human Immunodeficiency Virus Agents. *Antimicrob Agents and Chemother* 1988;32:1025-1030.

15. Van Rompay K, Cherrington J, Marthas M, Beradi C, Mulato A, *et al.* 9-[2-(Phosphonylmethoxy)propyl] Adenine Therapy of Established Simian Immunodeficiency Virus Infection in Infant Rhesus Macaques. *Antimicrob Agents and Chemother* 1996;40(11):2586-2591.
16. Robbins B, Greenhaw J, Connelly M, and Fridland A. Metabolic Pathways for Activation of the Antiviral Agent 9-(2-Phosphonylmethoxyethyl)Adenine in Human Lymphoid Cells. *Antimicrob Agents and Chemother* 1995;39:2304-2308.
17. Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-*R*-(2-phosphonomethoxypropyl)adenine (PMPA), Bis (isopropylloxymethylcarbonyl)PMPA. *Antimicrob Agents Chemother* 1998 Mar; 42(3):612-7
18. Heijntink R, Kruining J, Wilde G, Balzarini J, De Clercq E, and Schalm S. Inhibitory Effects of Acyclic Nucleoside Phosphonates on Human Hepatitis B Virus and Duck Hepatitis B Virus Infections in Tissue Culture. *Antimicrob Agents and Chemother* 1994;38:2180-2182.
19. Tsai C-C, Follis K, Sabo A, Beck T, Grant R, Bischofberger N, Benveniste R, and Black R. Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl)Adenine. *Science* 1995;270:1197-1199.
20. Miller C, Rosenberg Z, and Bischofberger N. Use of Topical PMPA to Prevent Vaginal Transmission of SIV, Oral Presentation. 1996, 9th International Conference on Antiviral Research, Japan.
21. Shaw J-P. In Vitro Metabolism of ¹⁴C-PMPA in Human and Animal Tissues. Gilead Sciences Report No. 96-DDM-1728-003. July 12, 1996.
22. Mulato AS and Cherrington JM. Anti-HIV Activity of Adefovir (PMEA) and PMPS in Combination with Antiretroviral Compounds: In Vitro Analyses. *Antiviral. Res.* 1997 Nov;36 (2):91-7
23. Fridland A, Gill SC. Intracellular Kinetics of ¹⁴C-PMPA in Rhesus Monkeys. Gilead Sciences Report No. P20001025, March 20, 2001.
24. Miller C, *et al.* Use of Topical PMPA to Prevent Vaginal Transmission of SIV. International Conference on Antiviral Research, Fukushima, 1996.
25. Wyand, M *et al.* Prevention of intravaginal transmission of SIV-infection in rhesus monkeys using PMPA gel. World AIDS Conference, Geneva, 1998
26. Fairchild, D. 14-Day Vaginal Tissue Irritation and Toxicity Study of PMPA in Rats, June 30 1997. (Data on file, Gilead Sciences, Inc.)
27. Rush R. A Vaginal Irritation Study in Rabbits with PMPA (GS-1278) Topical Gel, June 13, 1997. (Data on file, Gilead Sciences, Inc.)

Appendix I – Clinical Evaluations

Clinical Procedures – Female Participants	Screening	Enrollment Day-1 ⁴ /Day 0	Follow-Up Day 2 or 3	Follow- Up Day 7	Pharmacokinetic Day13	Follow-Up Day 14	Follow-up Day 21	Post-Study
Obtain written informed consent.	x							
Obtain informed consent and screen male partner before enrollment	x							
Collect or update demographic and locator information.	x	x	x	x	x	x	x	
Assign participant ID.	x							
Perform general physical exam	x							
Collect medical history	x							
Provide pre-test HIV counseling.	x							
Post test counseling; Provide results of HIV and STD test.		x						
Distribute: participant guidebook	x							
study product		x	x	x				
condoms	x	x	x	x				
Daily Study Record	x	x	x	x				
panty liners		x	x	x				
Observe participant apply first dose of study product ⁴		optional						
Review Daily Study Record and interview for adherence and/or acceptability.		x	x	x		x		
Conduct Behavioral, Follow-up Acceptability and Study Burden Assessments.		Behavioral				Follow-Up all cohorts Study Burden A/B	Study Burden C/D	
Collect urine specimen for pregnancy and pathogen testing.	x	x	if indicated	if indicated		x	C/D	
Perform pelvic examination.	x	x	x	x		x	C/D	
Perform colposcopy.		x	if indicated	if indicated		x	if indicated	
Collect blood specimens for PK ^{1, 4} (Cohorts A ₂ , B, C, and if necessary D)		x			x	24 hour draw only		if indicated
Collect blood specimens for HIV ² syphilis serology, hematology, blood chemistries, HIV viral load and CD4+ ³ and plasma storage (enrollment only).	x	x	to be done if visit replaces the Day 7 Visit in the B, C and D cohorts	x		x	C/D	
Count returned PMPA gel tubes			x	x		x		
Schedule next visit.	x	x	x	x		x		
Complete data collection forms.	x	x	x	x	x	x	x	
Conduct group or individual interviews								x

¹Specimens for the first 6 participants in PK study cohorts will be collected at the Day 0 Enrollment and the Day 13 Follow-up Visits. The schedule for the specimen collection is as follows: 0.0, 0.5, 1, 2, 4, 6, 8, 12 hours on both days and 24 hours post dosing on day 14 only.

²Specimens for HIV and syphilis testing will be collected only at the screening visit unless indicated at other visits.

³HIV-infected participants only

⁴All Enrollment Visit procedures EXCEPT administering first dose of PMPA gel and collecting PK blood specimens may be completed on Day –1 for PK sub-cohort participants.

Appendix I – Clinical Evaluations - Continued

Clinical Procedures – Male Sexual Partner Participants (B and D)	Screening / Enrollment Visit Day –42 to Day 0	Post-Study
Obtain written informed consent.	x	
Collect or update demographic and locator information.	x	
Provide pre-test HIV counseling.	x	
Collect blood specimens for HIV	if indicated	
Collect focused STD history.	x	
Perform genital exam	optional / if indicated	
Provide results of HIV test and post-test counseling.	x	
Distribute condoms	x	
Complete data collection forms.	x	
Conduct Follow-Up Acceptability and Study Burden Assessments		x
Conduct Individual Acceptability Interview		x

Appendix II - Laboratory Evaluations

Evaluation					Visit							
Test	Purpose	Specimen	Volume	Laboratory	Screening	Enrollment Day 0 (Day -1 PK only)	Follow-up Day 2 or 3	Follow-up Day 7	Follow-up Day 13	Follow-up Day 14	Follow-up Day 21	
HCG	Pregnancy	Urine	10 mL	on site	X	X				X		
Urinalysis ^c	Urinary Tract Infection	Urine	10 mL	on site	X	X				X	C/D Cohort	
Wet mount	<i>Trichomonas vaginalis</i> , <i>Candida albicans</i> ,	Swab/slide	n/a	on site	X	X	X	X		X	C/D Cohort	
pH	Vaginal pH Bacterial Vaginosis	pH stick	n/a	n/a	X	X	X	X		X	C/D Cohort	
Gram stain	Vaginal Flora Pattern	Swab/slide	n/a	CL ^a	X	X	X	X		X	C/D Cohort	
Pap smear ^d	Cervical Atypia	Site Specific	n/a	LL ^b	X							
LCR ^e	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i>	Urine	15-20 mL	CL	X							
EIA/WB ^f	HIV	Site Specific	8 – 10 ml	LL	X							
RPR	<i>T. Pallidum</i>			LL	X							
Blood chemistries	Liver/Renal Function Tests			LL	X	X	***	X		X		C/D Cohort
Pharmacokinetics	Safety	Red top	5 mL	Contract Lab		Day 0 Only			X	24 hour draw only		
CBC	Hematology	Site Specific	8 – 10 ml	LL	X	X	***	X		X	C/D Cohort	
Viral load	HIV-RNA	sno-strip	n/a	CL ^a	X	X	X	X		X	C/D Cohort	
Viral Load / Resistance ^g	HIV-RNA/HIV genotyping	Purple top	10 mL	CL ^a	X	X resistance	***	X		X resistance	C/D Cohort	
CD4+	CD4+	Site Specific	8 – 10 mL	LL	X							
Viral load / Resistance ^g	HIV-RNA/HIV genotyping	CVL	10 mL	CL ^a	X	X resistance	X	X		X resistance	C/D Cohort	
Plasma archive ^h	Archive	Site Specific	8 – 10 mL	LL		X						
Serum archive ^h	Archive	Site Specific	8 – 10 mL	LL		X						

^aCL: Central Lab ^bLL: Local Lab

^cIf suggests UTI send for urine culture

^dOmit if participant has documentation of Pap results dated within the last 3 months

^eAs necessary according to clinicians' discretion, based upon clinical indications, at enrollment or follow-up visits

^fFor female participants and cohort B and D male sexual partners. Not to be done if HIV-infected status is documented by medical records

^gPlasma will be collected and stored for HIV drug resistance genotyping. Resistance testing will be performed on selected samples as described in section 7.4.4

^hStored at local repository and to be destroyed at the end of the study – one year from final participant's completion of follow-up (across sites)

*** To be collected if the Day 2 or 3 Visit replaces the Day 7 Visit

Appendix III - Outcomes, Diagnostics, and Follow-Up Procedures

Participants may withdraw or be discontinued from study treatment according to the guidelines in sections 3.9, 4.5.1, and 7.21 or according to criteria listed in the following table. Participants with any abnormal condition will be treated according to standard clinical practice.

Condition	Product Use	Evaluation	Follow-up and Treatment Action
Deep Epithelial Disruption (Ulceration)	Adverse experience, discontinue product use	Swab for culture for herpes simplex. (Herpes serology optional) Syphilis serology.	Re-evaluate in 5 to 7 days. If the ulcer has become worse or not healed in 5 to 7 days, perform a biopsy. Ask the participant to return in 7 to 10 days for a follow-up syphilis serology.
Superficial Epithelial Disruption (Abrasion/Peeling)	Continue	Because sexual activity and product application are probable causes of abrasion, information about these activities must be gathered at the time of detection and recorded on the CRF. Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 hours. If the condition is worse, discontinue product use. If the condition is the same, continue product use.
Generalized erythema or severe edema: A localized area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema	Adverse experience, discontinue product use	Naked eye evaluation and/or colposcopy.	Re-evaluate in 5 to 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 evaluated to be endometrial bleeding with no other source, continue product use. Re-evaluate in 72 hours if participant reports the bleeding / spotting has not resolved.
Suspected cervicitis (findings on exam such as discharge from cervical os)	Provisionally Continue	Evaluate for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> .	Re-evaluate in 48-72 hours. If the condition is worse, discontinue product use.
Petechial hemorrhage	Continue	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 to 72 hours. If the condition is significantly worse, discontinue product use. If the condition is the same, continue product use.
Ecchymosis	Continue	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 to 72 hours. If the condition is significantly worse, discontinue product use. If the condition is the same, continue product use.
Mild to moderate erythema or edema: A localized area of less than 50% of vulvar surface or combined vaginal and cervical surface	Continue	Naked eye evaluation and/or colposcopy.	Re-evaluate by speculum examination in 48 to 72 hours. If the condition is significantly worse, discontinue product use. If the condition remains the same, 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 to 5 days. If resolved, restart product use.
- 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 IV – SAMPLE INFORMED CONSENT

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Sample Informed Consent Form Division of AIDS, NIAID, NIH

Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel Version 2.0 29 May 2002 Cohort A - Sexually Abstinent HIV Uninfected Women

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:
INFORMED CONSENT:

You are being asked to take part in the research study named above. This research study is being done to test an experimental gel called PMPA Gel. 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 which 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 THE STUDY:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA Gel is inserted in the vagina. Another purpose is to find out women’s and men’s opinions of PMPA Gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 96 women and 24 men from 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, including the 14 days you use the gel.

PROCEDURES:

Main Study

You will be screened to see if you can enroll in the study. If you agree to join the study and enroll, you will begin using PMPA Gel on the day you enroll. You will be instructed to use the vaginal gel for two weeks. You will be asked to come back to the clinic for follow-up three times – 2 to 3 days, 1 week and 2 weeks after enrollment. Three weeks after enrollment, the study staff will contact you by phone for follow-up. If you have any problems you may be asked to come to the clinic for additional follow-up visits. If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. You will also be asked to participate in a group interview about 5-6 weeks after you enroll in the study.

Pharmacokinetic Study

Some participants in this study will be asked to take part in a pharmacokinetic study (“PK study”) of PMPA Gel. This study will test whether PMPA Gel is absorbed from the vagina into the blood by testing blood samples after PMPA Gel is inserted into the vagina. If you are asked to take part in the PK study, we will explain that study to you and ask you to sign a separate informed consent form for it.

Each visit is described below.

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 about 1 – 2 hours. To find out if you are eligible for the study you will be asked some questions, have a general physical exam, a pelvic exam, give a urine sample and have about 40 mL (or about 3 tablespoons) of blood drawn. The questions will be about you, your health, and your sexual practices. Some people may be embarrassed by questions about their sexual history. You may choose not to answer any of the questions if you wish. If at any time during the screening it is determined that you are not eligible for the study, the screening process and your visit will end.

If your answers to the questions show that you may be eligible for the study, 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 may mean to know your HIV and STD status, and whether you are prepared to receive your HIV and STD test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are willing to have HIV and STD testing, 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, liver, and kidneys. Then you will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs and other possible problems. If your exams and tests show that you have HIV or 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 ends. 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. You must receive your HIV test results to be in this study.

If the test results show that you are infected with HIV, you will not be eligible to be in this study. However, we will refer you for medical care and other services you may need. If other 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 this study, you will be asked some questions about your past use of vaginal products, your past sexual history, and your opinions about vaginal products. You will give urine to test for infections, and pregnancy, and about 40 mL (or 3 tablespoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam. 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 finished. 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 exams and tests show no problems, you will be entered into the study.

The participants in this group who have joined this study and who have also agreed to join the PK Study will blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form.

You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form. Your Enrollment Visit may take place over two days.

During the Study:

You will be given tubes of PMPA Gel with applicators and instructions on how to use them. Two different strengths of the gel will be tested in this study. You will put about 4mL (1 teaspoon) of the gel into your vagina once or twice a day for 14 days. The strength you use, and whether you use it once or twice a day, will depend on when you join the study.

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 nurse or doctor if you feel itching or burning, notice a change in your vaginal discharge like a bad smell, different color or have any bleeding from your vagina. You will bring your Daily Study Record and your used and unused tubes of PMPA Gel to your follow-up visits.

Day 2 or 3 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel and whether you had any medical problems or discomfort since your last visit. You will have a pelvic exam. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit. You will insert the vaginal gel as directed for another 4 - 5 days, and then return here for a Follow-Up Visit.

Day 7 Follow-Up Visit:

This visit will take about 1 hour and will be like the Day 2 or 3 Follow-up Visit. You will also give blood (about 20 mL or 4 teaspoons) for testing to check on your overall health, liver, and kidneys. You will insert PMPA Gel as directed for another 7 days, and then return here for a Follow-Up Visit.

Day 13 Pharmacokinetic Visit:

The participants in this group who have joined this study and who have also agreed to join the PK Study will return to the clinic on Day 13 to have blood drawn 40 mL (or 3 tablespoons) over 24 hours as explained in the PK Study consent form.

Day 14 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, and whether you had any medical problems or discomfort since your last visit. You will be asked some questions on your opinions of PMPA Gel and the study. You will give urine to test for infections, and pregnancy, and about 20 mL (or 4 teaspoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam with the lens. A picture will be taken of the inside of your vagina.

Day 21 Follow-Up Phone Contact or Clinic Visit:

The study staff will contact you by telephone 7 days after you stopped using PMPA Gel. You will be asked whether you had any medical problems or discomfort since your last visit. If you have had any problems, you may be asked to come to the clinic to check on the problems. Depending on what the problem is, you may have a general physical exam, or a pelvic exam or give urine or blood for testing.

Group Interview:

About 2-6 weeks after you finish your study visits, you will take part in a group interview with other women who were in the study, to talk about what it was like to use PMPA Gel. There will be about 2-8 other women in the group. The group will meet once for 1 - 2 hours. The discussion will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion.

Contact Procedures:

Once you join the study and start using the gel, 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** do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in the study:

- have vaginal sex
- have anal sex
- receive oral sex (any oral contact with the vagina)
- douche
- use any vaginal product other than PMPA Gel in your vagina including feminine hygiene products (such as tampons)
- insert fingers, sex toys or any other products into the vagina
- use intravenous 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 staff 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 right away to the study staff. The study staff 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 lens. 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 PMPA Gel before the end of the 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of PMPA Gel (used and unused) to the study site.

Some of your blood that is left over after all required study testing is done may be stored and used for HPTN 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 your stored blood without your permission.

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.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

Women in this study will be the first women to insert PMPA Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. It is not known what effects PMPA Gel will have on the vagina. Some possible effects are dryness, itching, burning, or pain. You also may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

It is possible that PMPA Gel could be absorbed from the vagina into the blood. Based on animal studies, the amount of PMPA absorbed from the vagina should be small and should not produce side effects outside the vagina. If the gel is absorbed into the blood, it is not known whether this will cause any bad effects.

In this study, PMPA is used as a gel. PMPA also has been given to people in other studies as an injection (or “shot”) or pill, as a treatment for HIV infection. In these studies, PMPA was well tolerated, but some people did have side effects.

Some people who received PMPA as an injection experienced the following mild side effects: headache, fatigue, dizziness, nausea, abdominal pain, changes in their sense of taste, and pain or discomfort in their eyes when exposed to bright light. Minor laboratory test abnormalities were also noted in some participants, including changes in results of tests to measure liver, muscle, pancreas or kidney function and decreases in the amount of some white blood cells. No one experienced any serious side effects.

Some people who received PMPA as a pill experienced headache, abdominal pain, flatulence, nausea, vomiting, and abnormal electrocardiograms (EKG). EKGs were normal at follow-up visits. One patient reported peripheral neuritis (unusual sensations in the feet and hands). Other participants had important laboratory test abnormalities including changes in results of tests to measure liver and muscle function. Depression was the only side effect that happened in more than 5% of the participants.

PMPA is a type of drug called an “antiviral nucleotide.” Side effects seen with this and antiviral nucleotides which have been approved by the FDA — when injected or taken as a pill — include: nerve disorders, inflammation of the pancreas, seizures, changes in mental status, sleep problems, headaches, hair loss, agitation, nausea, vomiting, diarrhea, kidney toxicity, skin rashes, painful mouth sores, changes in liver function, liver failure, build up of lactic acid in the body, low blood cell counts, infections, cancer, and death.

[Sites to include animal data if permissible by local IRB guidelines] PMPA also has been tested in animals. In studies using doses ten times higher than you would receive in this study, side effects included kidney or liver damage, diarrhea, decreased red blood cells, a reduction in the amount of lymph tissue in the body and damage to the lining of the intestines. Some adult monkeys receiving PMPA at high doses for more than 10 months had changes in their bones, including bone deformities and fractures. Young monkeys exposed to PMPA before birth and then treated after birth with higher doses of PMPA also had bone changes. In studies where PMPA gel was tested on the vaginas of rats there were no side effects. In studies where PMPA gel was tested on rabbit vaginas there was some mild irritation, no ulcers or erosion were seen.

It is possible that PMPA Gel could cause any of the effects listed above or other effects that we do not yet know about. This includes effects leading to death or permanent disability. The study doctors and nurses will closely watch your medical condition during the study. If you have any side effects, you should call the nurse or doctor right away.

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 participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if you are known by someone else in taking part in the group interview.

PREGNANCY:

It is not known whether PMPA Gel has any effect on pregnancy, or whether it has any 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 have agreed to not have vaginal sex while using PMPA gel. However, if you do for any reason have vaginal sex while using PMPA gel, you must use an acceptable form of birth control. Acceptable forms of birth control include study provided male condoms, oral contraceptives (birth control pills), injectables and Norplant that you have used for at least three months.

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using PMPA 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 PMPA 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 HIV or other STDs, 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 PMPA Gel as instructed;
- you have a bad reaction to PMPA Gel;
- you become pregnant;
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 each visit when you have a pelvic exam. You will receive (insert site-specific amount of money) for each visit when you have a pelvic exam with the lens. You will receive (insert site-specific amount of money) for the group interview.

CONFIDENTIALITY:

Your research records, including the photographs 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, study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE:

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

Volunteer's name

Volunteer's signature

Date

Witness' name

Witness' signature

Date

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Cohort B - Sexually Active HIV Uninfected Women**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You are being asked to take part in the research study named above. This research study is being done to test an experimental gel called PMPA Gel. 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 which 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:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA is inserted in the vagina. Another purpose is to find out women’s and men’s opinions of PMPA Gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 96 women and 24 men from 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, including the 14 days you use the gel.

PROCEDURES:

Main Study

You will be screened to see if you can enroll in the study. If you agree to join the study and enroll, you will begin using PMPA Gel on the day you enroll. You will be asked to come back to the clinic for follow-up three times – 2 to 3 days, 1 week and 2 weeks after enrollment. Three weeks after enrollment, the study staff will contact you by phone for follow-up. If you have any problems you may be asked to come to the clinic for additional follow-up visits. If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. You will also be asked to participate in a group interview about 5-6 weeks after you enroll in the study.

Pharmacokinetic Study

Some participants in this study will be asked to take part in a pharmacokinetic study (“PK study”) of PMPA Gel. This study will test whether PMPA Gel is absorbed from the vagina into the blood by testing blood samples after PMPA Gel is inserted into the vagina. If you are asked to take part in the PK study, we will explain that study to you and ask you to sign a separate informed consent form for it.

Each visit is described below.

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 about 1 – 2 hours. To find out if you are eligible for the study you will be asked some questions, have a general physical exam, a pelvic exam, give a urine sample and have about 40 mL (or 3 tablespoons) of blood drawn. The questions will be about you, your health, your male sexual partner and your sexual practices. Some people may be embarrassed by questions about their sexual history. You may choose not to answer any of the questions if you wish. If at any time during the screening it is determined that you are not eligible for the study, the screening process and your visit will end.

If your answers to the questions show that you may be eligible for the study, 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 may mean to know your HIV and STD status, and whether you are prepared to receive your HIV and STD test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are willing to have HIV and STD testing, 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, liver, and kidneys. Then you will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs and other possible problems. If your exams and tests show that you have HIV or 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 also be asked to give his informed consent and will be asked about his health and sexual practices. He will be counseled and tested for HIV. If he is not willing to give his written consent or if at any time during his screening process it is found that he is not eligible for the study, neither of you will be eligible for the study.

Enrollment Visit:

This visit will take place within 5 days after your next menstrual period ends. By the time of this visit, your male sexual partner must come to the study site to give his informed consent to take part in the study, and to answer some questions to confirm his eligibility.

This visit will take about 1 hour. We will tell you all 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. You must receive your HIV test results to be in this study.

If the test results show that you are infected with HIV you will not be eligible to be in this study. However, we will refer you for medical care and other services you may need. If other 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 this study, you will be asked some questions about your past use of vaginal products, your past sexual history, and your opinions about vaginal products. You will give urine to test for infections, and pregnancy, and about 40 mL (or 3 tablespoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam. 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 finished. 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 into the study.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn 40 mL (or about 3 tablespoons) over 12 hours as described in the PK Study consent form.

You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form. Your Enrollment Visit may take place over two days.

During the Study:

You will be given tubes of PMPA Gel with applicators and instructions on how to use them. Two different strengths of the gel will be tested in this study. You will put about 4 mL (1 teaspoon) of the gel into your vagina once or twice a day for 14 days. The strength you use, and whether you use it once or twice a day, will depend on information gathered from women who have finished their part of the study before you join the study. You are asked to have vaginal sex with your sexual partner as many times a week as you usually do which must be at least 2 times per week. You and your sexual partner must use condoms given to you by study staff each time you have sex. On the days that you have sex, you are asked to insert the gel up to 2 hours before having sex.

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 nurse or doctor if you feel itching or burning, notice a change in your vaginal discharge like a bad smell, different color or have any bleeding from your vagina. You will bring your Daily Study Record and your used and unused tubes of PMPA Gel to your follow-up visits.

Day 2 or 3 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel and whether you had any medical problems or discomfort since your last visit. You will have a pelvic exam. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit.

You will insert the vaginal gel as directed for another 4 - 5 days, and then return here for a Follow-Up Visit.

Day 7 Follow-Up Visit:

This visit will take about 1 hour and will be like the Day 2 or 3 Follow-up Visit. You will also give blood (about 20 mL or 4 teaspoons) for testing to check on your overall health, liver, and kidneys. You will insert PMPA Gel as directed for another 7 days, and then return here for a Follow-Up Visit.

NOTE: If the women in the first group who have already finished the study do not have any problems with the PMPA Gel, you may not need to have both the Day 2 or 3 and the Day 7 Follow up Visits. We will tell you if you will be asked to come for both or only one of these two visits before you sign this form. You will have blood drawn during one of these visits only.

- ? Day 2 or 3 Visit only with blood draw.
 - ? Day 7 Visit only with blood draw.
 - ? Both Visits with blood draw on Day 7 only.
- (Study staff to check appropriate box for visit schedule)

Day 13 Pharmacokinetic Visit:

The participants in this group who have joined this study and who have also agreed to join the PK will return to the clinic on Day 13 to have blood drawn 45 mL (or 3 tablespoons) over 24 hours as explained in the PK Study consent form.

Day 14 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, your sexual activity and whether you had any problems since your last visit. You will be asked some questions on your opinions of PMPA Gel and the study. You will give urine to test for infections, and pregnancy and about 20 mL (or 4 teaspoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam with the lens. A picture will be taken of the inside of your vagina.

Day 21 Follow-Up Phone Contact or Clinic Visit:

The study staff will contact you by telephone 7 days after you stop using PMPA Gel. You will be asked whether you had any medical problems or discomfort since your last visit. If you have had any problems, or you may be asked to come to the clinic to check on these problems. Depending on what the problem is you may have a general physical exam or a pelvic exam or give urine or blood for testing.

Group Interview:

About 2-6 weeks after you finish your study visits, you will take part in a group interview with other women who were in the study, to talk about what it was like to use PMPA Gel. There will be about 2-8 other women in the group. The group will meet once for 1 - 2 hours. The discussion will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion.

Contact Procedures:

Once you join the study and start using the gel, 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 48 hours (2 days) before your Enrollment Visit.

You **must not** do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in this study:

- have anal sex
- receive oral sex (any oral contact with the vagina)
- douche
- use any vaginal product other than PMPA Gel in your vagina including feminine hygiene products (such as tampons)
- insert fingers, sex toys or any other products into the vagina
- use intravenous 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 have sex only with the male sexual partner who has consented to be in this study with you. You are asked to have vaginal sex with this partner as many times a week as you usually do (at least 2 times per week), and to use study provided condoms every time you have sex.

You are asked to tell the study staff about any medications you take while in the study. You are asked to not 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 right away to the study staff. The Study staff 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 lens. 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 PMPA Gel before the end of the 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of PMPA Gel (used or unused) to the study site.

Some of your blood that is left over after all required study testing is done may be stored and used for HPTN 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 your stored blood without your permission.

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.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

Women in this study will be the first women to insert PMPA Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. It is not known what effects PMPA Gel will have on the vagina. Some possible effects are dryness, itching, burning, or pain. You also may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

It is possible that PMPA Gel could be absorbed from the vagina into the blood. Based on animal studies, the amount of PMPA absorbed from the vagina should be small and should not produce side effects outside the vagina. If the gel is absorbed into the blood, it is not known whether this will cause any bad effects.

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.

In this study, PMPA is used as a gel. PMPA also has been given to people in other studies as an injection (or “shot”) or pill, as a treatment for HIV infection. In these studies, PMPA was well tolerated, but some people did have side effects.

Some people who received PMPA as an injection experienced the following mild side effects: headache, fatigue, dizziness, nausea, abdominal pain, changes in their sense of taste, and pain or discomfort in their eyes when exposed to bright light. Minor laboratory test abnormalities were also noted in some participants, including changes in results of tests to measure liver, muscle, pancreas or kidney function and decreases in the amount of some white blood cells. No one experienced any serious side effects.

Some people who received PMPA as a pill experienced headache, abdominal pain, flatulence, nausea, vomiting, and abnormal electrocardiograms (EKG). EKGs were normal at follow-up visits. One patient reported peripheral neuritis (unusual sensations in the feet and hands). Other participants had important laboratory test abnormalities including changes in results of tests to measure liver and muscle function. Depression was the only side effect that happened in more than 5% of the participants.

PMPA is a type of drug called an “antiviral nucleotide.” Side effects seen with this and antiviral nucleotides which have been approved by the FDA — when injected or taken as a pill — include: nerve disorders, inflammation of the pancreas, seizures, changes in mental status, sleep problems, headaches, hair loss, agitation, nausea, vomiting, diarrhea, kidney toxicity, skin rashes, painful mouth sores, changes in liver function, liver failure, build up of lactic acid in the body, low blood cell counts, infections, cancer, and death.

[Sites to include animal data if permissible by local IRB guidelines] PMPA also has been tested in animals. In studies using doses ten times higher than you would receive in this study, side effects included kidney or liver damage, diarrhea, decreased red blood cells, a reduction in the amount of lymph tissue in the body and damage to the lining of the intestines. Some adult monkeys receiving PMPA at high doses for more than 10 months had changes in their bones, including bone deformities and fractures. Young monkeys exposed to PMPA before birth and then treated after birth with higher doses of PMPA also had bone changes. In studies where PMPA gel was tested on the vaginas of rats there were no side effects. In studies where PMPA gel was tested on rabbit vaginas there was some mild irritation, no ulcers or erosion were seen.

It is possible that PMPA Gel could cause any of the effects listed above or other effects that we do not yet know about. This includes effects leading to death or permanent disability. The study doctors and nurses will closely watch your medical condition during the study. If you have any side effects, you should call the nurse or doctor right away.

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 participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if you are known by someone else in taking part in the group interview.

PREGNANCY:

It is not known whether PMPA Gel has any effect on pregnancy, or whether it has any 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 study provided condoms each time you have sex while in the study.

You also must use birth control while in this study. Acceptable forms of birth control include study provided male condoms, oral contraceptives (birth control pills), injectables and Norplant that you have used for at least three months.

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using PMPA 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 PMPA 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, 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 HIV or other STDs, or have any 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 PMPA Gel;
- you become pregnant;
- your partner withdraws voluntarily or has been withdrawn from the study without his consent,
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 each visit when you have a pelvic exam. You will receive (insert site-specific amount of money) for each visit when you have a pelvic exam with the lens. You will receive (insert site-specific amount of money) for participation in the group interview.

CONFIDENTIALITY:

Your research records, including the photographs 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. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the FDA, NIAID, study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE:

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

Volunteer's name **Volunteer's signature** **Date**

Witness' name **Witness' signature** **Date**

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Cohort C - Sexually Abstinent HIV Infected Women**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You are being asked to take part in the research study named above. This research study is being done to test an experimental gel called PMPA Gel. 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 which 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 THE STUDY:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 PMPA 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 PMPA Gel protects against HIV, we must first make sure that it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA is inserted in the vagina. We would also like to find out if there is any difference in the amount (more, less, or the same) of HIV found in the fluids of the vagina when HIV infected women use PMPA gel. Another purpose is to find out women’s and men’s opinions of PMPA Gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 96 women and 24 men from 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, including the 14 days you use the gel.

PROCEDURES:

Main Study

You will be screened to see if you can enroll in the study. If you agree to join the study and enroll, you will begin using PMPA Gel on the day you enroll. You will be asked to come back to the clinic for follow-up four times – 2 to 3 days, - 1 week, 2 weeks, and 3 weeks after enrollment. If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. You will also be asked to participate in a group interview about 5-6 weeks after you enroll in the study.

Pharmacokinetic Study

Some participants in this study will be asked to take part in a pharmacokinetic study (“PK study”) of PMPA Gel. This study will test whether PMPA Gel is absorbed from the vagina into the blood by testing blood samples after PMPA Gel is inserted into the vagina. If you are asked to take part in the PK study, we will explain that study to you and ask you to sign a separate informed consent form for it.

Each visit is described below:

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 about 1 – 2 hours. To find out if you are eligible for the study you will be asked some questions, have a general physical exam, a pelvic exam, give a urine sample and have about 50 mL (or 3½ tablespoons) of blood drawn. The questions will be about you, your health, and your sexual practices. Some people may be embarrassed by questions about their sexual history. You may choose not to answer any of the questions if you wish. If at any time during the screening it is determined that you are not eligible for the study, the screening process and your visit will end.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical documentation that you have been infected with and are being treated for HIV. You may be asked to show the study staff your medical records. If medical documentation is not available, you will be asked to 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 also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

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. 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 will also 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 ends. 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 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 past use of vaginal products, your past sexual history, and your opinions about vaginal products. You will give urine to test for infections, and pregnancy, and about 60 mL (or 4 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a pelvic exam and cervical lavage. The clinician will take some fluids to test for HIV level. 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 finished. 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 into the study.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn 40 mL (or about 3 tablespoons) over 12 hours as described in the PK Study consent form.

You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form. Your Enrollment Visit may take place over two days.

During the Study:

You will be given tubes of PMPA Gel with applicators and instructions on how to use them. Two different strengths of the gel will be tested in this study. You will put about 4 mL (1 teaspoon) of the gel into your vagina once or twice a day for 14 days. The strength you use, and whether you use it once or twice a day will depend on information gathered from women who have finished their part of the study before you join the study.

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 nurse or doctor if you feel itching or burning, notice a change in your vaginal discharge like a bad smell, different color or have any bleeding from your vagina. You will bring your Daily Study Record and your used and unused tubes of PMPA Gel to your follow-up visits.

Day 2 or 3 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel and whether you had any medical problems or discomfort. You will have a pelvic exam and cervical lavage. The clinician will take some fluids to test for HIV level. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit.

You will insert the vaginal gel as directed for another 4 - 5 days, and then return here for a Follow-Up Visit.

Day 7 Follow-Up Visit:

This visit will take about 1 hour and will be like the Day 2 or 3 Follow-up Visit. You also will give blood (about 30 mL or 2 tablespoons) for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will insert PMPA Gel as directed for another 7 days, and then return here for a Follow-Up Visit.

NOTE: If the women in the first group who have already finished the study do not have any problems with the PMPA Gel, you may not need to have both the Day 2 or 3 and the Day 7 Follow up Visits. We will tell you if you will be asked to come for both or only one of these two visits before you sign this form. You will have blood drawn during one of these visits only.

<p>? Day 2 or 3 Visit only with blood draw.</p> <p>? Day 7 Visit only with blood draw.</p> <p>? Both Visits with blood draw on Day 7 only.</p> <p>(Study staff to check appropriate box for visit schedule)</p>

Day 13 Pharmacokinetic Visit:

The participants in this group who have joined this study and who have also agreed to join the PK Study will return to the clinic on Day 13 to have blood drawn 45 mL (or 3 tablespoons) over 24 hours as explained in the PK Study consent form.

Day 14 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, and whether you had any medical problems or discomfort. You will be asked some questions on your opinions of PMPA Gel. You will give urine to test for infections, and pregnancy, and about 30 mL (or 2 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a cervical lavage and a pelvic exam with the lens. The clinician will take some fluids to test for HIV level. A picture will be taken of the inside of your vagina.

Day 21 Follow-Up Visit:

This visit will take place 7 days after you stop using PMPA Gel. This visit will take about 1 hour. You will give urine to test for infections and about 30 mL (or 2 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a pelvic exam and cervical lavage. The clinician will take some fluids to test for HIV level. You will be asked whether you had any medical problems or discomfort since your last visit. If you have had any problems, you also may have a general physical exam or a pelvic exam with the lens. At the end of the study, you will be asked some questions on your opinions of the study.

Group Interview:

About 2-6 weeks after you finish your study visits, you will take part in a group interview with other women who were in the study, to talk about what it was like to use PMPA Gel. There will be about 2-8 other women in the group. The group will meet once for 1 - 2 hours. The discussion will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion.

Contact Procedures:

Once you join the study and start using the gel, 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 48 hours (2 days) before your Enrollment Visit and during the entire time while in the study:

- have vaginal sex
- have anal sex
- receive oral sex (any oral contact with the vagina)
- douche
- use any vaginal product other than PMPA Gel in your including feminine hygiene products (such as tampons)
- insert fingers, sex toys or any other products into the vagina
- use intravenous 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 staff about any medications you take 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 right away to the study staff. The Study staff 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 lens. 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 PMPA Gel before the end of the 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of PMPA Gel (used or unused) to the study site.

Samples of your blood and vaginal fluids will be tested to see if the HIV virus in your body shows resistance. Resistance is when changes in the virus make the medications that treat HIV stop working or not work as well against the virus.

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 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 your stored blood without your permission.

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.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and/or HIV test results. If you have HIV, knowing your HIV status 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.

Women in this study will be the first women to insert PMPA Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. It is not known what effects PMPA Gel will have on the vagina. Some possible effects are dryness, itching, burning, or pain. You also may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

It is not known what effect PMPA Gel could have on the HIV virus, for example there may be a risk of becoming infected with a more active or resistant type of HIV virus even if condoms are used. It is not known what effect of PMPA Gel could have on the disease condition in HIV-infected people.

It is possible that PMPA Gel could be absorbed from the vagina into the blood. Based on animal studies, the amount of PMPA absorbed from the vagina should be small and should not produce side effects outside the vagina. If the gel is absorbed into the blood, it is not known whether this will cause any bad effects.

In this study, PMPA is used as a gel. PMPA also has been given to people in other studies as an injection (or “shot”) or pill, as a treatment for HIV infection. In these studies, PMPA was well tolerated, but some people did have side effects.

Some people who received PMPA as an injection experienced the following mild side effects: headache, fatigue, dizziness, nausea, abdominal pain, changes in their sense of taste, and pain or discomfort in their eyes when exposed to bright light. Minor laboratory test abnormalities were also noted in some participants, including changes in results of tests to measure liver, muscle, pancreas or kidney function and decreases in the amount of some white blood cells. No one experienced any serious side effects.

Some people who received PMPA as a pill experienced headache, abdominal pain, flatulence, nausea, vomiting, and abnormal electrocardiograms (EKG). EKGs were normal at follow-up visits. One patient reported peripheral neuritis (unusual sensations in the feet and hands). Other participants had important laboratory test abnormalities including changes in results of tests to measure liver and muscle function. Depression was the only side effect that happened in more than 5% of the participants.

PMPA is a type of drug called an “antiviral nucleotide.” Side effects seen with this and antiviral nucleotides which have been approved by the FDA — when injected or taken as a pill — include: nerve disorders, inflammation of the pancreas, seizures, changes in mental status, sleep problems, headaches, hair loss, agitation, nausea, vomiting, diarrhea, kidney toxicity, skin rashes, painful mouth sores, changes in liver function, liver failure, build up of lactic acid in the body, low blood cell counts, infections, cancer, and death.

[Sites to include animal data if permissible by local IRB guidelines] PMPA also has been tested in animals. In studies using doses ten times higher than you would receive in this study, side effects included kidney or liver damage, diarrhea, decreased red blood cells, a reduction in the amount of lymph tissue in the body and damage to the lining of the intestines. Some adult monkeys receiving PMPA at high doses for more than 10 months had changes in their bones, including bone deformities and fractures. Young monkeys exposed to PMPA before birth and then treated after birth with higher doses of PMPA also had bone changes. In studies where PMPA gel was tested on the vaginas of rats there were no side effects. In studies where PMPA gel was tested on rabbit vaginas there was some mild irritation, no ulcers or erosion were seen.

It is possible that PMPA Gel could cause any of the effects listed above or other effects that we do not yet know about. This includes effects leading to death or permanent disability. The study doctors and nurses will closely watch your medical condition during the study. If you have any side effects, you should call the nurse or doctor right away.

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. There also is a risk to your privacy if you are known by someone else in taking part in the group interview.

PREGNANCY:

It is not known whether PMPA Gel has any effect on pregnancy, or whether it has any 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 have agreed to not have vaginal sex while using PMPA gel. However, if for any reason you do have vaginal sex while using PMPA gel, you must use an acceptable form of birth control. Acceptable forms of birth control include study provided male condoms, oral contraceptives (birth control pills), injectables and Norplant that you have used for at least three months.

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using PMPA 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 PMPA 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 PMPA Gel;
- you become pregnant;
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 visit when you have a pelvic exam. You will receive (insert site-specific amount of money) for each visit when you have a pelvic exam with the lens. You will receive (insert site-specific amount of money) for participation in the group interview.

CONFIDENTIALITY:

Your research records, including the photographs 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, study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE:

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

Volunteer's name **Volunteer's signature** **Date**

Witness' name **Witness' signature** **Date**

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Cohort D - Sexually Active HIV Infected Women**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You are being asked to take part in the research study named above. This research study is being done to test an experimental gel called PMPA Gel. 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 which 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:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA is inserted in the vagina. We would also like to find out if there is any difference in the amount (more, less, or the same) of HIV found in the fluids of the vagina when HIV infected women use PMPA gel. Another purpose is to find out women’s and men’s opinions of PMPA Gel.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 96 women and 24 men from 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, including the 14 days you use the gel.

PROCEDURES:

Main Study

You will be screened to see if you can enroll in the study. If you agree to join the study and enroll, you will begin using PMPA Gel on the day you enroll. You will be asked to come back to the clinic for follow-up four times – 2 to 3 days, - 1 week, 2 weeks, and 3 weeks after enrollment. If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. You will also be asked to participate in a group interview about 5-6 weeks after you enroll in the study.

Pharmacokinetic Study

Some participants in this study will be asked to take part in a pharmacokinetic study (“PK study”) of PMPA Gel. This study will test whether PMPA Gel is absorbed from the vagina into the blood by testing blood samples after PMPA Gel is inserted into the vagina. If you are asked to take part in the PK study, we will explain that study to you and ask you to sign a separate informed consent form for it.

Each visit is described below.

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 about 1 – 2 hours. To find out if you are eligible for the study you will be asked some questions, have a general physical exam, a pelvic exam, give a urine sample and have about 40 mL (or 3 tablespoons) of blood drawn. The questions will be about you, your health, your male sexual partner and your sexual practices. Some people may be embarrassed by questions about their sexual history. You may choose not to answer any of the questions if you wish. If at any time during the screening it is determined that you are not eligible for the study, the screening process and your visit will end.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical documentation that you have been infected with and are being treated for HIV. You may be asked to show the study staff your medical records. If medical documentation is not available, you will be asked to 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 also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

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. 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 will also 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 also be asked to give his informed consent and will 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 it is found that he is not eligible for the study, neither of you will be eligible for the study.

Enrollment Visit:

This visit will take place within 5 days after your next menstrual period ends. By the time of this visit, your male sexual partner must come to the study site to give his informed consent to take part in the study, 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 past use of vaginal products, your past sexual history, and your opinions about vaginal products. You will give urine to test for infections, and pregnancy, and about 60 mL (or 4 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a pelvic exam and cervical lavage. The clinician will take some fluids to test for HIV level. 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 finished. 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 into the study.

The participants who have joined this study and who have also agreed to join the PK Study will have blood drawn 40 mL (or about 3 tablespoons) over 12 hours as described in the PK Study consent form.

You will begin using the PMPA Gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

The participants in this group who have joined this study and who have also agreed to join the PK Study will have blood drawn, 40 mL (or 3 tablespoons) over 12 hours as explained in the PK Study consent form. Your Enrollment Visit may take place over two days.

During the Study:

You will be given tubes of PMPA Gel with applicators and instructions on how to use them. Two different strengths of the gel will be tested in this study. You will put about 4 mL (1 teaspoon) of the gel into your vagina once or twice a day for 14 days. The strength you use, and whether you use it once or twice a day, will depend on information gathered from women who have finished their part of the study before you join the study. You are asked to have vaginal sex with your sexual partner as many times a week as you usually do which must be at least 2 times per week. You and your sexual partner must use condoms given to you by study staff each time you have sex. On the days that you have sex, you are asked to insert the gel up to 2 hours before having sex.

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 nurse or doctor if you feel itching or burning, notice a change in your vaginal discharge like a bad smell, different color or have any bleeding from your vagina. You will bring your Daily Study Record and your used and unused tubes of PMPA Gel to your follow-up visits.

Day 2 or 3 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, your sexual activity and whether you had any problems since your last visit. You will have a pelvic exam and cervical lavage. The clinician will take some fluids to test for HIV level. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit. You will insert PMPA gel as directed for another 4 – 5 days, and then return here for a Follow-up Visit.

Day 7 Follow-Up Visit:

You will insert the vaginal gel as directed for another 4 - 5 days, then return here for a Follow-Up Visit. This visit will take about 1 hour and will be like the Day 2 or 3 Follow-up Visit. You will also give blood (about 30 mL or 2 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will insert PMPA Gel as directed for another 7 days, and then return here for a Follow-Up Visit.

NOTE: If the women in the first group who have already finished the study do not have any problems with the PMPA Gel, you may not need to have both the Day 2 or 3 and the Day 7 Follow up Visits. We will tell you if you will be asked to come for both or only one of these two visits before you sign this form. You will have blood on one of these visits only.

- | |
|---|
| <p>? Day 2 or 3 Visit only with blood draw.</p> <p>? Day 7 Visit only with blood draw.</p> <p>? Both Visits with blood draw on Day 7 only.</p> <p>(Study staff to check appropriate box for visit schedule)</p> |
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Day 13 Pharmacokinetic Visit:

The participants in this group who have joined this study and who have also agreed to join the PK Study will return to the clinic on Day 13 to have blood drawn 45 mL (or 3 tablespoons) over 24 hours as explained in the PK Study consent form.

Day 14 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, your sexual activity and whether you had any problems since your last visit. You will be asked some questions on your opinions of PMPA Gel. You will give urine to test for infections, and pregnancy, and about 30 mL (or 2 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a pelvic exam with the lens and a cervical lavage. The clinician will take some fluids to test for HIV level. A picture will be taken of the inside of your vagina.

Day 21 Follow-Up Visit:

This visit will take place 7 days after you stop using PMPA Gel. This visit will take about 1 hour. You will give urine to test for infections, and about 30 mL (or 2 tablespoons) of blood for testing to check on your overall health, immune system, liver, kidneys, and HIV level. You will have a pelvic exam and a cervical lavage. The clinician will take some fluids to test for HIV level. You will be asked whether you had any medical problems or discomfort since your last visit. If you have had any problems, you also may have a general physical exam or a pelvic exam with the lens. At the end of the study, you will be asked some questions on your opinions of the study.

Group Interview:

About 2-6 weeks after you finish your study visits, you will take part in a group interview with other women who were in the study, to talk about what it was like to use PMPA Gel. There will be about 2-8 other women in the group. The group will meet once for 1 - 2 hours. The discussion will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion.

Contact Procedures:

Once you join the study and start using the gel, 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 48 hours (2 days) before your Enrollment Visit.

You **must not** do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in this study:

- have anal sex
- receive oral sex (any oral contact with the vagina)
- douche
- use any vaginal product other than PMPA Gel in your vagina including feminine hygiene products (such as tampons)
- insert fingers, sex toys or any other products into the vagina
- use intravenous 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 have sex only with the male sexual partner who has consented to be in this study with you. You are asked to have vaginal sex with this partner as many times a week as you usually do (at least 2 times per week), and to use study provided condoms every time you have sex.

You are asked to tell the study staff about any medications you take while in the study. You are asked to not 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 right away to the study staff. The Study staff 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 lens. 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 PMPA Gel before the end of the 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of PMPA Gel (used or unused) to the study site.

Samples of your blood and vaginal fluids will be tested for resistance to see if the HIV virus in your body shows resistance. Resistance is when changes in the HIV virus make the medications that treat HIV stop working or not work as well against the virus.

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 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 your stored blood without your permission.

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.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

Women in this study will be the first women to insert PMPA Gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. It is not known what effects PMPA Gel will have on the vagina. Some possible effects are dryness, itching, burning, or pain. You also may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

It is not known what effect PMPA Gel could have on the HIV virus, for example there may be a risk of becoming infected with a more active or resistant type of HIV virus even if condoms are used. It is not known what effect of PMPA Gel could have on the disease condition in HIV-infected people.

It is possible that PMPA Gel could be absorbed from the vagina into the blood. Based on animal studies, the amount of PMPA absorbed from the vagina should be small and should not produce side effects outside the vagina. If the gel is absorbed into the blood, it is not known whether this will cause any bad effects.

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.

In this study, PMPA is used as a gel. PMPA also has been given to people in other studies as an injection (or “shot”) or pill, as a treatment for HIV infection. In these studies, PMPA was well tolerated, but some people did have side effects.

Some people who received PMPA as an injection experienced the following mild side effects: headache, fatigue, dizziness, nausea, abdominal pain, changes in their sense of taste, and pain or discomfort in their eyes when exposed to bright light. Minor laboratory test abnormalities were also noted in some participants, including changes in results of tests to measure liver, muscle, pancreas or kidney function and decreases in the amount of some white blood cells. No one experienced any serious side effects.

Some people who received PMPA as a pill experienced headache, abdominal pain, flatulence, nausea, vomiting, and abnormal electrocardiograms (EKG). EKGs were normal at follow-up visits. One patient reported peripheral neuritis (unusual sensations in the feet and hands). Other participants had important laboratory test abnormalities including changes in results of tests to measure liver and muscle function. Depression was the only side effect that happened in more than 5% of the participants.

PMPA is a type of drug called an “antiviral nucleotide.” Side effects seen with this and antiviral nucleotides which have been approved by the FDA — when injected or taken as a pill — include: nerve disorders, inflammation of the pancreas, seizures, changes in mental status, sleep problems, headaches, hair loss, agitation, nausea, vomiting, diarrhea, kidney toxicity, skin rashes, painful mouth sores, changes in liver function, liver failure, build up of lactic acid in the body, low blood cell counts, infections, cancer, and death.

[Sites to include animal data if permissible by local IRB guidelines] PMPA also has been tested in animals. In studies using doses ten times higher than you would receive in this study, side effects included kidney or liver damage, diarrhea, decreased red blood cells, a reduction in the amount of lymph tissue in the body and damage to the lining of the intestines. Some adult monkeys receiving PMPA at high doses for more than 10 months had changes in their bones, including bone deformities and fractures. Young monkeys exposed to PMPA before birth and then treated after birth with higher doses of PMPA also had bone changes. In studies where PMPA gel was tested on the vaginas of rats there were no side effects. In studies where PMPA gel was tested on rabbit vaginas there was some mild irritation, no ulcers or erosion were seen.

It is possible that PMPA Gel could cause any of the effects listed above or other effects that we do not yet know about. This includes effects leading to death or permanent disability. The study doctors and nurses will closely watch your medical condition during the study. If you have any side effects, you should call the nurse or doctor right away.

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 participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if you are known by someone else in taking part in the group interview.

PREGNANCY:

It is not known whether PMPA Gel has any effect on pregnancy, or whether it has any 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 study provided condoms each time you have sex while in the study.

You also must use birth control while in this study. Acceptable forms of birth control include study provided male condoms, oral contraceptives (birth control pills), injectables and Norplant that you have used for at least three months.

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using PMPA 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 PMPA 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 any 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 PMPA Gel;
- you become pregnant;
- your partner withdraws voluntarily or has been withdrawn from the study without his consent,
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 each visit when you have a pelvic exam. You will receive (insert site-specific amount of money) for each visit when you have a pelvic exam with the lens. You will receive (insert site-specific amount of money) for participation in the group interview.

CONFIDENTIALITY:

Your research records, including the photographs 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. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the FDA, NIAID, study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE:

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

Volunteer's name **Volunteer's signature** **Date**

Witness' name **Witness' signature** **Date**

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Pharmacokinetic Study**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You are being asked to take part in the research study named above. You already have consented to take part in the main part of this study, in which you will apply PMPA Gel and have study visits to check on the effects of PMPA Gel. You are one of 6 women in your group being asked to take part in additional research procedures as a further check on the safety of PMPA. Before you decide whether or not to take part in the additional research procedures, we would like to explain the purpose of the procedures, any risks and benefits to you and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY:

This consent form gives you information about the additional procedures which will be discussed with you. Once you understand the procedures, 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 additional procedures, it is important that you know the following:

- Your participation is entirely voluntary.
- You may decide to not take part and still be in the main part of the study; either as a part of another group, or as part of the same group after six other women in your group have finished the additional procedures.
- 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 THE STUDY:

The purpose of the additional procedures is to perform a “pharmacokinetic study” or “PK study” of PMPA Gel. This study will test whether the active ingredient of PMPA Gel is absorbed from the vagina into the blood, and how long it stays in the blood if absorbed. Up to 24 women will take part in the PK study.

PROCEDURES:

After you read this form you will have as much time as you need to ask questions to make sure you fully understand the PK study. No PK study procedures will be started before the study has been fully explained to you and you have signed this form.

At your Enrollment Visit, in addition to the main study procedures that you already consented to, you will insert your first dose of PMPA Gel at the clinic. Then your blood (about 5 mL or 1 teaspoon per draw) will be drawn 8 times over the next 12 hours. Your Enrollment Visit for the main study and PK study may take place over 1 or 2 days. The study staff will tell you whether your Enrollment Visit will be scheduled for 1 day or 2 days.

<p>? One Day Enrollment Visit</p> <p>? Two Day Enrollment Visit</p> <p>(Study staff to check appropriate box for visit schedule)</p>
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Your blood will be tested to see if it contains PMPA. You may not have to check into the clinic, but you will have to return to the clinic at the times told to you by the study nurse. You will have your blood drawn prior to inserting your first dose of PMPA gel then ½ hour, 1, 2, 4, 6, 8 and 12 hours after inserting the gel. At day 13 you will also have blood drawn 24 hours after inserting the gel.

The study nurse may draw your blood by giving you a needle stick for each draw, or you may have an intravenous (IV) line inserted. An IV line is a small closed off tube inserted into a vein that can be opened and closed to draw blood many times without needing to have a needle stuck through your skin each time.

After using PMPA Gel for 13 days, you will return to the clinic, insert PMPA Gel when you arrive, and have blood drawn 9 times over the next 24 hours. (See schedule above) The blood will be tested to see if it contains PMPA. You will not have to check into the clinic, but you will have to return to the clinic at the times told to you by the study nurse.

Depending on which group you are in you also may be asked to return for 2 additional blood draws at 48 and 72 hours after inserting the gel at the clinic.

If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects.

RISKS and/or DISCOMFORTS:

Some people get sore where blood is drawn and may feel dizzy or faint. You may have a bruise or swelling where the needle goes into your arm. The study nurse or doctor will give you medical help if you need it.

BENEFITS:

You will receive no direct benefit from taking part in the PK study. However, you or others may benefit in the future from information learned from this study.

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 PMPA Gel;
- you become pregnant;
- the study is cancelled by the Food and Drug Administration (FDA), the National Institute of Allergy and Infectious Diseases, (NIAID), or the company that makes PMPA Gel; 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 each of the two sets of blood draws. You will receive (insert site-specific amount of money) per visit if you are asked and return for the 48 and 72 hour blood draws.

CONFIDENTIALITY:

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

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*).

SIGNATURE PAGE:

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

Volunteer's name

Volunteer's signature

Date

Witness' name

Witness' signature

Date

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Male Partners of HIV Uninfected Sexually Active Participants – Cohort B**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You and your partner are being asked to take part in the research study named above. This is a study of an experimental gel called PMPA Gel. Before you decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be 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:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 yet approved PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA is inserted in the vagina. Another purpose 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). About 96 women and 24 men from 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:

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. Some people may be embarrassed by these questions. You may choose not to answer any of these questions if you wish. You may have a genital exam to determine whether you can be in this study. The genital exam is optional; you may choose not to have a genital exam. If at any time during the screening it is determined that you are not eligible for the study, the screening process will end, and you and your partner will not be able to join the study.

If the answers to the questions show that you may have a sexually transmitted disease (STD) you and your partner will not be eligible for the study. We will refer you for medical care and counseling.

If your answers to the questions show that you may be eligible for the study you will have counseling about HIV and other STDs. You will talk about HIV/AIDS and other STDs, HIV tests, what it may mean to know your HIV status, and whether you are prepared to receive your HIV test results. You will also talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are willing to have HIV testing you will give about 10 mL (or 2 teaspoons of blood) for the test. Your test results will be available [Sites to specify when results will be available]. You must receive your HIV test results to be in the study. You may be asked to return to the clinic for your test results. If your test results show that you are infected with HIV, you and your partner will not be eligible for the study. We will refer you for medical care and other services that you may need.

If you and your partner are eligible for the study, and agree to take part, you will be asked to have vaginal sex together as many times a week as you usually do, which must be at least two times per week while you are using the PMPA gel. You must use condoms given to you by the study staff each time you and your partner have sex.

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

At the end of the study, you will be asked some questions and have an individual interview to talk about your experience with the gel and the study. The interview will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion. This will take about two hours of your time.

If your partner stops the study early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects.

Contact Procedures:

Once you join the study and your partner starts using the gel, 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:

If you agree to be in the study you **must not** do the following while in the study:

- have oral contact with your partner's vagina (oral sex)
- have anal sexual intercourse
- insert fingers, sex toys or any other products into your partner's vagina
- use intravenous drugs except for medical use.

RISKS and/or DISCOMFORTS:

Because you will have sex with your partner after she has put PMPA Gel in her vagina it is possible that some of the gel will come into contact with your skin. It is not known whether PMPA Gel causes side effects when it comes into contact with the penis or the skin around the penis. Therefore 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.

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 participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community.

BENEFITS:

You will receive no direct benefit from taking part in this study. However, you or others may benefit in the future from information learned in this study. If you have any symptoms of sexually transmitted diseases, 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;
- you have a bad reaction to PMPA Gel;
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 each visit. You will also receive (insert site-specific amount of money) for completing the individual interview.

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, the study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE

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

Volunteer's name

Volunteer's signature

Date

Witness' name

Witness' signature

Date

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

**Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel
Version 2.0 29 May 2002
Male Partners of HIV Infected Sexually Active Participants – Cohort D**

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You and your partner are being asked to take part in the research study named above. This is a study of an experimental gel called PMPA Gel. Before you decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be 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:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 yet approved PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA is inserted in the vagina. Another purpose 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). About 96 women and 24 men from 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:

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. Some people may be embarrassed by these questions. You may choose not to answer any of these questions if you wish. You may have a genital exam to determine whether you can be in this study. The genital exam is optional; you may choose not to have a genital exam. If at any time during the screening it is determined that you are not eligible for the study, the screening process will end, and you and your partner will not be able to join the study.

If the answers to the questions show that you may have a sexually transmitted disease (STD) you and your partner will not be eligible for the study. We will refer you for medical care and counseling.

If your answers to the questions show that you may be eligible for the study, you will be asked for medical documentation that you have been infected with HIV. If medical documentation is not available, you will be asked to 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 status, and whether you are prepared to receive your HIV test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are willing to have HIV testing (if necessary) you will give about 10 mL (or 2 teaspoons of blood) for the test. Your test results will be available [Sites to specify when results will be available]. You must receive your HIV test results to be in the study. You may be asked to return to the clinic for your test results. If your test results show that you are not infected with HIV, you and your partner will not be eligible for the study.

If you and your partner are eligible for the study, and agree to take part, you will be asked to have vaginal sex together as many times a week as you usually do, which must be at least two times per week while you are using the PMPA gel. You must use condoms given to you by the study staff each time you and your partner have sex.

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

At the end of the study, you will be asked some questions and have an individual interview to talk about your experience with the gel and the study. The interview will be audio taped. To maintain the confidentiality of participants, everyone will be addressed only by a nickname or a first name of their choosing during the discussion. This will take about two hours of your time.

If your partner stops the study early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects.

Contact Procedures:

Once you join the study and your partner starts using the gel, 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:

If you agree to be in the study you **must not** do the following while in the study:

- have oral contact with your partner's vagina (oral sex)
- have anal sexual intercourse with your partner
- insert fingers, sex toys or any other products into your partner's vagina
- use intravenous drugs except for medical use.

RISKS and/or DISCOMFORTS:

Because you will have sex with your partner after she has put PMPA Gel in her vagina it is possible that some of the gel will come into contact with your skin. It is not known whether PMPA Gel causes side effects when it comes into contact with the penis or the skin around the penis. Therefore 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.

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.

It is not known what effect PMPA Gel could have on the HIV virus, for example there may be a risk of becoming infected with a more active or resistant type of HIV virus even if condoms are used. It is not known what effect of PMPA Gel could have on the disease condition in HIV-infected people.

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.

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:

You will receive no direct benefit from taking part in this study. However, you or others may benefit in the future from information learned in this study. If you have any symptoms of sexually transmitted diseases, 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;
- you have a bad reaction to PMPA Gel;
- the study is cancelled by the FDA, NIAID, or the company that makes PMPA Gel; 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 each visit. You will also receive (insert site-specific amount of money) for completing the individual interview.

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, the study monitors, and the company that makes PMPA Gel.

[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*).

SIGNATURE PAGE

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

Volunteer's name

Volunteer's signature

Date

Witness' name

Witness' signature

Date

Appendix IV – SAMPLE INFORMED CONSENT

Page 1 of 9

Sample Informed Consent Form Division of AIDS, NIAID, NIH

Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel Version 2.0 29 May 2002 Cohort V - Sexually Abstinent HIV Uninfected Women – Vehicle Only

PRINCIPAL INVESTIGATOR: (Site Specific) PHONE:

INFORMED CONSENT:

You are being asked to take part in the research study named above. This research study is being done to test an experimental gel called PMPA Gel. 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 which 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 THE STUDY:

PMPA Gel is made as a “vaginal microbicide.” It is made to be inserted into the vagina to protect people from getting HIV during sex. HIV is the virus that causes AIDS. PMPA Gel is “experimental.” This means that we do not yet know 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 PMPA 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 PMPA Gel protects against HIV, we must first make sure it is safe. The main purpose of this study is to find out if there are any bad effects when PMPA Gel is inserted in the vagina. Another purpose is to find out women’s and men’s opinions of the gel.

The vaginal gel we will be asking you to use will not have any of the experimental drug PMPA in it. It is a plain vaginal gel like KY Jelly, Replens, or Wet except it has been made especially for this study and has not been used in the general population.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 96 women and 24 men from 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, including the 14 days you use the gel.

PROCEDURES:

You will be screened to see if you can enroll in the study. If you agree to join the study and enroll, you will begin using the vaginal gel on the day you enroll. You will be asked to come back to the clinic for follow-up three times - two to three days, 1 week and 2 weeks after enrollment. Three weeks after enrollment, the study staff will contact you by phone for follow-up. If you have any problems you may be asked to come to the clinic for additional follow-up visits. If you stop the study treatment early, you will be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. Each visit is described below.

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 about 1 – 2 hours. To find out if you are eligible for the study you will be asked some questions, have a general physical exam, a pelvic exam, give a urine sample and have about 40 mL (or about 3 tablespoons) of blood drawn. The questions will be about you, your health and your sexual history. Some people may be embarrassed by questions about their sexual history. You may choose not to answer any of the questions if you wish. If at any time during the screening it is determined that you are not eligible for the study, the screening process and your visit will end.

If your answers to the questions show that you may be eligible for the study, 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 may mean to know your HIV and STD status, and whether you are prepared to receive your HIV and STD test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are willing to have HIV and STD testing, 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, liver, and kidneys. You will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs and other possible problems. 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 ends. 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. You must receive your HIV test results to be in this study.

If the test results show that you are infected with HIV, you will not be eligible to be in this study. However, we will refer you for medical care and other services you may need. If other 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 this study, you will give urine to test for infections and about 40 mL (or about 3 tablespoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam. 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 finished. 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 exams and tests show no problems, you will be entered into the study.

You will begin using the vaginal gel as directed on the day of the Enrollment Visit, then return here in 2 to 3 days for a follow-up visit.

During the Study:

You will be given tubes of vaginal gel with applicators and instructions on how to use them. You will put about 4 mL (1 teaspoon) of the gel into your vagina at bedtime for 14 days.

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 nurse or doctor if you feel itching or burning, notice a change in your vaginal discharge like a bad smell, different color or have any bleeding from your vagina. You will bring your Daily Study Record and your used and unused tubes of vaginal gel to your follow-up visits.

Day 2 or 3 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel and whether you had any medical problems or discomfort since your last visit. You will have a pelvic exam. Unless a problem is seen on the pelvic exam, the lens will not be used at this visit. You will insert the vaginal gel at bedtime for another 5 nights, and then return here for a Follow-Up Visit.

Day 7 Follow-Up Visit:

This visit will take about 1 hour and will be like the Day 2 or 3 Follow-up Visit. You will also give blood (about 20 mL or 4 teaspoons) of blood for testing to check on your overall health, liver, and kidneys. You will insert the vaginal gel as directed for another 7 days, and then return here for a Follow-Up Visit.

Day 14 Follow-Up Visit:

This visit will take about 1 hour. You will review your Daily Study Record with the study staff and answer questions about your use of the gel, and whether you had any medical problems or discomfort since your last visit. You will give urine to test for infections and pregnancy and about 20 mL (or 4 teaspoons) of blood for testing to check on your overall health, liver, and kidneys. You will have a pelvic exam with the lens. A picture will be taken of the inside of your vagina.

Day 21 Follow-Up Phone Contact or Clinic Visit:

The study staff will contact you by telephone 7 days after you stopped using the vaginal gel. You will be asked whether you had any medical problems or discomfort since your last visit. If you have had any problems, you may be asked to come to the clinic to check on the problems. Depending on what the problem is, you may have a general physical exam, or a pelvic exam or give urine or blood for testing.

Contact Procedures:

Once you join the study and start using the gel, 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** do the following starting 48 hours (2 days) before your Enrollment Visit and during the entire time while in the study:

- have vaginal sex
- have anal sex
- receive oral sex (any oral contact with the vagina)
- douche
- use any vaginal product other than the vaginal gel in your vagina including feminine hygiene products (such as tampons)
- insert fingers, sex toys or any other products into the vagina
- use intravenous 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 staff 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 right away to the study staff. The study staff 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 lens. 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 vaginal gel before the end of the 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of the vaginal gel (used and unused) to the study site.

Some of your blood that is left over after all required study testing is done may be stored and used for HPTN 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 your stored blood without your permission.

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.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

Women in this study will be the first women to insert this kind of plain vaginal gel in the vagina. Therefore, it is important to use the gel only as instructed by the study staff. Even though this kind of vaginal gel is a lot like KY Jelly, Replens or Wet, it is not known what effects this vaginal gel will have on the vagina. Some possible effects are irritation, itching, or pain. You also may have discharge if the gel comes out of the vagina. The study staff will give you panty liners in case you need them.

The study doctors and nurses will closely watch your medical condition during the study. If you have any side effects, you should call the nurse or doctor right away.

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 participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community.

PREGNANCY:

It is not known whether the vaginal gel has any effect on pregnancy, or whether it has any 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 have agreed to not have vaginal sex while using the vaginal gel. However, if you do for any reason have vaginal sex while using the vaginal gel, you must use an acceptable form of birth control. Acceptable forms of birth control include study provided male condoms, oral contraceptives (birth control pills), injectables and Norplant that you have used for at least three months.

If you become pregnant during the study you should tell your study doctor or nurse right away. You will stop using the vaginal 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 the vaginal 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 HIV or other STDs, 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 vaginal gel as instructed;
- you have a bad reaction to the vaginal gel;
- you become pregnant;
- the study is cancelled by the FDA, NIAID, or the company that makes the vaginal gel; 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 each visit when you have a pelvic exam. You will receive (insert site-specific amount of money) for each visit when you have a pelvic exam with the lens.

CONFIDENTIALITY:

Your research records, including the photographs 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, study monitors, and the company that makes the vaginal gel.

[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*).

SIGNATURE PAGE:

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

Volunteer's name **Volunteer's signature** **Date**

Witness' name **Witness' signature** **Date**