

HIV Prevention Trials Network

PROTOCOL CLARIFICATION MEMORANDUM #6 11 April 2007 for HPTN 039 Protocol Version 3.0 dated 13 September, 2004

Summary of Clarification

The purpose of this memo is to correct a stipulation in the protocol requiring the retest of 10% of the HSV-2 positive enrollment samples at the HPTN Central Laboratory. This retesting of HSV-2 status would be redundant, since all HSV-2 positive enrollment samples (as determined by site laboratories) are already being confirmed by Western blot retesting at the University of Washington in Seattle, Washington.

In Section 9.3 of the protocol, regarding

Quality Control And Quality Assurance Procedures

it is stated that:

Throughout the course of the study, the HPTN CL will retest 10% of all HSV-2 positive enrollment samples for HSV-2 antibody for quality assurance (QA) purposes,

and that

HSV-2 WB tests will be conducted at the University of Washington in Seattle, WA, USA on all samples for enrolled participants at all sites to confirm their HSV-2 positive status.

With the issuance of this Clarification Memorandum, the 10% retesting of HSV-2 positive samples at the HPTN Central Laboratory will be eliminated.

This change will not have any effect on participant safety, the risk-to-benefit ratio of study participation, or the study informed consent forms.

Letter of Amendment #7

DATE: 09 February 2006

RE: LETTER OF AMENDMENT #7 FOR HPTN 039, Version 3.0, dated 13 September, 2004

“A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals”

TO: All Investigators and corresponding Institutional Review Boards and Ethics Committees participating in and reviewing HPTN 039

FROM: Scott Mitchell Rose, Senior Clinical Research Manager, FHI

THE FOLLOWING INFORMATION MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) FOR THEIR REVIEW AND APPROVAL.

PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE AND APPROVALS IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES.

Re: HSV PCR testing of GUD swabs will be conducted during the study, and/or at the end of the study, instead of only at the end of the study. The results of this testing will be sent directly to the SDMC only, and will not be shared with the sites or the rest of the protocol team until after completion of the study.

5.4 Follow-Up Visits: Monthly (Months 1 To 12 or 18) currently states:

Clinical Procedures

For participants who report genital symptoms:

- Perform genital exam and collect swab of anogenital ulcers or other anogenital findings thought to be HSV-related, for end of study testing.

-and-

Laboratory Procedures

For swabs from participants with genital ulcers or other possible HSV-related anogenital findings:

- Storage of swabs for end of study testing to determine etiology by PCR at UW.

5.4 Follow-Up Visits: Monthly (Months 1 To 12 or 18) has been modified to state:

Clinical Procedures

For participants who report genital symptoms:

- Perform genital exam and collect swab of anogenital ulcers or other anogenital findings thought to be HSV-related, for testing at UW.

-and-

Laboratory Procedures

For swabs from participants with genital ulcers or other possible HSV-related anogenital findings:

- Storage of swabs for testing to determine etiology by PCR at UW

5.5 Quarterly Visits (Months 3, 6, 9, 12, and 15) currently states:

Clinical Procedures

For participants with anogenital ulcers or other anogenital findings thought to be HSV-related:

- Perform genital exam and collect swab of anogenital ulcers, or other genital findings thought to be HSV-related, for end of study testing.

-and-

Laboratory Procedures

For swabs from participants with genital ulcers or other possible HSV-related genital findings:

- Storage of swabs for end of study testing to determine etiology by PCR at UW.

5.5 Quarterly Visits (Months 3, 6, 9, 12, and 15) has been modified to state:

Clinical Procedures

For participants with anogenital ulcers or other anogenital findings thought to be HSV-related:

- Perform genital exam and collect swab of anogenital ulcers, or other genital findings thought to be HSV-related, for testing at UW.

-and-

Laboratory Procedures

For swabs from participants with genital ulcers or other possible HSV-related genital findings:

- Storage of swabs for testing to determine etiology by PCR at UW.

9.1 Specimen Storage And Possible Future Research Testing currently states:

Study site staff will store all sera and swabs from genital lesions collected in this study at least through the end of the study.

9.1 Specimen Storage And Possible Future Research Testing has been modified to state:

Study site staff will store all sera and swabs from genital lesions collected in this study at least through the end of the study or until they are shipped to the Central Laboratory or UW Laboratory for testing.

Letter of Amendment #6

DATE: 23 August 2005

RE: LETTER OF AMENDMENT #6 FOR HPTN 039, Version 3.0, dated 13 September, 2004

“A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals”

TO: All Investigators and corresponding Institutional Review Boards and Ethics Committees participating in and reviewing HPTN 039

FROM: Scott Mitchell Rose, Senior Clinical Research Manager, FHI

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PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE AND APPROVALS IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES.

Re: Dispensation of open label acyclovir to participants that present with genital or oral ulcers during the Exit Visit.

5.6 Exit Visit (Month 12 or Month 18) currently states:

The exit visit will be identical to the quarterly follow-up visit, however, in addition, syphilis (including titer if RPR is reactive) and treponemal serologies will be performed and sites will provide results by telephone, or in person according to when the result is available, and ensuring that results are communicated to the participant. Participants with positive serology will be referred according to local standard of care. No study medication will be dispensed at this visit.

5.6 Exit Visit (Month 12, ~~or~~ Month 18 **or early termination**) has been modified to state:

The exit visit will be identical to the quarterly follow-up visit, however, in addition, syphilis (including titer if RPR is reactive) and treponemal serologies will be performed and sites will provide results by telephone, or in person according to when the result is available, and ensuring that results are communicated to the participant. Participants with positive serology will be referred according to local standard of care. No **blinded** study medication will be dispensed at this visit. **In the event that a participant has genital or oral**

symptoms and the clinician feels that open label acyclovir would be beneficial for the participant open label acyclovir may be dispensed at this visit. The site should document efforts to retrieve the bottle of open label medication and conduct accountability within a reasonable timeframe after the drug is dispensed to the participant.

HIV Prevention Trials Network

PROTOCOL CLARIFICATION MEMORANDUM #5

HPTN 039 Protocol Version 3.0 dated 13 September, 2004

20 June 2005

Summary of Clarification

The purpose of this memo is to further specify parameters for pregnancy testing; that it is not required for participants that are currently pregnant. Not testing a participant who is believed to still be pregnant (there must be an initial positive pregnancy test in the participant's files) does not add a risk to the participant or fetus due to the fact that the participant is immediately removed from study drug use when confirmed pregnant.

Pregnancy Testing

Pregnancy testing is required at the specified time points in the protocol for all women except those that are:

1. Over the age of 60; or,
2. Documented as being surgically sterile, i.e., after hysterectomy or tubal ligation, or
3. Over the age of 50 and reporting 12 months of amenorrhea in the absence of hormonal therapy
4. Currently pregnant (having had positive pregnancy test and site staff believe that the participant remains pregnant).

Note: Should site staff believe that there is a possibility that a participant is no longer pregnant a pregnancy test should be performed. In order to re-start study medications, two consecutive negative pregnancy tests must be received (refer to protocol section 4.5).

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PROTOCOL CLARIFICATION MEMORANDUM #4

HPTN 039 Protocol Version 3.0 dated 13 September, 2004

14 March 2005

Summary of Clarification

The purpose of this memo is to specify parameters for pregnancy testing, as well as to clarify genital examinations in relation to telephone visits.

Pregnancy Testing

Pregnancy testing is required at the specified time points in the protocol for all women except those that are:

1. Over the age of 60; or,
2. Documented as being surgically sterile, i.e., after hysterectomy or tubal ligation, or
3. Over the age of 50 and reporting 12 months of amenorrhea in the absence of hormonal therapy

Telephone Visits

For participants reporting current genital symptoms during a telephone visit, participants should be encouraged to report to the clinic for a genital examination as soon as possible. Should a participant be unwilling or unable to report to the clinic for a genital examination, it shall not be considered a protocol event.

HIV Prevention Trials Network

PROTOCOL CLARIFICATION MEMORANDUM #3

HPTN 039 Protocol Version 3.0 dated 13 September, 2004

21 December, 2004

Summary of Clarification

The purpose of this memo is to clarify procedures in HPTN 039 pertaining to screening participants that are HSV-2 seropositive as determined by Focus HSV-2 EIA with index ratio <3.5 (or index ratio >0.9 and \leq 3.4 by conventional rounding methods with UW Western blot positive test specific for HSV-2 antibodies). The clarification is that should the 60 day window between screening and enrollment be exceeded, that the Wb positive test will be used as the screening value and site staff will not have to re-test for HSV-2 by Focus EIA at the next screening visits. All other screening visit procedures must be performed.

Letter of Amendment #5

DATE: 5 November 2004

RE: LETTER OF AMENDMENT #5 FOR HPTN 039, Version 3.0, dated 13 September, 2004

“A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals”

TO: All Investigators and corresponding Institutional Review Boards and Ethics Committees participating in and reviewing HPTN 039

FROM: Scott Mitchell Rose, Senior Clinical Research Manager, FHI

THE FOLLOWING INFORMATION MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) FOR THEIR REVIEW AND APPROVAL.

PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE AND APPROVALS IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES.

I. CONTINUATION OF BLINDED STUDY DRUG FOR UP TO 60 DAYS AFTER THE FIRST HIV POSITIVE RESULT TEST COLLECTION DATE TO ALLOW PARTICIPANTS TIME TO CONSIDER PARTICIPATION IN THE ANCILLARY (SEROCONVERTER) STUDY

2.3 Study Design

Currently states:

Participants will be followed for 12 or 18 months after enrollment. Participants who become HIV-infected (i.e., seroconvert to HIV) at any time during this 12 or 18-month period will be offered enrollment into a six month ancillary study. The objective of this ancillary study is to assess the affect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”). This ancillary study will have its own protocol and Informed Consent Forms.

Has been modified to state:

Participants will be followed for 12 or 18 months after enrollment. Participants who become HIV-infected (i.e., seroconvert to HIV) at any time during this 12 or 18-month period will be offered enrollment into a six month ancillary study. **In order to give seroconverters time to consider participation in the ancillary study after they receive notification of their HIV-positive status, they will be offered the opportunity to stay on-study for up to an additional 60 days after the date of the collection of the first HIV positive sample.**

During this period, seroconverters will return to the site for monthly visits and a final visit (if necessary) at the end of the 60 days. The objective of this ancillary study is to assess the affect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”). This ancillary study will have its own protocol and Informed Consent Forms.

5.6 Exit Visit (Month 12 or Month 18)

Language has been added at the end of the section stating:

As described below in Section 5.8, participants who become HIV-infected during the study will be offered continuation in the study for a 60-day period after the date of the collection of the first HIV positive sample to give them time to decide about participating in the ancillary study. During this period, participants will continue to return to the site for monthly visits. At the end of the 60-day period, participants who have not already decided about enrollment in the ancillary study will have a final visit where they will be asked about their decision and terminated from the study.

5.8 Post-Test Visits For Persons Who Test HIV-Positive After Enrollment

Currently states:

Participants will cease to have study visits for the HPTN 039 main protocol and no further data will be collected from them for this protocol once their HIV infection has been confirmed.

Has been modified to state:

Seroconverting participants will be offered the option to continue on study for a 60-day period following the date of collection of the first HIV positive sample. During this period, participants will continue to return to the site for monthly visits. At the end of the 60-day period, participants who have not already decided about enrollment in the ancillary study will have a final visit where they will be asked about their decision and terminated from the study.

6.2 Adverse Event Reporting Requirements

Currently states:

Any participant who is determined to be HIV positive during follow-up will be terminated from the study. Since use of all study drug will be discontinued at the point of confirmed HIV seroconversion, deaths and SAEs after HIV infection will not be reported.

Has been modified to state:

Any participant who is determined to be HIV positive during follow-up will be **offered continuation in the study for a 60-day period from the date of the first HIV positive sample blood draw. During this period, participants will continue to return to the site for monthly visits. At the end of the 60-day period, participants who have not already decided about enrollment in the ancillary study will have a final visit where they will be asked about their decision and terminated from the study. While study drug is still being used during the 60-day study extension period, deaths and SAEs will continue to be collected and reported as per protocol.**

8.5.2 Care For Participants Identified As HIV-Infected

Currently states:

Lastly, participants who become HIV-infected while they are in the study will be offered enrollment into a six-month ancillary study to assess affect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”) through a separate protocol, Informed Consent Forms, and maintenance of the initial treatment randomization . Participants will cease to have study visits for the HPTN 039 main study protocol and no further data will be collected from them for this protocol once their HIV-infection has been confirmed.

Has been modified to state:

Lastly, participants who become HIV-infected while they are in the study will be offered enrollment into a six-month ancillary study to assess affect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”) through a separate protocol, Informed Consent Forms, and maintenance of the initial treatment randomization . **These participants will be offered continuation in the study for a 60-day period from the date of the first HIV positive sample blood draw. During this period, participants will continue to return to the site for monthly visits. At the end of the 60-day period, participants who have not already decided about enrollment in the ancillary study will have a final visit where they will be asked about their decision and terminated from the study.**

Enrollment Consent Men and Women

Currently States:

Every Three Month Visits

Sometimes an HIV test result is not clearly positive but is also not negative. In that case we will test your blood again until we know for sure whether or not you are infected with HIV.

If your HIV test result shows that you are infected with HIV, you will no longer be followed in this study. If you become HIV-infected, the study staff will talk with you about this test

result and what this means for you. The staff will obtain a second blood test to confirm the initial positive test and you will be referred for care and additional counseling and other studies and services available to you.

In addition, if your HIV test result shows that you are infected with HIV you will be offered enrollment into a study aimed at determining whether daily acyclovir lowers the amount of HIV virus in your blood during the first six months after you become HIV-infected. This is based on studies that have found that genital herpes may increase HIV levels in early HIV infection. This study will last approximately six additional months and will have its own informed consent forms for you to review and sign should you decide to join this study.

Has been modified to state:

Every Three Month Visits

Sometimes an HIV test result is not clearly positive but is also not negative. In that case we will test your blood again until we know for sure whether or not you are infected with HIV.

If your test result shows that you have become infected with HIV, ~~you will no longer be followed in this study. If you become HIV-infected~~ the study staff will talk with you about this test result and what this means for you. The staff will obtain a second blood test to confirm the initial positive test and you will be referred for care and additional counseling and other studies and services available to you.

In addition, if your HIV test result shows that you are infected with HIV you will be offered enrollment into a study aimed at determining whether daily acyclovir lowers the amount of HIV virus in your blood during the first six months after you become HIV-infected. This is based on studies that have found that genital herpes may increase HIV levels in early HIV infection. This study will last approximately six additional months and will have its own informed consent forms for you to review and sign should you decide to join this study. **If you need time to decide whether to participate in this additional study, you will be offered continuation in this study for a 60-day period from the date of your first HIV positive test sample. During these 60 days, we will ask you to come back to the clinic for your regular monthly visit(s). You may decide that you do or do not want to participate in the additional study at any time during the 60 days. If you have not already decided by the end of the 60 day period, you will have a final visit where we will ask for your decision and you will be terminated from this study. If you decide not to participate in the additional study, you will no longer be followed in this study and you will no longer receive study drug.**

II. PROVISION FOR ACYCLOVIR TO BE USED FOR ORAL HERPES TREATMENT

4.1 Study Drug Formulation And Regimen

Currently states:

All participants will be asked to return to the clinic (as part of a regularly scheduled study visit, or an interim visit if outbreak occurs between visits) and receive a standard dose of open label acyclovir (400 mg three times a day for five days) for recurrent genital herpes. Participants will only be offered this treatment if the Investigator or designee (must be a clinician) believes that it would be beneficial to the participant.

Has been modified to state:

All participants will be asked to return to the clinic (as part of a regularly scheduled study visit, or an interim visit if outbreak occurs between visits) and receive a standard dose of open label acyclovir (400 mg three times a day for five days) for recurrent genital herpes. Participants will only be offered this treatment if the Investigator or designee (must be a clinician) believes that it would be beneficial to the participant. **In addition, should participants have oral sores during the study, and the clinician feels that it would be beneficial to the participant's health, participants may be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with study medication.**

Enrollment Consent Form Men and Women

Currently states:

Acyclovir For Genital Sores During The Study

If you have ano and/ or genital sores during the study, and your clinician feels that this will be beneficial to your health, you will be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with your study medication. This is the standard dose of acyclovir that is used to treat a recurrence of genital herpes.

Has been modified to state:

Acyclovir For Genital Sores During The Study

If you have ano and/ or genital sores during the study, and your clinician feels that this will be beneficial to your health, you will be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with your study medication. This is the standard dose of acyclovir that is used to treat a recurrence of genital herpes. **In addition, should you have oral sores during the study, and your clinician feels that it will be beneficial to your health, you may be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with your study medication.**

III. LONG-TERM SPECIMEN STORAGE

The following language has been added as clarification:

Long-Term Storage Specimens will be shipped to the CL for storage with the following exceptions:

- 1. Local Regulations prohibit the shipping of samples outside of the country or region.**
- 2. Some sites desire to have specimens from each participant stored on-site after study completion. This is only acceptable if sufficient sample for testing is also shipped to the CL.**

HPTN 039

**A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir
For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive,
HIV Seronegative Individuals**

A Study of the HIV Prevention Trials Network

Sponsored by:

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

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Version 3.0

September 13, 2004

HPTN 039

**A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir
For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive,
HIV Seronegative Individuals**

A Study of the HIV Prevention Trials Network

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US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institute on Drug Abuse
US National Institute of Mental Health

US National Institutes of Health

I, the Site Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years from the end of the study, unless directed otherwise by the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center (CORE). Publication of the results of this study will be governed by HPTN and DAIDS policies. Any presentation, abstract, or manuscript will be made available by the investigators to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Site Principal Investigator

Signature of Site Principal Investigator

Date

HPTN 039

A phase III, randomized, double-blind, placebo-controlled trial of acyclovir for the reduction of HIV acquisition among high-risk HSV-2 seropositive, HIV seronegative individuals

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HPTN 039

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
CDC	Centers for Disease Control and Prevention
CFR	(United States) Code of Federal Regulations
CL	(HPTN) Central Laboratory
CORE	(HPTN) Coordinating and Operations Center
CRPMC	(NIAID) Clinical Research Products Management Center
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	ethics committee
EIA	enzyme immunoassay
ELISA	enzyme linked immunosorbent assay
FDA	(United States) Food and Drug Administration
FHI	Family Health International
GUD	Genital Ulcer Disease
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
IFA	Immunofluorescence Assay
IRB	institutional review board
LDMS	Laboratory Data Management System
LE	leukocyte esterase
LL	local laboratory
LSHTM	London School of Hygiene and Tropical Medicine
MRL	Meridian Research Laboratories
MSM	men who have sex with men
NAAT	Nucleic Acid Amplification Test
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
OCP	oral contraceptive pills
PCR	polymerase chain reaction
PHI	Protected Health Information
RNA	ribonucleic acid
ROC	DAIDS Regulatory Operations Center
SAE	serious adverse event

SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	(HPTN) Statistical and Data Management Center
SSP	Study Specific Procedures manual
STD	sexually transmitted disease
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States of America
USAID	United States Agency for International Development
UW	University of Washington
WB	Western blot
WHO	World Health Organization
WSM	women who have sex with men

HPTN 039

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

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HPTN 039

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

SCHEMA

- Purpose:** To determine the efficacy of twice daily acyclovir in preventing HIV infection among high-risk HIV-negative, HSV-2 seropositive women and men who have sex with men (WSM, MSM).
- Design:** Phase III, multi-site, randomized, double-blind, placebo-controlled, two-arm trial.
- Population:** High-risk HIV-negative, HSV-2-seropositive WSM and MSM.
- Study Size:** Between 2820 and 3012 WSM and MSM (1410 or 1506 per arm).
- Treatment Regimen:** Study participants will be randomized in a 1:1 ratio to:
- Acyclovir 400 mg po bid, or
 - Matching placebo po bid for 12 or 18 months of follow-up.
- Study Duration:** Approximately 3 years total;
Participants will be followed for 12 or 18 months.
- Primary Objective:** To measure the efficacy of twice daily acyclovir suppressive therapy in preventing HIV infection among HSV-2 seropositive, HIV-negative WSM and MSM at high risk for HIV infection.
- Secondary Objectives:** To determine the effect of twice daily acyclovir suppressive therapy on reducing the occurrence and frequency of genital ulcers among HIV-negative HSV-2 seropositive persons.
- To assess adherence with twice daily acyclovir suppressive therapy among HIV-negative HSV-2 seropositive persons.
- Study Sites:**
- Harare, Zimbabwe;
 - Lusaka, Zambia;
 - Lima, Iquitos, and Pucallpa, Peru;
 - Seattle, WA, USA;
 - New York, NY, USA;
 - San Francisco, CA, USA;
 - Johannesburg, South Africa

1. INTRODUCTION

1.1 Background

The presence of genital ulcers has been suggested as a potential risk factor for HIV acquisition since the start of the HIV epidemic^{1,2}. Numerous epidemiologic studies have supported the association of genital ulcers in general, and genital herpes in particular, with acquisition of HIV infection³⁻⁶. Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcers worldwide. This has been well-documented in developed countries and has recently been shown in the developing world⁷⁻⁹. Both case-control^{1-3;5;10} and cohort studies^{4;11-13} have shown that prior HSV-2 infection is associated with an increased risk for HIV acquisition. Estimates of relative risk for HIV infection associated with HSV-2 infection ranged from 1.2 to 8.5¹⁴. In a recent meta-analysis including over 17,000 persons in 21 studies, the overall risk of HIV acquisition in persons with serologically documented HSV-2 infection was 2.8 (95% CI 2.1, 3.7). An estimate derived from methodologically more rigorous studies that documented HSV-2 infection preceded HIV acquisition, yielded an estimate of 2.1 (95% CI 1.4, 3.2)¹⁵. Elevated risk has been observed in male-to-male, male-to-female and female-to-male transmission and in studies conducted both in the developing and the developed world.

The population attributable risk of HSV-2 for incident HIV infection increases in parallel with the HSV-2 seroprevalence in the population, reaching almost 50% at 80% HSV-2 seroprevalence, such as has been found among HIV-negative women in sub-Saharan Africa.

The most compelling epidemiologic data about the relative effect of HSV-2 seropositivity on HIV acquisition is based on recent analyses of the Rakai community-randomized STD intervention trial¹⁶. Drs. Gray and Brookmeyer have analyzed data from the 174 retrospectively-identified monogamous heterosexual HIV-discordant couples in this trial and assessed the probability of HIV transmission and acquisition per coital act, with covariates of age, gender, genital ulcers, other STD diagnoses, and serum viral load in the HIV-infected partner. The probability of HIV transmission per coital act was 0.0017 overall and somewhat higher for female-to-male transmission (0.0022) than male-to-female transmission (0.0013, $p=0.34$). Of note, HSV-2 seropositivity increased the risk of HIV acquisition among HIV-negative partners approximately five-fold (0.002 versus 0.0004 per-contact acquisition probability, $p<0.001$). Other significant risk factors for HIV acquisition were young age, partner's serum HIV level, and lack of circumcision, but other STD diagnoses did not significantly increase acquisition or transmission risk. HIV transmission risk was also increased five-fold, but this increase was found among HIV-infected partners with a history of genital ulcer disease (0.0062 vs 0.00012 among those without a history of GUD ($p=0.002$) and not due to HSV-2 seropositivity alone. Compared to HIV-discordant HSV-2 seronegative concordant couples, the corresponding estimate for couples where both partners were HSV-2 seropositive but neither reported a history of genital ulcer disease was 0.0027 (R. Gray, unpublished data). These data suggest a 5-fold increased per coitus risk of HIV acquisition rates

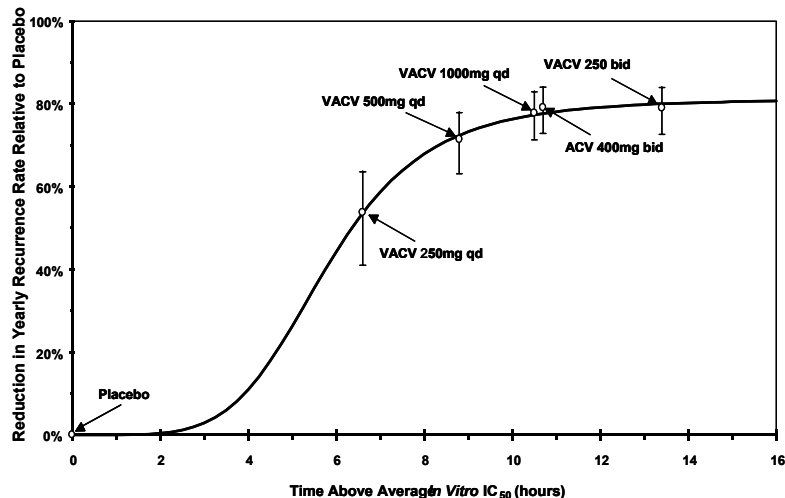
among HIV-discordant seroconcordant couples associated with HSV-2 seropositivity in the HIV-negative partner, and a 5-fold increased per contact transmission risk by HIV-infected partners with symptomatic genital ulcer disease (the majority of which were shown to be due to HSV-2 in the Rakai population).

These epidemiologic observations are supported by the biology of genital herpes infections. Acquisition of HIV may be facilitated by mucosal disruption. Additionally, as herpetic ulcerations are associated with an influx of CD4-bearing lymphocytes^{17;18}, a larger number of target cells for HIV attachment and entry are present in the genital tract of persons during HSV-2 reactivation. Both mucosal disruption and the presence of increased numbers of activated CD4 cells increase the likelihood that any potential exposure to HIV will result in HIV acquisition.

The biologic interaction between HSV-2 and HIV not only enhances transmission and acquisition of HIV, but HIV infection is associated with more frequent reactivation of HSV-2. Several studies have demonstrated that HIV infection can lead to three to four times as frequent HSV-2 reactivation¹⁹⁻²¹. The presence of herpetic ulcers and lesions allowing an entry point for HIV in the uninfected individual and the finding of high copy numbers of HIV-1 RNA in HSV-2 lesions in HIV-infected individuals make controlling HSV-2 infections an important goal for HIV prevention^{22;23}.

Anti-HSV medications

Efficacy. Antiviral medication can suppress both symptomatic and asymptomatic reactivation of HSV-2. Acyclovir 400 mg twice a day is the most widely studied and clinically utilized regimen, and the newer antiviral regimens have not been shown to be superior. As shown in the figure below, twice daily acyclovir reduces the frequency of recurrences 80% compared to placebo, a slightly higher reduction than can be achieved with once daily regimens of valacyclovir. Furthermore, acyclovir 400 mg po bid has been shown to reduce viral shedding from 9.9% of the days to 0.5% of days in immunocompetent women²⁴. Acyclovir reduces viral shedding during clinical reactivation and subclinical episodes by comparable amounts (95% and 94% respectively). While a once daily regimen might be associated with higher compliance in terms of proportion of doses taken, the critical factor in the suppression of recurrences is the time above average in-vitro IC₅₀ as shown below (Glaxo SmithKline, unpublished data). Thus the duration of time without adequate antiviral coverage is likely to be longer with a missed daily dose than a missed bid dose.



Safety. Acyclovir has been administered on a daily basis for up to 10 years without significant adverse effects. In terms of safety and tolerability, few if any antimicrobials rival acyclovir's record. Acyclovir has a safety profile that compares favorably with many over-the-counter medications. In fact, Burroughs Wellcome had petitioned the FDA to allow over-the-counter marketing of acyclovir for therapy of recurrent genital herpes. No safety concerns about this drug emerged at that time, based on analyses of adverse event reporting from clinical trials and of monitoring of toxicity in clinical use of acyclovir for over 50,000 patients^{25,25}. The safety of oral acyclovir has been examined in data from 4702 clinical trial patients exposed to acyclovir, epidemiologic and safety studies with 71,653 patients who received a least one prescription for acyclovir, and subsequently through the reporting of adverse drug events. Early in its development, acyclovir received extensive safety evaluation as it was among the first widely used nucleoside analogues, and was used cautiously. However, the rate of adverse events in clinical trials is very similar in the drug and placebo groups, with most common reports of headache and nausea in both groups. In one long-term suppression study of 1,200 people, the most frequent adverse experiences reported for acyclovir 400 mg bid were nausea (4.8%) and diarrhea (2.4%). In the same study, the most frequent adverse experiences reported in the placebo group were diarrhea (2.7%), nausea (2.4%), and headache (2.2%). Serious events, attributable to oral acyclovir in doses used for the treatment of genital herpes, have not been noted. In addition, oral acyclovir has been given in doses up to 800 mg five times a day for 21 days without serious adverse effects.²⁵ Renal insufficiency and CNS effects have been noted rarely and primarily in patients receiving high dose intravenous acyclovir, usually in the setting of co-morbid conditions.

Based on data from a pregnancy registry that followed 749 women with first trimester exposure to acyclovir, acyclovir use does not appear to result in an increased frequency or unusual distribution of birth defects as compared with the general population^{26, 27} (Acyclovir package insert). Recent trials of daily acyclovir used at the end of pregnancy to prevent abdominal deliveries, and endorsement of such approach by the American College of Obstetricians and Gynecologists, indicate the lack of safety concerns with acyclovir²⁸. The pharmacology of acyclovir supports its safety: the initial step in activation of acyclovir is phosphorylation with a virally-

encoded thymidine kinase which is present only in cells with active viral replication. Acyclovir has fewer side effects than antibiotics used in previous mass treatment studies, such as in the Rakai STD community intervention.

Resistance. Clinically significant resistance to acyclovir has been described in immunocompromised patients, including advanced HIV infection (CD4<100)^{29;30}. Only a few cases of acyclovir-resistant herpes in immunocompetent persons have been described and no transmission of resistant strains has been documented^{31;32}. Most commonly, resistance is mediated by mutant strains that lack thymidine kinase³³. The frequency of such strains with in-vitro resistance, which does not necessarily imply clinically-significant resistance, has remained at <3.5% in healthy populations (>5000 patients) examined before and after introduction of acyclovir. Recent data suggest that topical, not oral, acyclovir is a risk factor for in vitro resistance³⁴. Other data suggest that intermittent rather than daily administration of acyclovir is a risk factor for development of resistance to acyclovir in immunocompromised patients³⁵. As acyclovir-resistant mutants arise spontaneously, and acyclovir decreases the amount of replicating virus, suppressive therapy may be less likely to lead to emergence of resistant strains than episodic therapy, particularly among immunocompromised persons whose lesions contain large amounts of virus, allowing proliferation of acyclovir-resistant strains. However, emergence of less sensitive strains was not seen in immunocompetent patients who received acyclovir episodically for one year, received it intermittently on weekends, or who were given suboptimal doses³⁶⁻³⁸. Patients who received suppressive acyclovir for as long as 6 years did not have recurrent HSV-2 episodes with acyclovir-resistant strains after stopping therapy³⁹.

Sequential specimens from patients who participated in daily home culture studies on and off therapy with daily acyclovir have been tested for resistance and have indicated that breakthrough shedding was rare and not caused by resistant strains⁴⁰. Six (3%) of 181 isolates documented reduced susceptibility to acyclovir, but all disappeared spontaneously and were followed by recovery of sensitive viral isolates⁴¹. A CDC surveillance survey in 1997-98 found <1% in vitro resistance in a total of over 1800 persons (including both HIV-infected and HIV-uninfected persons) in the 10 participating cities^{34;42}. Isolation of strains with reduced susceptibility (>2 mcg/ml in the plaque neutralization assay) was more common (3%) in HIV-infected patients. The significance of these in vitro findings is unclear, as these patients did not have clinically refractory herpes.

Defining clinical resistance to acyclovir remains an area of some controversy; clinical resistance varies with the immune status of the host. Thus, for highly immunosuppressed patients there are case reports of clinically refractory lesions in persons whose isolates were above 4 mcg/ml by the plaque neutralization assay. In most cases, these were HIV-positive persons and clinical resistance was seen with isolates above 10 mcg/ml^{29;43}. Only rare cases of clinically refractory disease have been reported in HIV-negative immunocompetent persons. The question about whether widespread prolonged acyclovir use would markedly enhance HSV-2 resistance was evaluated in a mathematical model by Blower et al. In modeling the development of acyclovir

resistance in a population treated with episodic acyclovir, Blower predicted that with wide use, acyclovir resistance may rise to up to 36% in 50 years. However, this detrimental effect was balanced by decreased HSV-2 prevalence of 74% with widespread antiviral treatment⁴⁴.

These data clearly indicate that the mechanism of resistance and clinical significance is different in HSV-2 infections than in HIV or bacterial infections. Specifically, risk factors such as chronic therapy that are associated with development of resistance to antibiotics or anti-HIV medications are not necessarily risk factors for development of HSV resistance to acyclovir. Widespread population-based use of acyclovir may lead to reduced susceptibility of circulating strains of HSV-2, but the critical questions are over what time period and the balance of risk to benefits. These data can be modeled hypothetically, but the question can only be answered experimentally. The first issue is whether the efficacy of the drug will result in an appropriate benefit. For resource-poor countries and perhaps even for the U.S., the “benefit” requires reduction in HIV acquisition—the purpose of this study. Whether HSV-2 resistance will emerge from breakthrough infections is something that can be evaluated subsequently in future studies. The strategy for acyclovir use for HIV prevention, if this trial is effective, is a temporary one, perhaps useful in many countries for a 5-15 year period until effective HIV vaccines and other prevention approaches become available. Hence, the risk for causing widespread HSV-2 resistance will likely be low, based on both current experimental and mathematical modeling data.

Adherence: Adherence is an issue with use of any medication. The adherence rate of twice daily acyclovir among those at risk of HIV infection is uncertain. However, all published clinical trials of acyclovir to suppress herpes shedding or ulcerations had significant efficacy, indicating a significant effect even if adherence was not perfect. In addition, preliminary findings in a study of genital HIV and HSV-2 shedding among 212 rural Zimbabwean sex workers, approximately 60% of whom were HIV-positive, found that 82% of women completed the 3 months of follow-up and missed doses (confirmed by pill count) with suppressive acyclovir 400 mg bid were only observed at 2.9% of visits⁴⁵.

While there is some preference for once daily dosing of medications, the amount of time without adequate antiviral levels would be even greater if a once daily medication dose is missed compared with bid medication. Even though adherence to medication in previous studies likely varied, the overall efficacy of acyclovir remained excellent. For example, in a four-month study of suppressive acyclovir, the proportion of pills taken by patients was 97% in the acyclovir recipients receiving 200 mg 5 times a day and 98% in those receiving acyclovir 200 mg bid. Furthermore, the rate of compliance did not differ in those with and without breakthrough recurrences (97% vs. 98%)⁴⁶. Conversely, Straus et al. showed that breakthrough recurrences are not always associated with missed doses⁴⁷. Similarly, in a study of acyclovir 400 mg bid and asymptomatic viral shedding, breakthrough shedding occurred in 5 women, of which only one was non-adherent and took only 61% of the study pills in the preceding 2 weeks⁴⁰. Overall, the women took a median of 98% of the study drug

during the 5-month study. None of the published articles on the use of suppressive therapy demonstrated that non-adherence was associated with a decreased overall efficacy of acyclovir.

As with many medications, the amount of adherence required for 80% reduction in HSV-2 reactivation (the level used in the power calculations) is unknown. However, the ease of administration, excellent tolerability and lack of adverse effects likely lead to high rates of compliance, particularly for persons who are in a clinical trial in which acyclovir is being tested as a method to prevent HIV acquisition. Even though the published literature has addressed primarily the use of acyclovir in patients who had clinically evident, and sometimes severe, symptomatic genital herpes, it is encouraging to note such high rates of compliance with a twice-daily medication.

Previous studies have found that factors that can motivate adherence include patient and community-level education, and an investigator approach that includes counseling and close follow-up. Strategies to promote adherence need to be tailored differently for preventive versus therapeutic therapies⁴⁸. A randomized trial of several strategies to promote and monitor adherence to daily isoniazid for preventive tuberculosis (TB) therapy among injection drug users in Baltimore indicated that overall adherence was 80% and was highest among the subset randomized to supervised care, and enhanced with peer counseling⁴⁹. The extensive literature on TB preventive therapy and oral contraceptive pills (OCPs)⁵⁰ summarize a number of strategies to increase adherence that will be utilized in this study, including explicit information about setting a regular time of day to take the pill, providing and monitoring knowledge about the drug, and providing explicit instructions about what to do if pills are missed.

The reasons for poor adherence can be complex, and often go beyond the doctor-patient relationship⁵¹. There are 4 key aspects of treatment adherence: the patient, the social milieu, the treatment regimen, and the program support offered. Increased pill burden, complex daily dosing regimes and high side effect profiles negatively influence adherence⁵¹⁻⁵³. The literature from HIV antiretroviral therapy (ART) indicates that pill boxes, electronic devices, telephone reminders, home visits, a single cognitive-behavioral intervention⁵⁴ and incentives all can increase adherence. In general, the more comprehensive strategies were associated with higher adherence⁴⁸. With respect to this study, some of the approaches used to increase adherence for ART are costly and less relevant for this multi-site international trial, which involves a simple, nontoxic, prevention strategy.

1.2 Rationale

Epidemiologic data consistently indicate an association between HSV-2 seropositivity and HIV acquisition among both heterosexuals and MSM. Serologically documented HSV-2 infection, regardless of history of clinically-recognized genital herpes, is a significant risk factor for HIV acquisition. HSV-2 is highly prevalent in high-risk heterosexuals in Africa (over 80% of HIV seroconverters among the monogamous Rakai HIV-discordant couples were HSV-2 seropositive) and in high-risk HIV-

negative MSM in the US (30-50% HSV-2 prevalence) and Peru (50% in HIV-negative and 85% of HIV-positive MSM).

Given that genital herpes is a significant risk factor for HIV acquisition, a critical research question relates to the efficacy of daily suppressive therapy in HSV-2 seropositive individuals in reducing HIV acquisition (susceptibility) by suppressing HSV-2 reactivation in high risk HIV-negative individuals. This study is a proof-of-concept trial, designed to assess the overall efficacy of twice daily HSV-2 suppressive therapy — 400 mg of acyclovir — in preventing HIV infection among high risk, HSV-2 seropositive WSM and MSM. It will provide a simple and direct measure of the relative reduction in incident HIV infections by suppressing herpes reactivation and diminishing the enhancement of HIV susceptibility due to genital herpes.

Acyclovir is safe, highly effective, and available generically, and acyclovir resistance has not been a problem. Thus, acyclovir provides an ideal “probe” to directly test the association between HSV-2 and HIV susceptibility.

Acyclovir was selected as the optimal medication for HSV-2 suppression, based on previous efficacy studies in both HIV-positive and HIV-negative individuals. The argument has been made that a once daily regimen might be associated with higher compliance in terms of proportion of doses taken. However, the critical factor may be duration of time (or area under the curve) in which anti-virals are providing HSV-2 suppression; that interval is likely to be greater with fewer missed doses in a twice daily regimen than a once daily regimen.

Over 50 clinical trials of acyclovir therapy demonstrate 80-90% reduction in days with genital lesions, thus supporting our assumption of an overall 80% effect size in our power calculations. The dose of acyclovir 400 mg po bid was chosen as the preferred dose from both clinical and economic perspectives. Acyclovir 400 mg bid has been an effective regimen for suppression of clinical recurrences as well as asymptomatic viral shedding. This dose has been used in many studies, including several that lasted for many years (up to 10 years). While adherence to medication in these studies likely varied, the overall efficacy of acyclovir remained excellent. Other currently available regimens include famciclovir, which is also given bid, and valacyclovir, which can be given once daily. However, acyclovir is currently available generically for a fraction of the cost of valacyclovir (\$69 for a year’s supply of generic acyclovir 400 mg bid). The preferred strategy is to use the medication that is most likely to be available in the participating communities after the trial. Thus, acyclovir was selected based on efficacy, cost (given that acyclovir is now available generically, and thus would be the most sustainable and cost-effective herpes medication available), minimal side effects, and an available placebo.

Previous studies in developed countries indicate high adherence with twice daily acyclovir for prevention of HSV-2 reactivation, and high efficacy even when adherence was approximately 85%. High adherence is anticipated in the sites participating in this trial through a combination of approaches that include clear

explanation about the rationale of the study (i.e., that they are being randomized to acyclovir or placebo to see if it will prevent HIV acquisition), the safety of acyclovir from many previous studies, and monthly visits in which adherence will be assessed and barriers to adherence will be addressed by the study staff. The research staff will be trained in previously-evaluated effective strategies to promote adherence, including clear and simple counseling messages related to adherence, the safety of acyclovir, and plans to manage nonadherence^{48;55}. Peer outreach workers have been found to be effective for recruitment, retention, and adherence assessment in some sites, such as trained MSM outreach workers in Peru, which will be used by sites to enhance adherence. Lastly, sites will attempt to assist study participants with child care and family planning needs to enhance adherence with study visits and the protocol.

This double blind, placebo-controlled intervention trial of daily antiviral HSV-2 suppressive therapy for HIV prevention has reasonable risks and benefits to the participants. First, although the observational data indicate an increased risk of HIV infection among HSV-2 seropositive persons, a reduction in HIV infection due to daily HSV-2 suppression has not yet been tested or demonstrated. Second, participants in the placebo arm will be provided more than the standard of care for many U.S. settings, by provision of episodic antiviral treatment for symptomatic herpes outbreaks.

In summary, the HPTN provides a unique opportunity to assess the effect of HSV-2 suppression on reducing HIV acquisition among MSM and WSM populations who have the highest HSV-2 seroprevalence and HIV incidence rates globally. This proof-of-concept trial is designed to assess the overall efficacy of twice daily HSV-2 suppressive therapy — 400 mg of acyclovir — in preventing HIV infection among high risk, HSV-2 seropositive heterosexual women and MSM. This study will provide a simple and direct measure of the relative reduction in incident HIV infections by suppressing HSV-2 reactivation, thus diminishing the enhancement of HIV susceptibility caused by genital herpes. Preventive and therapeutic candidate HSV-2 vaccines are being developed and, in the future, a highly efficacious HSV-2 vaccine could supplant acyclovir. Lastly, even if ART therapy reduces HIV transmission among HIV-discordant couples and proves to have higher efficacy than acyclovir, our study findings will be valuable in two ways:

- 1) The mechanism of acyclovir's effect differs and would likely be complementary to the effects of ART.
- 2) The populations that can benefit from acyclovir are much larger than those that will be utilizing ART therapy, based on HSV-2 seroprevalence relative to the proportion of HIV+ with CD4<200 or symptomatic AIDS who would be eligible for ART in developing countries as it becomes available.

Procurement of study drug has been supported in part by a contribution from Glaxo SmithKline.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

- To measure the efficacy of twice daily acyclovir suppressive therapy in preventing HIV infection among HSV-2 seropositive WSM and MSM at high risk for HIV infection.

2.2 Secondary Objectives

- To determine the effect of twice daily acyclovir suppressive therapy on reducing the occurrence and frequency of genital ulcers among HIV-negative HSV-2 seropositive persons.
- To assess adherence with twice daily acyclovir suppressive therapy among HIV-negative HSV-2 seropositive persons.

2.3 Study Design

This is a phase III, multi-site, randomized, double-blind, placebo-controlled trial. Between 2820 and 3012 high-risk, HIV-negative, HSV-2 seropositive WSM and MSM will be enrolled. Women who have sex with men (WSM) will be enrolled at study sites in Lusaka, Zambia, Harare, Zimbabwe, and Johannesburg, South Africa. Men who have sex with men (MSM) will be enrolled at study sites in Lima, Iquitos, and Pucallpa, Peru; Seattle, WA, USA; New York City, NY, USA; and San Francisco, CA, USA.

Due to slow enrollment at the time of the printing of this version of the protocol, participant follow-up is increased from 12 months to 18 months. Newly enrolled participants will be followed for 18 months after enrollment. In addition, the Protocol Team will evaluate the benefit and feasibility of extending follow-up for currently enrolled participants at each site (extending from 12 to 18 months). Following this evaluation, the re-consent process will be further examined in the first month of implementation at each site involved in the process. The protocol team will then determine whether a particular site will continue re-consenting participants at that site. The sample size for the study will ultimately be determined by the proportion of currently enrolled participants who will be followed for 12 vs 18 months.

HSV-2 serostatus will be determined from samples taken at screening by Focus Technologies™ (formerly MRL) HSV-2 EIA. Participants with a low positive index between and including 0.9 and 3.4 according to the Focus serology, but are HSV-2 positive by the University of Washington's HSV-2 Western blot test, will also be eligible. HIV serostatus will be determined according to the algorithms presented in Appendices II and III. Confirmatory second samples will only be drawn in case of discordant test results on the first sample or if mandated by local law.

Pre-test, risk reduction, and post-test counseling will be provided to all participants; HSV-2 counseling will include information on the natural history of HSV-2, clinical

manifestations, recognition of prodromal symptoms and lesions, risk of transmission during subclinical reactivation as well as symptomatic herpetic lesions, and the epidemiologic and clinical data about HSV-2 and HIV interactions.

Participants who meet the study eligibility criteria will be offered enrollment in the study, and those willing to take part will be randomized to either twice daily oral 400 mg acyclovir or twice daily placebo throughout follow-up. Randomization will be stratified by site. Within each stratum, a variable-size block randomization scheme will be implemented. Female volunteers will also be tested for pregnancy at both screening and enrollment; pregnancy at time of screening or enrollment will be an exclusion criterion. For participants who are found to have one or more bacterial STD(s), every effort should be made to provide free treatment and follow-up care, in accordance with WHO and CDC guidelines, for international and domestic sites, respectively. If abnormal discharge or other clinical evidence of bacterial STDs is detected and/or if the wet mount demonstrates *T. vaginalis* or bacterial vaginosis, participants may be enrolled; however, bacterial STD treatment or a referral for free treatment at a local clinic should be offered during the enrollment visit (unless awaiting RPR/FTA confirmation of active syphilis infection). All participants, regardless of study arm, will be counseled on the importance of using condoms every time they have intercourse to prevent STD and HIV transmission. Participants will be followed for 12 or 18 months after enrollment. Participants who become HIV-infected (i.e., seroconvert to HIV) at any time during this 12 or 18-month period will be offered enrollment into a six month ancillary study. The objective of this ancillary study is to assess the effect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”). This ancillary study will have its own protocol and Informed Consent Forms.

Monthly follow-up visits will be conducted to dispense study drug, collect bottles with any unused study drug from the prior month for a pill count, and provide adherence and condom counseling as well as condoms. A brief sexual history (number of partners, HIV serostatus of partners, if known), will be obtained. Female participants will be asked about their menstrual history since the last visit and, if indicated, be tested for pregnancy. These monthly assessments will enable more accurate assessment of adherence (both in terms of number of doses and clustering of missed doses which may have a greater impact on efficacy than total number of missed doses). In addition, the monthly clinical and behavioral assessments of herpes prodromal symptoms and other symptoms of genital herpes, and sexual activity will minimize recall bias, and thereby maximize the validity and reliability of the secondary outcome data.

Every 3 months, follow-up visits will be more extensive and include the following procedures in addition to the monthly assessments:

- A genital exam ([examination of anal and genital regions](#)) for signs of STD and genital ulcers.
- A more extensive sexual behavior questionnaire.

- HIV pre-test, risk reduction, and post-test counseling.
- Blood draw for HIV antibody testing.
- For female participants: a urine pregnancy test.

HIV incidence will be ascertained by HIV-1 EIA with Western blot (WB) or IFA confirmation according to one of the HIV algorithms provided in Appendices II and III. Thus, timing of HIV seroconversion will be ascertained within a three-month interval, which will enable more precise analyses of HIV seroconversion with respect to risk behavior, HSV-2 symptoms, and adherence with study drug. The presence of concurrent STDs, including syphilis and chancroid, will be assessed via questionnaire and supplemented by directed clinical exam, swab collection, NAAT testing, and other HSV-related genital findings, and by serologic testing for syphilis at enrollment and the end of study follow-up.

For participants in both study treatment arms who present to the clinic with clinically evident genital herpes, episodic therapy with acyclovir 400 mg tid for 5 days, a standard regimen recommended in the 2002 CDC STD Treatment Guidelines, will be offered in addition to the study regimen (2002 CDC STD Treatment Guidelines). Genital lesions and other HSV-related genital findings will be swabbed and stored at -20°C to send to the University of Washington Virology laboratory to be evaluated by PCR for pathogens at a later date. Other symptomatic bacterial STDs will be treated in U.S. sites according to 2002 CDC STD treatment guidelines and according to WHO and local Ministry of Health guidelines in non-US sites (i.e., every effort will be made to provide or refer participants for free syndromic STD treatment to participants with vaginal and urethral discharge, genital ulcer disease or specific laboratory-confirmed STD diagnoses based on a positive wet mount, RPR, gonorrhea or chlamydia test).

2.4 Serologic Assays For HSV-2 Infection

Type-specific serologic assays must include detection of antibodies to HSV-2 glycoprotein G. Tests based on glycoprotein G are now available in ELISA format from Focus Technologies (formerly MRL Diagnostics), Cypress, CA. These kits have been approved by the FDA for diagnosis of HSV in adults, including pregnant women. Focus tests include two ELISA kits called HerpesSelect™-1 ELISA and HerpesSelect™-2 ELISA that detect antibodies to baculovirus recombinant glycoproteins gG-1 and gG-2, respectively.

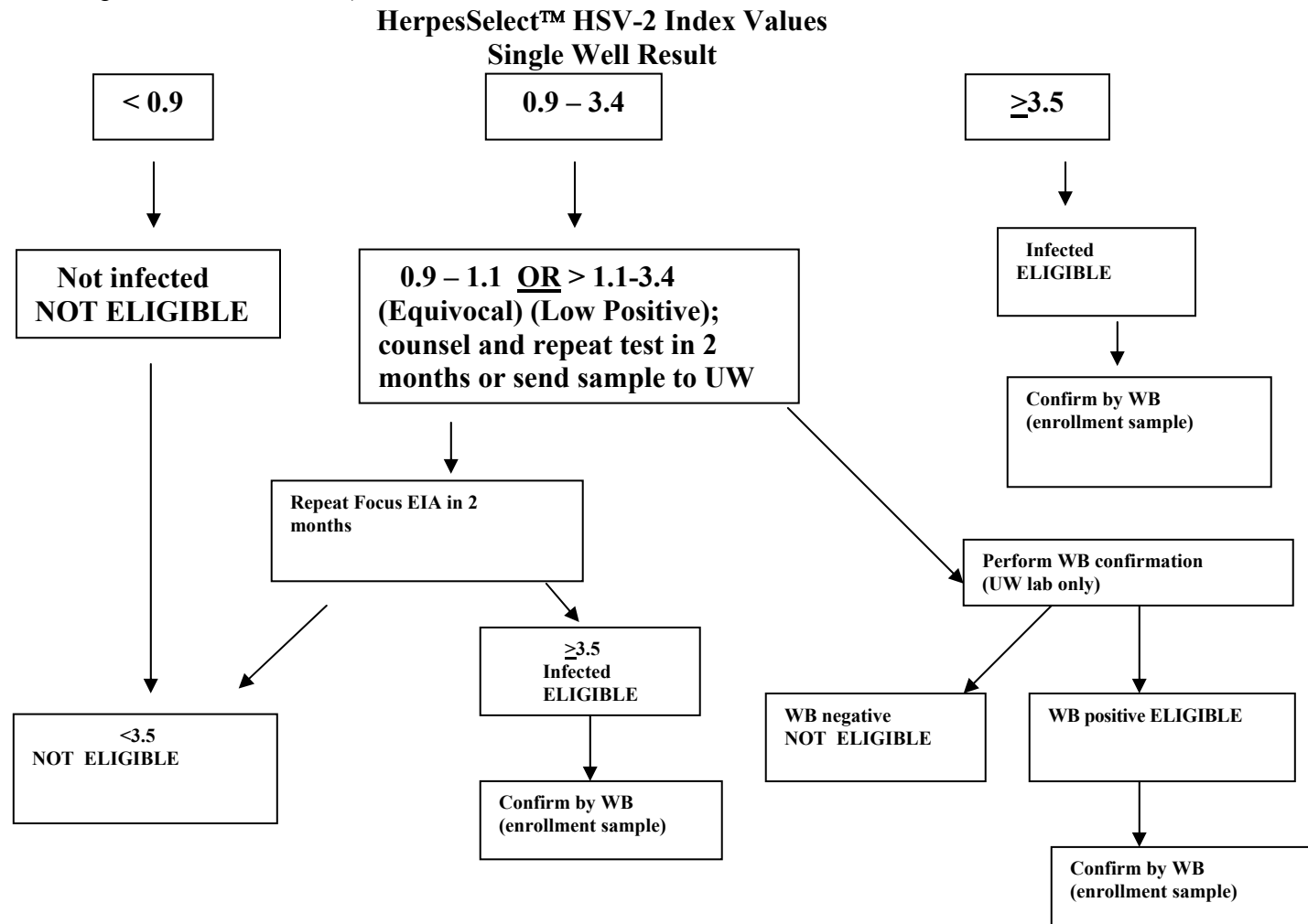
Performance of commercial gG-based tests. The sensitivity, specificity for HSV-2, and HSV-2 prevalence in the populations in which these tests have been evaluated, are summarized below:

Sensitivity, specificity and other performance characteristics of HerpesSelect™-2 ELISA				
	Population	HSV-2 prevalence	Sensitivity	Specificity
HerpeSelect™-2 ELISA	STD clinic patients	33%	96%	97%
HerpeSelect™-2 ELISA	Pregnant women	24%	100%	96%

While the Focus ELISA has been used extensively on sera from Western Europe and the US, evaluations of the test on sera from Africa are less available. Some lack of specificity has been noted with sera from central and South Africa (R. Ballard, personal communication 2001). Investigations are underway to understand the decreased specificity in these samples, including the comparison of the HerpeSelect™-2 ELISA to type-specific WB at University of Washington for detection of HSV-2 antibodies in 174 samples from participants in the STD mass treatment trial in Rakai, Uganda, received from Dr. Ron Gray. HSV-2 antibodies were detected by WB in 140 and by ELISA in 163. Thus, the sensitivity of the ELISA appears excellent (100%, or 97%, if equivocal EIAs with a positive WB are considered as false negative), but specificity was reduced to 81%. However, the average index ratio was 2.3 for the sera that were reactive by EIA but negative by WB, compared to a mean index ratio of 10.5 for sera reactive by both EIA and WB. Thus, the specificity of the HerpeSelect™-2 ELISA in African sera can be increased by using a higher cut-off, such as index values ≥ 3.5 for this trial, with confirmation of positive tests by HSV-2 WB in Dr. Rhoda Ashley's laboratory at UW. Of interest, among a sample of approximately 200 sera from the Zimbabwe HPTN site, there was 100% concordance between the Focus EIA results and HSV-2 antibodies detected by type-specific WB in Dr. Rhoda Ashley's laboratory (J. Brown, personal communication 2002).

For the purpose of participant accrual the gG2-based Focus Technologies™ EIA will be used to screen and enroll subjects at each of the trial sites. Subjects who are HSV-2 gG2 positive (index ratio ≥ 3.5) will be eligible to enroll. All those who enter the trial will have sera sent to the University of Washington for WB confirmation; only those whose sera are confirmed by HSV-2 WB will be included in the analyses. Individuals whose index ratio is between and including 0.9 and 3.4 will not be eligible for the study unless the University of Washington's Western blot testing is performed and shows that the individual is positive for HSV-2 antibodies. If their index ratio is between and including 0.9 and 3.4 and the UW Western blot is not performed, they will be counseled regarding the meaning of this test result. If they remain interested in study participation, they are advised to return for renewed screening after 2 months. If their index ratio is ≥ 3.5 , and if they are HIV negative and meet all other eligibility criteria, they are eligible for enrollment at that time.

Section 2.4 Serologic Assays For HSV-2 Infection, page 24, flow chart) with addition of optional HSV-2 WB confirmatory testing under the low positive/equivocal results block):



NOTE: Individuals whose index ratio is between and including 0.9 and 3.4 will not be eligible for the study unless Western Blot testing is performed at UW and shows that the individual is positive for HSV-2.

3 STUDY POPULATION

Between 2820 and 3012 high risk HIV-negative, HSV-2 positive WSM and MSM will be selected for the study according to the criteria in Section 3.1, 3.2, and the guidelines in Section 3.4. They will be recruited as described in Section 3.3 and randomized to study drug as described in Section 7.4. Conditions for withdrawal from the study are described in Section 3.6.

The following study sites will participate in this trial, of which three sites will recruit high-risk WSM and four sites will recruit high-risk MSM.

- Harare, Zimbabwe
- Lusaka, Zambia
- Lima, Iquitos, and Pucallpa, Peru
- Seattle, WA, USA
- New York, NY, USA
- San Francisco, CA, USA
- Johannesburg, South Africa

3.1 Inclusion Criteria

Men and women who meet **all** of the following criteria **are eligible** for inclusion in this study:

- Of minimum age or older, at which independent informed consent can be provided per the laws in the relevant country.
- HIV-negative according to the algorithms provided in Appendices II or III, or 2 negative independent rapid tests*
- HSV-2 seropositive as determined by Focus HSV-2 EIA with index ratio ≥ 3.5 (or index ratio >0.9 and ≤ 3.4 by conventional rounding methods with UW Western blot positive test specific for HSV-2 antibodies. This UW Western blot positive result may precede the 60-day window between screening and enrollment).
- Not intending to move out of the area for the duration of study participation.
- Willing and able to:
 - provide independent written informed consent.
 - undergo clinical evaluations.
 - take study drug as directed.
 - adhere to follow-up schedule.
 - provide adequate locator information.

* For study screening purposes, HIV infection status assessed via Rapid Testing only will be ascertained using two different rapid immunochromatographic tests; in the event that results from the two tests are discordant, Western Blot or IFA test will be performed. Once a participant has enrolled in the study, follow-

up HIV testing will be performed according to the algorithm in Appendices II or III.

Behavioral eligibility criterion for men:

- At least 1 episode of anal intercourse with another man within the past 6 months.

Behavioral eligibility criterion for women:

- At least one episode of unprotected vaginal sex in the past 6 months.

3.2 Exclusion Criteria

MSM and WSM who meet **any** of the following criteria are **not eligible** for this study:

- Known history of adverse reaction to acyclovir.
- Current or planned use of famciclovir, valacyclovir, or acyclovir (except those medications provided by study staff prior to the enrollment visit or during the study) for genital HSV (use of short-course antiviral therapy for herpes zoster after the enrollment visit or between screening and enrollment is allowed).
- Known plans for travel away from study site for > 2 months.

Exclusion criterion specific for MSM

- In a mutually monogamous relationship with an HIV-negative partner throughout the past two years.
- Reports sex at birth as female.

Exclusion criterion specific for WSM

- Pregnant as confirmed by a urine pregnancy test at screening and enrollment.

Abnormal discharge, other clinical evidence of STDs, including herpes ulcers, and/or a wet mount positive for *T. vaginalis* or bacterial vaginosis **do not** constitute exclusion criteria. Participants may be enrolled at the same visit that treatment or a referral for free treatment is offered to the participant.

3.3 Recruitment Process

Screening for this study will take place over at least two visits and must be completed within 60 days prior to enrollment. All required procedures can be completed in two Screening Visits and one Enrollment Visit; additional visits may be conducted if needed, for example, if a participant wants more time to consider whether to participate in the study.

After providing written informed consent for screening, potential study participants will complete an interviewer-administered behavioral eligibility checklist and undergo HIV, HSV-2, and STD counseling and testing. All screening data of enrolled participants will be collected at SCHARP. A screening log will be maintained at the study site.

Presumptively eligible participants will be provided information about their test results and the study at their second Screening Visit. Participants who meet all eligibility criteria at this visit and remain interested in study participation will be scheduled to return for their Enrollment visit, or will be offered enrollment at this same visit. At the Enrollment Visit they will complete the informed consent process and provide written informed consent to take part in the study. They will also have the opportunity to provide informed consent to long-term storage and future testing of blood obtained from them. Participants will then be assigned at random to one of the two study treatment arms and provided with supplies of condoms and the assigned study drug, instructions for study drug use, adherence counseling, and instructions to contact study staff with questions about the study, reports of genital symptoms, side effects or other problems.

Regardless of the number of visits required, screening and enrollment procedures must be completed within a 60-day interval. The screening period starts on the day that the screening informed consent is signed. If a participant is not randomized within 60 days of beginning the screening process, the screening process must be repeated.

For volunteers who do not meet the eligibility criteria, the screening process will be discontinued when ineligibility is determined. Participants who are ineligible for any reason other than HIV infection may be rescreened, completing all screening procedures from the beginning.

3.4 Co-Enrollment Guidelines

Study participants may not be co-enrolled in other HIV vaccine or prevention trials to reduce participant burden with study visits; to facilitate high levels of adherence and retention, including compliance with study medications; to avoid potential unblinding of HIV vaccine trials; and to avoid confounding in interpretation of the primary endpoint data.

Persons who have previously participated in HIV vaccine trials will be eligible to participate in this trial after they have completed follow-up.

3.5 Participant Retention

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain him or her for the entire study period. A maximum of 10% annual loss-to-follow-up of enrolled participants is targeted based on the

rates of loss-to-follow-up from the EXPLORE and Vaxgen trials that are ongoing at domestic sites that will participate in the HPTN 039 trial.

While study site staff is responsible for developing and implementing local standard operating procedures to achieve high levels of follow-up, the following procedures are examples of locator devices and retention techniques that will be implemented across sites:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.
- Thorough explanation of the importance of both study treatment groups to the overall success of the study.
- Completion of extensive locator form at the study Screening Visits (with multiple means to contact participants and to include place of residence and important landmarks, if use of postal address is not feasible) to be updated at every study visit.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up of missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

For each participant, clinic staff will obtain confidential contact information. Each study site will develop its own Locator Form, and determine the best way to collect this information for its own study population. This information will be updated during each study visit. In the event that a participant misses a scheduled appointment, clinic staff will try to establish communication with the participants through all possible means (e.g., telephone, e-mail, mail contact, and home or workplace visits). The importance of attending all scheduled follow-up visits will be emphasized to study participants at each visit.

3.6 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol co-Chairs and Biostatistician. Participants also may be withdrawn if the study sponsors or government or regulatory authorities terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5 below) of participants who terminate from the study prior to the end

of the 12 or 18 month follow-up period, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4 STUDY DRUG

4.1 Study Drug Formulation And Regimen

Study drug will be supplied as matching tablets containing 400 mg of acyclovir plus excipients, or placebo. Both active study drug and placebo will be dispensed in tamper-evident sealed bottles. Each bottle will contain a participant's monthly supply of study drug. Study drug will be stored at room temperature.

Study participants will be randomized to one of two arms:

- Acyclovir 400 mg po bid
- Acyclovir placebo po bid

for the duration of their participation in the study.

Participants will be instructed to take one tablet in the morning and one tablet in the evening, without dietary restrictions. Adequate fluid intake will be encouraged for participants in tropical settings.

If a participant misses a dose, he or she will be counseled to take the missed dose even if it is late or to double the subsequent dose, if they do not remember until their next dose.

Study staff will instruct the participants in the proper methods of storing the study medication.

All participants will be asked to return to the clinic (as part of a regularly scheduled study visit, or an interim visit if outbreak occurs between visits) and receive a standard dose of open label acyclovir (400 mg three times a day for five days) for recurrent genital herpes. Participants will only be offered this treatment if the Investigator or designee (must be a clinician) believes that it would be beneficial to the participant. Participants will be instructed to take the open-label acyclovir along with their routine daily dose of study medication.

If a participant is unable to report to the clinic for a scheduled visit, study drug may be delivered to the participant via in-person delivery by study staff or by certified courier. Study drug may be delivered to a participant by in-person delivery or certified courier for up to 3 months without a study visit taking place (this includes dispensing 3 months of study medication if it is known that the participant is not willing or able to have an on-site or off-site visit). If after three months a full study visit is not conducted (either on-site or off-site), study medication will not be provided to the participant until s/he participates in a full study visit. Dispensation of study medication should resume after completion of a full study visit.

Visits for the dispensation of study drug only may be conducted at the clinic, or at an off-site location approved by the participant, and local (and U.S. if applicable) Ethics Committee(s), maintaining participant confidentiality. Every effort should be made to encourage the participant to return to the clinic for his/her regularly scheduled study visit. Detailed procedures for the allowance of off-site visits, telephone data collection, and study drug delivery will be provided in the SSP manual.

4.2 Study Drug Supply And Accountability

Acyclovir and matching placebo tablets will be manufactured for the study in accordance with U.S. federal regulations. The study product will be packaged in bottles containing 70 tablets each, and made available to the study sites. An additional supply of acyclovir tablets for episodic treatment will be provided to the pharmacies. The specifics regarding drug supply will be covered in more detail in the Study Specific Procedures Manual (SSP).

The study sites will receive study drug in sufficient quantity for the anticipated number of study participants. Shipments to sites will occur in batches over the course of the study as needed for study completion, and as storage capacity at each site allows. All supplies must be stored in a limited access area that is securely locked.

For purposes of inventory accountability, only individuals named as study investigator, subinvestigator or their designees will have access to the study drugs for the purpose of distribution of these supplies to persons enrolled in the study. The site pharmacist or designee must maintain complete records of all study drugs received and subsequently dispensed to study participants. Each participant will be given a 35-day supply of study drug (70 tablets) at each monthly scheduled study visit. The number of unused pills will be recorded at the next visit. Returned pills will not be re-dispensed to study participants. All unused study medications must be kept at the site until the end of the study unless otherwise instructed. At that time, information regarding the return or destruction of study medications will be supplied. The procedures to be followed will be detailed in the SSP.

4.3 Adherence Assessment

High adherence to acyclovir or placebo will be important for determining the efficacy of acyclovir in preventing HIV acquisition in this trial. The aim is to optimize and monitor adherence without excessive or unsustainable resource utilization that would make the results of this trial less generalizable in terms of implementation in developing countries.

At each monthly visit, study staff will assess participant compliance with the assigned treatment regimen through a structured interview and tablet count. Study product adherence and occurrence of genital lesions and other genital symptoms will be assessed via clinical interview and evaluation of the number of tablets

remaining in the bottles returned from their prior monthly supply of study drug. In addition, study staff will provide counseling about issues related to compliance with the study protocol, including counseling about what to do if a participant misses a dose.

4.4 Treatment Interruptions

Use of study drug may be interrupted if the investigator decides to withdraw the study drug temporarily due to safety concerns for the participant, in consultation with the protocol chairs, or if the participant is unable/unwilling to comply with the study procedures. If a female participant becomes pregnant during the study, she will be counseled about the available data on the safety of acyclovir during pregnancy and discontinued from further use of study drug for the duration of her participation in the study.

Whenever use of study drug is interrupted, this will be recorded on the appropriate CRF. Participants who interrupt treatment will be asked to continue to complete follow-up for endpoint determination.

4.5 Considerations For Women Who Become Pregnant During The Study

During the informed consent process, local site staff will discuss with female study participants the available data on acyclovir and pregnancy. Based on data from a pregnancy registry that followed 749 women with first trimester exposure to acyclovir, acyclovir use does not appear to result in an increased frequency or unusual distribution of birth defects as compared with the general population. Recent trials of daily acyclovir toward the end of pregnancy to prevent abdominal deliveries, and endorsement of such approach by the American College of Obstetricians and Gynecologists, indicate the lack of safety concerns with acyclovir. However, given limited data on safety of daily suppressive acyclovir throughout pregnancy in developing countries, women who become pregnant will discontinue use of study drug for the duration of their participation in the study; however, should the participant later have two consecutive negative pregnancy test results, she may re-start study drugs. Episodic treatment of open label acyclovir may be offered at the discretion of the clinician to women during their second and third trimesters of pregnancy. Urine pregnancy tests will be performed at quarterly visits and women will be asked about missed or late periods at monthly visits; those who report late menstrual periods will have urine pregnancy tests performed at that monthly visit. Pregnant women will be maintained in follow-up to ascertain study endpoint information. Clinical status of infants born to women who became pregnant while enrolled in the trial will be obtained by interview of the woman after delivery; if a woman exits the study prior to completion of her pregnancy, every effort will be made to obtain this information.

4.6 Concomitant Medications

Only concomitant prescription medications taken in relation to a Serious Adverse Event will be recorded on applicable study case report forms.

5 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Appendix I. Presented below is additional detail on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the study-specific procedures manual.

5.1 Screening Visit 1 (up to Day -60)

Written informed consent for screening will be obtained before any screening procedures are initiated. Eligibility for the study will be determined over the course of the Screening Visits and Enrollment Visit, based on HIV and HSV-2 testing and the inclusion/ exclusion criteria in sections 3.1 and 3.2. Participants at sites without rapid HIV testing will be told when they can return for their HIV test results. As noted in Section 3.4, for participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined.

Administrative, Behavioral, And Regulatory Procedures

- Obtain informed consent for screening.
- Collect demographic information.
- Obtain locator information.
- Administer behavioral eligibility checklist.
- Provide condoms.
- Schedule next visit.

Clinical Procedures

- Provide HIV and HSV-2 pre-test and risk reduction counseling.
- Collect blood.
- Provide all available test results and post-test counseling.

For female volunteers:

- Collect urine sample.

Laboratory Procedures

- HIV serology.
- HSV-2 serology.

For female volunteers:

- Urine pregnancy test.

5.2 Screening Visit 2 (between Day –60 and Enrollment)

Administrative, Behavioral, And Regulatory Procedures

- Provide information about the study.
- Update locator information.
- Provide condoms.
- Provide all available test results.
- Schedule next visit (unless the participant is enrolled during this visit).
- Obtain a second blood sample (only if repeat testing of HIV or HSV-2 is necessary).

Clinical Procedures

- Provide HIV and HSV-2 test results and post-test counseling.

5.3 Enrollment Visit - Baseline (Day 0)

Written informed consent for study participation will be obtained before any “on-study” procedures are initiated. For participants whose eligibility is not confirmed at this visit, the screening and enrollment process will be concluded when ineligibility is determined. If a screened volunteer returns more than 60 days after screening, he or she must repeat all screening procedures and a second enrollment visit will need to be scheduled.

Administrative, Behavioral, And Regulatory Procedures

- Obtain informed consent for study participation.
- Obtain random assignment.
- Update locator information.
- Obtain informed consent for storage of blood for future testing (optional)
- Provide condoms.
- Schedule next visit.

Clinical Procedures

- Obtain medical history.
- Administer risk behavior & sexual history questionnaire (must take place prior to risk reduction counseling).
- Administer questionnaire to assess symptomatic STDs, including genital ulcer disease, vaginal discharge and rectal symptoms.
- Administer questionnaire to assess 3-month history of symptomatic STDs, such as genital ulcer disease, vaginal discharge and rectal symptoms.
- Provide risk reduction counseling.
- Perform genital exam for signs of STDs.

- Collect specimens for STD baseline assessment:
 - > MSM:
 - ⇒ Rectal swab
 - ⇒ urine
 - > WSM:
 - ⇒ cervical and vaginal swabs
 - ⇒ urine
- Collect blood.
- Provide all available test results.
- Treat bacterial STDs, if clinically indicated, or refer for free treatment.
- Supply study drug, instructions, and adherence counseling.

Laboratory Procedures

- STD testing as follows:
 - > MSM:
 - ⇒ rectal gonorrhea culture.
 - ⇒ urine LE; if > trace or urethritis symptoms:
gonorrhea / chlamydia rapid, or NAAT, or urethral culture
 - > WSM:
 - ⇒ cervical swabs for gonorrhea and chlamydia (culture, or rapid, or NAAT)
 - ⇒ vaginal pH, wet mount for clue cells, whiff test and T. vaginalis
 - ⇒ gram stain (to be sent for batched reading at the end of the study), and
 - ⇒ trichomonas In-pouch™ local
 - ⇒ urine pregnancy test (with a sensitivity of 50 mIU/ml hCG).
- Storage of blood for confirmatory WB for HSV-2 antibodies at the University of Washington.
- Syphilis serology (including titer if initial test is reactive). Confirm with a treponemal specific test if initial test is reactive.
- Storage of genital lesions swabs at -20°C for later evaluation of etiology of genital ulcers and any other genital findings thought to be HSV-related by PCR testing at UW.
- Storage of left-over sera for CL and on-site specimen archive (to be tested for HIV, in the case of positive result on the first post-enrollment HIV test, and/or creatinine in the event of renal insufficiency).

The sites will have a chain of custody that will provide for the storage conditions of the samples. Each sample type will have a different processing and storage condition depending on the internal procedures the site uses.

5.4 Follow-Up Visits: Monthly (Months 1 To 12 or 18)

The following activities will take place **each month**:

Administrative, Behavioral, And Regulatory Procedures

- Update locator information.
- Provide study drug for following month and adherence counseling.
- Provide condoms.
- Schedule next visit.

Clinical Procedures

- Assess compliance by clinical interview and tablet count.
- Administer questionnaire to assess symptomatic STDs, including genital ulcer disease, vaginal discharge and rectal symptoms.
- Administer risk behavior & sexual history questionnaire (must take place prior to risk reduction counseling).
- Provide risk reduction counseling.
- Syndromically treat (or refer for free treatment) participant-reported symptomatic bacterial STDs.
- Provide all available test results.

For participants who report genital symptoms:

- Perform genital exam and collect swab of anogenital ulcers or other anogenital findings thought to be HSV-related, for end of study testing.
- Treat (or refer for free treatment) symptomatic bacterial STDs syndromically.

Note: For ongoing chronic conditions in the absence of new anogenital symptoms, the clinician should consult with the Protocol Chair and Co-Chair, FHI, and SCHARP to determine whether a genital examination is warranted.

For women who report missed or late menstrual period:

- Obtain urine for pregnancy test.

Laboratory Procedures

For swabs from participants with genital ulcers or other possible HSV-related anogenital findings:

- Storage of swabs for end of study testing to determine etiology by PCR at UW.

For women who report missed or late menstrual period:

- Urine pregnancy test.

Site staff should make every effort to have participants report to the clinic for study visits (Monthly, Quarterly, Interim, or Exit). Participants may be unable to report to the clinic for a study visit for a variety of reasons. Should the participant be willing, site staff will conduct the appropriate visit off-site (not in the clinic), attempting to perform all protocol-required visit procedures while maintaining participant confidentiality. If a participant refuses any protocol-specified procedures, this should be appropriately documented in the clinic/chart notes. An approved off-site/remote visit SOP must be in place prior to conducting off-site visits, and site staff may conduct no more than 3 such consecutive visits

Determining that an off-site visit is necessary will be done only after all other options for scheduling the visit have been explored (e.g., earlier or later office hours, interim visits). All scheduling efforts will be documented in the participant's chart notes and/or contact logs. The actual off-site visit may take place within the visit window or after the window is closed; if it occurs outside of any study window it is considered an interim visit (see the Study Specific Procedures Manual for interim visit procedures and for more detailed approval steps for such a visit).

In-person contact with participants is the preferred method of collecting study data. However, there may be rare circumstances in which telephone contact may be the only method available for collecting data.

Telephone data collection is permitted only when ALL of the following conditions have been met:

1. a participant is unable to travel to the study site (e.g., due to physical incapacitation, being out of state)
2. conducting an in-person visit prior to the next regular visit is impractical
3. the visit to be conducted is a monthly visit (Screening, Enrollment, Quarterly, and Exit Visits NOT allowed)
4. site staff can verify the participant's correct identity
5. the participant's confidentiality is protected

Determining that a telephone visit is necessary will be done only after all other options for scheduling the visit have been explored (e.g., earlier or later office hours, interim visits, off-site visits). All scheduling efforts will be documented in the participant's chart notes and/or contact logs. The

actual phone visit may take place within the visit window or after the window is closed; if it occurs outside of any study window it is considered an interim visit (see the Study Specific Procedures Manual for interim visit procedures and for more detailed approval steps for such a visit).

5.5 Quarterly Visits (Months 3, 6, 9, 12, and 15)

In addition to the monthly visit procedures, the following procedures will be performed **each quarter**:

Clinical Procedures

- Perform genital exam.
- Ascertain HIV risk behaviors by standardized interview prior to counseling (must take place prior to risk reduction counseling).
- Administer questionnaire to assess 3-month history of symptomatic STDs, such as genital ulcer disease, vaginal discharge and rectal symptoms
- Provide HIV and STD pre-test and risk reduction counseling
- Assess whether there has been an unexplained weight gain greater than 5 pounds (2.3 kilograms), AND unexplained decreased urine output.
- Collect blood.
- Provide all available test results and post-test counseling.

For participants with anogenital ulcers or other anogenital findings thought to be HSV-related:

- Perform genital exam and collect swab of anogenital ulcers, or other genital findings thought to be HSV-related, for end of study testing.

For female participants:

- Obtain urine for pregnancy test.

Laboratory Procedures

- HIV serology.
- Storage of left-over sera for CL and on-site specimen archive.
- For unexplained weight gain greater than 5 pounds (2.3 kilograms) AND unexplained decreased urine output, perform serum creatinine testing.

For swabs from participants with genital ulcers or other possible HSV-related genital findings:

- Storage of swabs for end of study testing to determine etiology by PCR at UW.

- For female participants:
- Urine pregnancy test.

5.6 Exit Visit (Month 12 or Month 18)

As stated in Section 2.3 above, participants will have scheduled exit visits either at Month 12 or Month 18, dependent upon the duration of their follow-up period.

The exit visit will be identical to the quarterly follow-up visit, however, in addition, syphilis (including titer if RPR is reactive) and treponemal serologies will be performed and sites will provide results by telephone, or in person according to when the result is available, and ensuring that results are communicated to the participant. Participants with positive serology will be referred according to local standard of care. No study medication will be dispensed at this visit.

For participants that are terminating early from the protocol due to HIV seroconversion, the syphilis test should be performed on the second or confirmatory blood draw if available. All other syphilis serology for non-seroconverters will be performed from the first blood draw.

5.7 Interim Visit (ad hoc)

An interim visit includes any visit taking place 5 days before or after a scheduled monthly visit date. The study specific procedures manual will state in detail how these visits will be handled, and the type of forms that should be completed depending on the nature of the visit. All visits will be documented in the participant's study record.

Participants will be instructed to report to the clinic whenever they have a question or a health problem, or if they need additional drug supplies or condoms. Some further reasons for interim visits may include:

- Adverse events;
- Problems with study regimen compliance or possible side effects;
- STD symptoms.

Participants also will be instructed to return to the clinic if they have symptoms of genital herpes between scheduled study visits (i.e., prodromal symptoms or anogenital lesions) for clinical evaluation and additional episodic treatment (acyclovir 400 mg tid for 5 days, as described in the 2002 CDC STD Treatment Guidelines). Genital lesions and other HSV-related anogenital findings will be swabbed and stored at -20° to subsequently assess etiology of these findings by PCR. Symptomatic bacterial STDs will be treated in U.S. sites according to 2002 CDC STD treatment guidelines and according to WHO or local Ministry of Health guidelines in non-US sites (i.e., free syndromic bacterial STD treatment will be offered or referral for free treatment to participants with vaginal and urethral discharge or genital ulcer disease).

5.8 Post-Test Visits For Persons Who Test HIV-Positive After Enrollment

Individuals who test HIV-positive after enrollment will be counseled about the interpretation of the test result, and will have another blood test (on a second sample) for repeat HIV antibody testing to confirm the initial HIV positive result. They will be counseled about clinical and social services for persons who are HIV-infected and methods to reduce the likelihood of transmitting HIV to others. They will be scheduled for another visit in approximately two to three weeks to receive the second HIV result and for additional counseling about their HIV infection. If HIV infection is confirmed, they will be referred to any services and other studies for HIV infected persons.

Participants who are confirmed HIV positive during the first HIV test after enrollment will have their enrollment sample tested at the Central Laboratory PCR if possible.

Additionally, participants who become HIV-infected while they are in the study will be offered enrollment into a six-month ancillary study to assess effect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”). This study will have its own protocol and Informed Consent Forms. Participants will cease to have study visits for the HPTN 039 main protocol and no further data will be collected from them for this protocol once their HIV-infection has been confirmed.

6 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chairs, study site investigators, NIAID Medical Officer, CORE Protocol Specialist, HPTN Statistical and Data Management Center (SDMC) Biostatistician and Protocol Operations Coordinator, 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 SDMC at SCHARP will prepare routine study progress reports and reports of Serious Adverse Events (SAEs) experienced by study participants (blinded to treatment assignment) for review by the Protocol Team. The team will meet via conference

call every two weeks during the initial period of study implementation, and additional ad hoc calls will be convened if required.

This study is subject to oversight and periodic review by an independent Data Safety Monitoring Board (DSMB) (see section 7.7).

6.2 Adverse Event Reporting Requirements

Acyclovir has been studied extensively and has a very well -established safety profile with minimal toxicity. Therefore, Adverse Event (AE) collection will be restricted to SAEs only. Information on intercurrent illnesses and AEs not considered serious will not be collected during the course of this study.

Medically significant adverse events for acyclovir are rare. The most severe of these is acute renal failure, which has only been reported in persons with co-morbidities and diseases that predispose them to acute renal failure. Additionally, acute renal failure occurred in patients receiving intravenous acyclovir or who had taken a large overdose of oral drug. The main clinical manifestation of acute renal failure in the setting of acyclovir has been seizures. Therefore, renal function will be assessed by serum creatinine in the setting of seizures or symptoms of possible renal insufficiency (i.e., unexplained weight gain and decreased urine output). Seizures and acute renal failure will be documented in the CRF when such an event occurs. Any seizure or other clinical evidence of renal failure will be considered a reportable SAE regardless of severity. Other SAEs that will be reported are those thought to be related to acyclovir administration, with consultation between the site PIs and Protocol Chairs.

Malaria, tuberculosis, bacterial and parasitic causes of gastroenteritis, dengue fever and other viral and parasitic febrile illnesses are endemic diseases prevalent among the populations under study. Therefore, they will not be routinely reported as SAEs during the course of this study. However, any hospitalization of a study participant, for any reason other than childbirth or elective caesareans, will be reported as an SAE.

Any participant who is determined to be HIV positive during follow-up will be terminated from the study. Since use of all study drug will be discontinued at the point of confirmed HIV seroconversion, deaths and SAEs after HIV infection will not be reported.

All deaths, including those resulting from endemic diseases, occurring while participants are on study will be documented in the CRFs and reported as an SAE.

All SAEs as specified above will be collected on appropriate CRFs. Details will be provided in the SSP.

7 STATISTICAL CONSIDERATIONS

7.1 Review Of Study Design

This is a phase III, multi-site randomized, double-blind, placebo-controlled trial of twice daily acyclovir for prevention of incident HIV infection among HIV-negative, HSV-2 seropositive heterosexual women and MSM at high risk for HIV infection.

Between 2820 and 3012 high-risk, HIV-negative, HSV-2 seropositive heterosexual women and MSM will be enrolled in the study. All efforts will be made to maintain randomized participants in follow-up for their total follow-up period of 12 to 18 months. During this time, participants will be scheduled for testing of HIV seroconversion every three months. In addition, participants will return for monthly visits to receive study drug, return bottles with unused study drug from the prior month for a tablet count, and receive counseling about issues related to compliance with the study protocol. Compliance with the study treatment regimen and occurrence of genital lesions and other genital symptoms will be assessed via clinical interview and evaluation of the number of doses remaining in the bottles returned from the previous month's supply of study drug.

7.2 Study Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective, serologically confirmed HIV infection (as determined by the algorithms in appendix II/III or as adjudicated by the Endpoint Review Committee) will be assessed as the primary study endpoint.

7.2.2 Secondary Endpoints

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

- Occurrence and frequency of genital ulcers
- Proportion of doses missed by study participants assigned to twice daily acyclovir and twice daily placebo.

7.3 Accrual, Follow-Up, And Sample Size

The overall target sample size for the trial is between 2820 and 3012 (1410 or 1506 in each arm). WSM are anticipated to be enrolled in Zimbabwe, South Africa, and Zambia. MSM will be enrolled in Lima, Iquitos, and Pucallpa, Peru; Seattle, WA, New York City, NY, and San Francisco, CA.

As summarized in the background and rationale sections, previous cohort and nested case control studies of HIV negative, HSV-2 seropositive and seronegative

individuals suggest that HSV-2 increases the risk of acquisition of HIV by a factor of 2.1 to 2.8, as summarized in the Background section. Assuming that therapy will be 80%-90% effective, this study should be designed to detect an overall relative risk of approximately 0.5. This relative risk may vary depending on whether or not the individual is in a stable partnership and the HIV status of partner(s). Women who become pregnant will be discontinued from study medication but will continue to be followed for endpoint information and will be included in their respective randomization group in the primary analysis. The effect of this policy will be to attenuate the expected relative risk towards 1.0 but the effect will be quite small, assuming only about 5% of women become pregnant (and assuming the pregnancies are distributed randomly throughout the follow up period). To accommodate this effect, we have designed the study for an expected RR of 0.51.

Estimates of number of study participants required to meet the objectives of this study depend on the following:

- 1) expected rate of HIV seroconversion in the placebo group;
- 2) the relative reduction of incident HIV infection associated with acyclovir treatment;
- 3) power and size (type I rate) of the study;
- 4) duration of follow-up.

To determine the number of infections (L) that must be observed to achieve a given power (1-β) for a given relative risk (r) and type I error rate (α), the following formula is used (Fleming and Harrington, 1991):

$$L = \left\{ \frac{Z_{1-\alpha/2} + Z_{1-\beta}}{0.5 \log(r)} \right\}^2$$

Assuming a two-tailed $\alpha = 0.05$ and $r = 0.51$, 93 HIV seroconversions are required to achieve 90% power to detect an overall difference between the acyclovir and placebo groups.

The number of HIV negative individuals per arm (N) that must be followed to achieve a given number of events (L) depends on the duration of follow-up (f), the incidence rate in the baseline group (I), the relative risk (r) and the proportion lost to follow-up (l_f). The relationship between number of persons per arm and number of events is

$$N_{\text{arm}} \approx L / [I * f * (1+r) * (1-l_f)]$$

We assume a 3.5% annual incidence rate over the first 12 months of enrollment and a 2.7% annual seroincidence rate in year 2 in WSM and MSM averaged across the participating US and non-US sites. We assume 8% lost to followup in the first year and 2% every 6 months thereafter. The relative risk is 0.51. The target followup is either 12 or 18 months as outlined in section 2.3 above. Newly

enrolled participants will be followed for 18 months after enrollment. In addition, the Protocol Team will evaluate the benefit and feasibility of extending follow-up for currently enrolled participants at each site (extending from 12 to 18 months). Following this evaluation, the re-consent process will be further examined in the first month of implementation at each site involved in the process. The protocol team will then determine whether a particular site will continue re-consenting participants at that site, and whether participants who re-consented to additional follow-up will be followed for 12 or 18 months. The sample size for the study will ultimately be determined by the proportion of currently enrolled participants who will be followed for 12 vs 18 months.

Given similar incidence rates and enrollment numbers in the two risk groups (WSM and MSM), similar numbers of HIV seroconversions are expected in each group. With an expected number of 46.5 seroconversions and all other assumptions as above, the power to detect a relative risk of 0.51 in either risk group individually is 0.63 (without any adjustment for multiple testing), whereas the power to detect a relative risk of 0.427 is 0.80.

7.4 Random Assignment

Participants who meet the study eligibility criteria will be offered enrollment in the study, and those willing to take part will be assigned at random to either twice daily 400 mg acyclovir suppressive therapy or twice daily placebo. The randomization code will be maintained by the research biostatistician at the HPTN SDMC. Randomization will be stratified by site.

Within each stratum, a variable-size block randomization scheme will be implemented. Randomization numbers will be provided to the sites. Tablets of blinded study drug will be pre-packaged in monthly supplies and labeled with the participant's study drug number.

7.5 Blinding

Both participants and study personnel will be blinded to the treatment assignment. Placebo tablets that appear identical to the active drug will be prepared and packaged in a manner that is indistinguishable from the active drug. In spite of these precautions, a limited number of participants in the placebo arm may suspect that they are not receiving active treatment if they continue to have symptomatic herpes lesions. Participants will be counseled that they should not infer their randomization arm on this basis, as HSV recurrences occasionally occur in the setting of daily suppressive therapy.

Blinding will remain in place until the study is closed and all data are cleaned and determined to be ready for final analysis. Premature unblinding may be indicated in rare circumstances when a physician decides it is necessary for the provision of medical treatment. Should such a circumstance occur, the investigator should contact the NIAID Medical Officer, Protocol Chair and the SDMC prior to unblinding. Participants who become unblinded by the investigators will continue to be followed for endpoint determinations.

7.6 Data Analysis

7.6.1 Primary Analyses

Descriptive analyses will be carried out to determine if the randomization has resulted in treatment and control groups that are similar with respect to key baseline measures. Although treatment will be randomized by site, the distribution of other risk factors, including measures of exposure to HIV (e.g. percent time using condoms, number of partners, sexual practices) will be described by treatment group.

The primary analysis will be a survival analysis using Cox's proportional hazards model with time to detection of HIV infection as the outcome. The analysis will be based on the "intent to treat" principle and the test will be two-sided. The analysis will be stratified by risk group (MSM and heterosexual women) and a pooled relative risk will be calculated. Endpoint information will continue to be collected on women who become pregnant after randomization (although they will be discontinued from treatment during pregnancy) and these women will be included in the analysis in their original randomization group. Any other individuals who choose to discontinue study medication will be asked for permission to continue to collect endpoint information on them. Their results will also be included in the analysis in their original randomization group. Individuals who go on open label suppressive medication ("cross-overs") will be included in the original randomization group. Similarly, individuals who choose to go on open label suppressive medication will be asked to provide endpoint information and will be included in the analysis in their original randomization group. Individuals who drop out of the study and refuse further testing prior to completion of follow-up will be treated as uninformatively censored as of their last valid HIV test.

Interim monitoring for the trial is described in section 7.7.

7.6.2 Secondary Analyses

The primary analysis of the treatment effect will be pooled over the two risk groups: MSM and heterosexual women. As a secondary analysis, separate Cox regressions will be used to estimate the relative risk and confidence interval for a treatment effect in the heterosexual women and MSM subgroups.

Adherence will be measured monthly. The analysis of adherence will be structured to allow us to estimate the adherence rate, test for a difference in compliance between the placebo and treatment groups, test for a trend over time in the compliance rate and examine the relationship between adherence and markers of risky sexual behavior. Specifically, a logistic regression with proportion of tablets taken each month as the outcome and treatment group, clustering of missed doses, time on study and markers of risky sexual behavior as predictors, will be used. Since the analysis will involve repeated observations on individuals, robust variance estimates⁵⁶, will be used to evaluate statistical significance and compute confidence intervals. Standard methods for model checking will be used to check the assumption of a linear trend over time in compliance.

The relationship between compliance and risk of incident HIV infection will also be examined. A proportional hazards model with HIV infection as the endpoint and self-reported adherence, subgroup (women versus MSM) and their interaction as covariates (time-dependent in the case of adherence) will be fit to the data from those individuals randomized to acyclovir. If the adherence is related to risky sexual behavior then the relationship between adherence and risk of HIV infection may be found to differ between MSM (where risk of HIV infection is also related to risky sexual behavior) and women (where risk of HIV infection is likely to be less related to the woman's sexual behavior and more related to her partner's behavior).

A proportional hazards model will be used to evaluate the effect of treatment arm on recurrence of genital ulcers. Since genital ulcers may recur multiple times over the course of follow-up, the model for recurrent events described by Anderson and Gill⁵⁷ will be used for this analysis. Individuals will be considered to be not-at-risk for recurrences when they are being actively treated syndromically for herpes due to symptoms. The robust variance formulation described by Lin⁵⁸ will be used to adjust the p-values and confidence intervals if multiple recurrences occur in one or more individuals. In addition, survival analysis will be performed with time to first recurrence as the dependent variable.

Through modeling, exploratory analyses will be conducted to assess the relative contribution of suppression of clinical versus subclinical

reactivation using acyclovir. To address this problem, a proportional hazards model will be fitted, with HIV seroincidence as the outcome and i) self-reported presence of genital ulcers within the past 1 month (yes/no, as well as a continuous variable), and ii) self-reported adherence to acyclovir (proportion of doses and days in which both doses were missed) as covariates. Actual use of acyclovir as opposed to randomization assignment will be used for this analysis. The (negative of the) coefficient for lesions in this model will provide a measure of the decrease in risk associated with suppression of clinical lesions. The coefficient for acyclovir will provide a measure of the protective effect of treatment after controlling for the presence of clinical lesions. Presumably, this additional protective effect is related to suppression of subclinical disease.

7.7 Interim Efficacy Analysis

An independent Data Safety and Monitoring Board (DSMB) will be convened for this study. The DSMB will meet approximately every six months throughout the study. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy, and 2) make recommendations to the study investigators and DAIDS concerning the continuation, modification, or termination of the trial. The DSMB will consider study-specific data as well as relevant background knowledge about the disease, test agent, and/or patient population under study.

Analyses presented to the DSMB will include comparability of acyclovir and placebo groups at enrollment, compliance with the intervention, loss to follow-up rates, adverse event reports, and HIV incidence by treatment arm. Based on these analyses, the DSMB will make recommendations on whether to continue or halt the study. The study will be halted if the seroincidence of HIV is statistically significantly lower in the acyclovir group than in the placebo group, i.e., that effectiveness of acyclovir has been demonstrated. An O'Brien-Fleming stopping rule will be used to control the overall type I error rate of the study and provide guidance to the DSMB⁵⁹. The DSMB will also recommend halting the study if the HIV seroincidence among acyclovir users is higher than placebo users to the extent that the hypothesis of protective efficacy of acyclovir is very unlikely. The DSMB will make recommendations regarding adjustment of sample size, as required, if HIV incidence or follow-up rates are different than anticipated.

HIV seroincidence and safety results by randomization group will be available only to DSMB members and not to the research investigators until the trial is completed.

Further information about the DSMB is contained in a separate DSMB charter.

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

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

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

Subsequent to initial review and approval, the responsible local Institutional Review Boards/Ethical Committees (IRBs/ECs) will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs 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.

In addition, the results of all DSMB reviews of the study will be provided to the IRBs/ ECs.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, one for study screening and one for enrollment, based on the templates in Appendices IV/V and VII/VIII, that describe the purpose of the screening and the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable local and US regulations. An additional informed consent document will be developed for storage and future use of blood based on the template in Appendix VI, and an additional informed consent will be developed to include the new HIPAA regulations (Appendix IX, US sites only). The study site is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Before documenting their informed consent, participants will be given the opportunity to ask questions until they fully understand the study. They will be told that they can return at any time to obtain more information or have further questions answered. Participants will be offered a copy of their informed consent forms. Study staff will document the informed consent process as instructed in the study-specific procedures manual.

8.3 Risks

Acyclovir has been extensively evaluated for toxicity and found to be a very safe drug. The only AEs associated with this acyclovir regimen are nausea and vomiting (0.4-11.3% vs 0.2-14.0% on placebo), diarrhea (1.0-3.6% vs. 0.3-2.9%), or headaches (0-7.4% vs. 0-9.5%) as observed in more than 7500 clinical trial patients who received acyclovir in doses ranging from 0.2-4.0 grams per day. Serious AEs have not been observed.

Venipuncture is sometimes associated with discomfort during phlebotomy, dizziness, and rarely, an infection at the site of phlebotomy. Examination and swabbing of genital lesions can also be associated with discomfort. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV and HSV-2 test results. Trained counselors will be available to help participants deal with these feelings. Individuals who learn that they have HSV-2 or HIV infection, may experience anxiety or depression related to their test results.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial of HSV-infected individuals 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.

8.4 Benefits

Participants randomized to acyclovir may experience fewer anogenital ulcers during therapy with the study drug. Regardless of randomization arm, participants will be offered (at the discretion of the Investigator or designee) acyclovir 400 mg tid for 5 days during episodes of genital herpes identified during the study.

In addition, participants will receive HIV and STD counseling, testing, and genital exams in this study, as well as STD treatment. They will learn how to protect themselves from becoming infected with HIV and other STDs. They will also be referred for further counseling and treatment, if applicable. Participants will be provided with male condoms throughout the study.

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 use of HSV-2 suppressive therapy to prevent sexual transmission of HIV.

8.5 Access To HIV-Related Care

8.5.1 Counseling

All risk-reduction and pre-test counseling will take place after behavioral data collection. At each visit, the health educator/counselor will provide the study participant with information on methods of HIV transmission and prevention, use of condoms, and pre- and post test HIV counseling, if applicable.

HIV pre-test, risk reduction, and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing timepoint. Counseling will be provided in accordance with local standards of practice at each study site. In accordance with the policies of the US National Institutes of Health, participants must receive their HIV test results in order to take part in this study. The study site will document its counseling policies and procedures prior to study implementation for purposes of staff training and study monitoring.

8.5.2 Care For Participants Identified As HIV-Infected

This study will identify persons who are infected with HIV, either as part of the study screening process or during follow-up of enrolled participants. The enrollment blood sample will be tested at the Central Laboratory via PCR technique to determine whether participants who seroconvert at their first HIV test after enrollment were HIV positive at the enrollment visit; this test result should be communicated to the participant(s). Study staff will provide participants with their HIV test results in the context of post-test counseling. They also will refer persons found to be HIV-infected to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. Individuals who become HIV-infected during the trial will be referred to local providers for HIV-specific care. In addition, protocol team members will work with the health ministries of study countries to determine means of increasing the subsequent availability of acyclovir. Lastly, participants who become HIV-infected while they are in the study will be offered enrollment into a six-month ancillary study to assess affect of HSV-2 suppression on HIV-1 levels in the first six months after infection (“viral set-point”) through a separate protocol, Informed Consent Forms, and maintenance of the initial treatment randomization . Participants will cease to have study visits for the HPTN 039 main study protocol and no further data will be collected from them for this protocol once their HIV-infection has been confirmed.

8.6 Participant Reimbursement

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 form, and approved by the IRB/ECs.

8.7 Confidentiality

All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets and/or in lockable areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

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

US Sites only: All Protected Health Information (PHI) will be protected according to the provisions of the Health Insurance Portability and Accountability Act and will only be used or disclosed as allowed by the Privacy Rule pursuant to relevant waivers, authorizations or as required by Federal law.

8.8 Access To Effective Therapy

An important consideration for this trial is the feasibility of providing acyclovir after completion of the study, if efficacy is demonstrated. This discussion will require involvement of global HIV prevention and other funding agencies (such as UNAIDS, USAID, and WHO), site investigators, in-country public health officials, community representatives, and ethicists. Currently, WHO and UNAIDS are discussing discounted pricing for generic acyclovir for countries in which HSV-2 appears to be a significant cause of genital ulcer disease, and a possible risk for HIV transmission, based on a WHO/UNAIDS/LSHTM co-sponsored meeting on HIV and HSV-2 in February 2001 (HSV-2 Programmatic and Research Priorities in Developing Countries; www.who.int/HIV_AIDS/). Acyclovir is on the WHO Essential Drug List. Protocol Team investigators will initiate discussions with drug manufacturers and donor agencies in order to maximize access to acyclovir after study termination in the event the intervention is effective. During the third year of the study, the investigators will consider

issues related to “scaling up” the acyclovir intervention, and assess cost-effective approaches including targeting of the intervention to the highest-risk populations.

8.9 Communicable Disease Reporting Requirements

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

8.10 Study Discontinuation

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

9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (LL):

- Blood for HIV, HSV-2 and syphilis serology.
- Urine and genital swabs for STD testing.
- Urine for pregnancy testing.

Each study site will adhere to standards of good laboratory practice, the HPTN Manual of Laboratory Operations, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS).

9.2 Central Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the HPTN Central Laboratory (CL) and/or University of Washington Virology Laboratory:

- Swabs of genital lesions, frozen at -20°C , for PCR (UW).
- Sera for WB confirmation of HSV-2 positive status (UW)
- Sera for confirmation of HIV positive status after enrollment (CL, UW).
- Stored sera for central specimen archive (CL).

Each study site will adhere to standards of good laboratory practice and the HPTN Manual of Laboratory Operations for proper collection, processing, labeling, and transport of specimens for the CL. All specimens will be shipped in accordance with IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

9.3 Quality Control And Quality Assurance Procedures

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

Throughout the course of the study, the HPTN CL will retest 10% of all HSV-2 positive enrollment samples for HSV-2 antibody for quality assurance (QA) purposes. The HPTN CL and University of Washington Virology Laboratory will retest all HIV antibody-positive seroconversion specimens. The HPTN CL will test an equal number of HIV negative samples for HIV antibody. SCHARP will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the CL. All specimens will be shipped in accordance with the HPTN Manual of Laboratory Operations and IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

The CL will test the specimens for HIV antibody and SCHARP will compare the results of their tests with the results obtained by the local labs. CL staff will follow-up directly with site staff to resolve any quality assurance problems identified through this process.

HSV-2 WB tests will be conducted at the University of Washington in Seattle, WA, USA on all samples for enrolled participants at all sites to confirm their HSV-2 positive status.

9.4 Specimen Storage And Possible Future Research Testing

Study site staff will store all sera and swabs from genital lesions collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for their blood to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

9.5 Biohazard Containment

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

10 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

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

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

10.2 Study Coordination

Study implementation will be directed by this protocol as well as the SSP manual. The SSP manual will outline procedures for conducting study visits; data and forms processing; SAE assessment, management and reporting; dispensing study drugs and documenting product accountability; and other study operations.

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

Close cooperation between the study Investigator, NIAID Medical Officer, Protocol Specialist, Protocol Operations Coordinator, Biostatistician, Data Managers, and other study team members will be necessary in order to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and SAE incidence will be monitored closely by the study team. These rates also will be evaluated by representatives of the HPTN CORE and SDMC on a regular basis.

A Protocol Clarification Team — comprised of the Protocol Chair, Medical Officer, and Biostatistician and designees— will address issues related to study eligibility and SAE management and reporting as needed to assure consistent case management, documentation, and information sharing.

10.3 Study Monitoring

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

- verify compliance with human subjects and other research regulations and guidelines;

- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, CL, NIAID, and US and in-country government and regulatory authorities. Acceptable source documentation for each site will be specified prior to study start. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) prior to implementing the amendment except when necessary to protect the safety, the rights, or welfare of participants, or to eliminate apparent immediate hazards to participants.

10.5 Investigator's Records

The study site investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least three years after the completion of the study, unless directed otherwise by the HPTN CORE. Study records include administrative documentation — including site registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.6 Use Of Information And Publications

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

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APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR HPTN 039

		VISITS					
PROCEDURES		Screening Visit 1 (Up To Day -60)	Screening Visit 2 (Up To Enrollment)	Enrollment Visit (Day 0)	Follow-Up Visit (Monthly 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 Months)	Follow-Up Visit (Quarterly At 3, 6, 9, 12, 15 Months)	Exit Visit (12 or 18 Months)
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES							
	Obtain informed consent for screening	X					
	Collect demographic information	X					
	Obtain/ update locator information	X	X	X	X	X	X
	Administer eligibility checklist	X					
	Obtain informed consent for enrollment and optional storage of blood			X ¹			
	Assign randomization to study drug			X ¹			
	Provide condom counseling and distribute condoms	X	X	X	X	X	X
CLINICAL PROCEDURES							
	Provide HIV/STD pre-test counseling	X				X	X
	Provide HIV/STD risk reduction counseling	X		X	X	X	X
	Provide test results & HIV/STD post test counseling (as applicable)	X	X		X ²	X	X
	Collect unused study drug from previous month				X	X	X
	Evaluate remaining product dose & administer clinical interview for compliance assessment				X	X	X
	Provide adherence counseling			X	X	X	
	Obtain medical history			X		X	X
	Administer risk behavior & sexual history questionnaire			X	X	X	X
	Administer genital symptoms questionnaire			X	X	X	X
	Collect Blood	X	X ³	X		X	X
	Perform genital exam for STDs			X	X ³	X	X
Collect Samples for STD and pregnancy Baseline Assessment							
<i>For MSM:</i>	Rectal swabs and urine			X			
<i>For WSM:</i>	Vaginal and cervical swabs			X			
	Urine sample	X		X	X ³	X	X
	Collect swabs for participants with genital ulcers			X ³	X ³	X ³	X ³
	Treat, or refer for treatment, bacterial STDs (if clinically indicated)/syndromic management			X	X	X	X
	Dispense study product and instructions for use			X	X	X	
LAB PROCEDURES							
	HIV serology	X		X ³		X	X
	HSV-2 serology	X ¹					
	Syphilis serology (including titer)			X			X
	PCR for end of study testing for genital ulcer etiology (stored and later shipped to CL)			X ³	X ³	X ³	X ³
	Assess SAEs/ Serum Creatinine if seizures or symptoms of renal insufficiency (unexplained weight gain AND decreased urine output)					X	X
	Stored Sera (long term) for shipment to CL						
<i>For MSM:</i>	Rectal gonorrhea culture			X			
	Urine leukocyte esterase (LE) if positive (> trace +): gonorrhea/ chlamydia (urine NAAT, or rapid, or urethral swab culture)			X			
<i>For WSM:</i>	Cervical gonorrhea and chlamydia culture, or rapid, or NAAT			X			
	Vaginal pH, Gram Stain & culture (InPouch™) for trichomonas and wet mount (with whiff test)			X			
	Urine for pregnancy	X		X	X ³	X	X

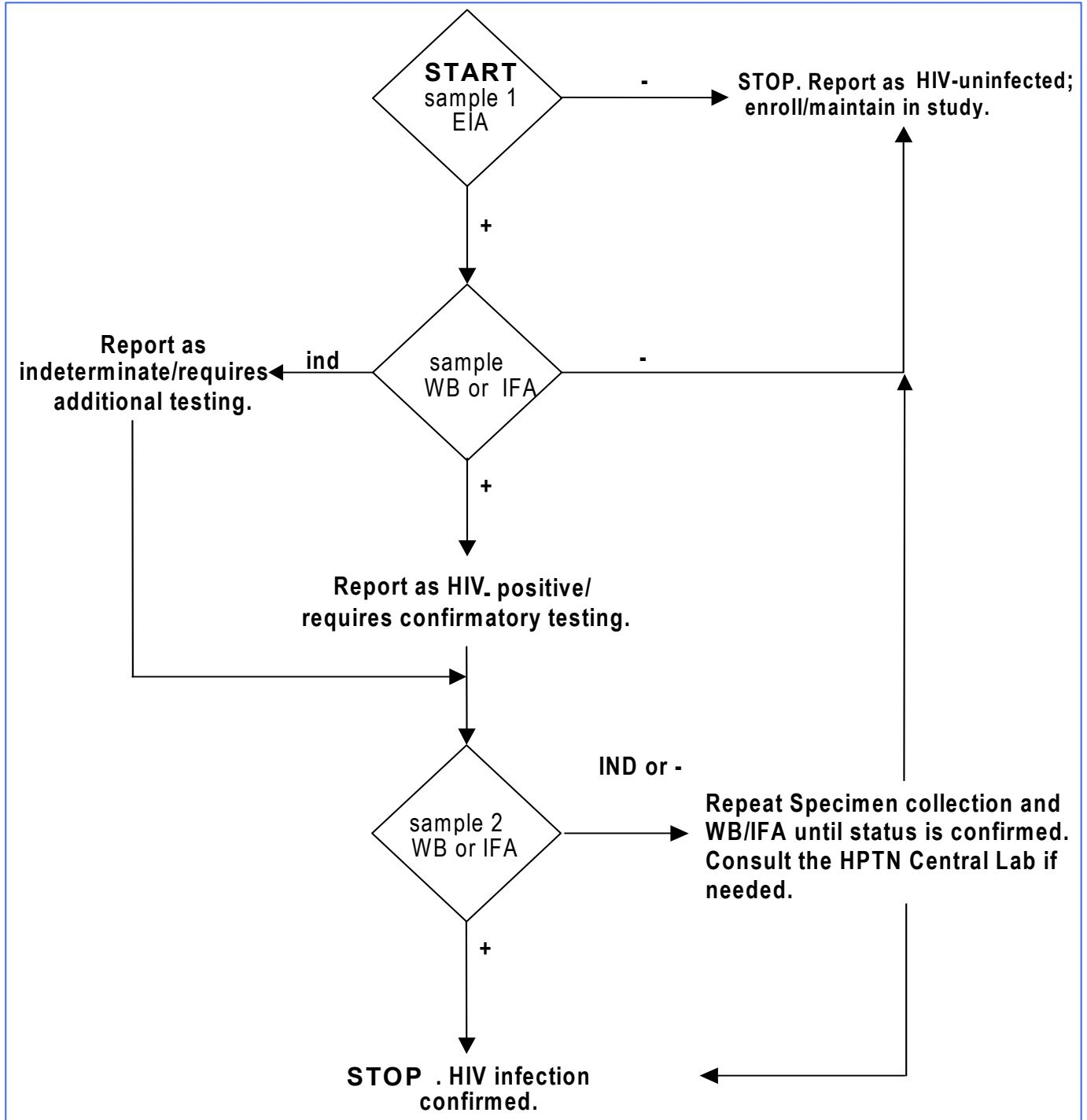
¹ If a screened volunteer returns more than 60 days after screening, he or she will need to repeat all screening visit procedures.

² Only if this visit follows a quarterly visit, when blood was drawn for HIV testing.

³ if indicated

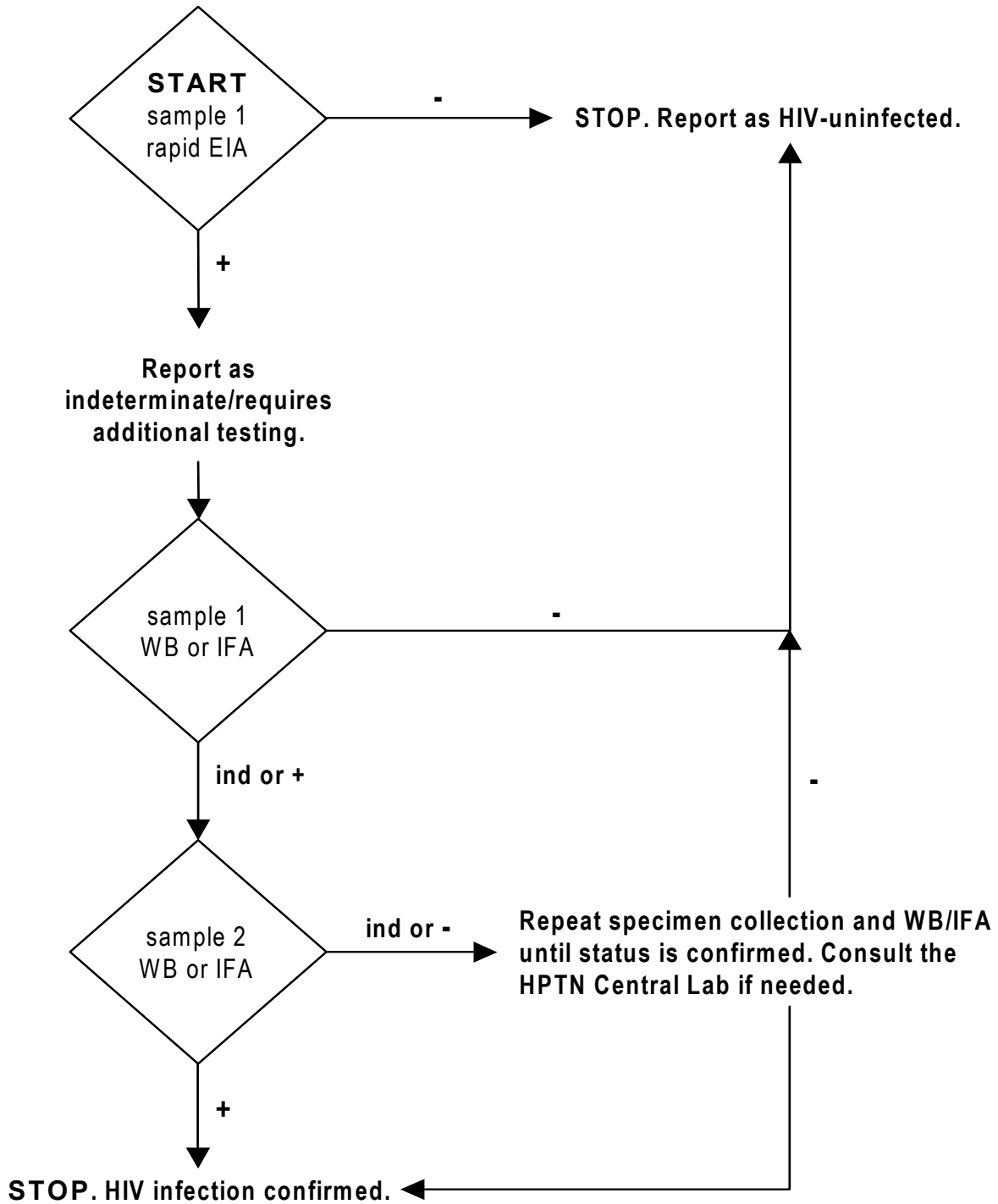
APPENDIX II: HIV TESTING ALGORITHM (NON-RAPID TESTING)

[NOTE: at screening only, confirmatory second samples will only be drawn in case of discordant test results on the first sample or if mandated by local law.]



APPENDIX III: HIV TESTING ALGORITHM (RAPID TESTING)

[NOTE: at screening only, confirmatory second samples will only be drawn in case of discordant test results on the first sample or if mandated by local law.]



APPENDIX IV: SAMPLE INFORMED CONSENT FOR SCREENING AT SITES ENROLLING MEN

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September, 2004

PRINCIPAL INVESTIGATOR: (US and/or in-country) PHONE:
[Complete with site-specific information]

INTRODUCTION:

You are being asked to volunteer for screening tests, including blood tests, examinations, and an interview. The purpose of these screening tests is to determine if you are eligible for a research study. This research study is about an approved and widely used drug for genital herpes, called acyclovir. Some people may not be able to join the research study because of information found during the screening visits.

Genital herpes is caused by a virus called “herpes simplex virus 2” or “HSV-2”. HSV-2 is passed from one person to another during sex, so it is called a “sexually transmitted disease” or “STD”. Many people do not realize that they have genital herpes. The purpose of this study is to learn if acyclovir helps prevent infection with the human immunodeficiency virus (HIV) by treating genital herpes infection. HIV is the virus that causes AIDS.

Before you decide whether or not you want to take part in the screening tests, you need to know the purpose of the screening tests, the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form provides information about the screening tests. The study staff will discuss the screening with you, and will answer your questions. After the screening has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the screening, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

Please note that:

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

you agree to have the screening tests, you do not have to join the research study.

PROCEDURES:

If you agree to participate in the screening test, you will have two visits here about two weeks apart:

- **The visit today (Screening Visit I)**
you will be interviewed;
you will receive counseling;
you will have blood drawn for HSV-2 and HIV antibody tests (your HIV antibody test results may be available during this visit; if so, you may receive counseling and your HIV antibody test results).
- **A visit in about 2 weeks (Screening Visit II) –**
you will receive counseling and your test results (if you did not receive your HIV antibody test results during Screening Visit I, you will receive these results during this visit);
you will find out if you are eligible for the study.

Screening Visit I:

Your first visit will last about one hour and a half. The study staff will ask you where you live and some other questions about yourself. They will ask questions about your sexual history. You may be embarrassed by these questions.

You will be counseled about HIV and other STDs and provided with free condoms. You will also be counseled about getting an HIV and HSV-2 blood tests.

The study staff will draw 10 ml of blood (less than 1 tablespoon) from you. Your blood will be tested for HIV and HSV-2. You may receive the results of your HIV test as well as further information and counseling at this visit.

If your HIV test result is available today and it shows that you are infected with HIV, you cannot participate in this study. If you have HIV, the study staff will talk with you about this test result and what this means for you. You will be referred for care and additional counseling and other studies available to you. Sometimes an HIV test result is not clearly positive but is also not negative. This is called an “indeterminate result”. In this case we will draw your blood and test it again until we know for sure whether you are or are not infected with HIV.

Your HSV-2 (and HIV if not presented to you today) test will be results will be available about 14 days later. You will be scheduled to come back here to receive your results at that time.

Screening Visit II (after 14-60 days):

You will receive counseling, further information about the study, and the results of your HIV (if not presented to you during Screening Visit I) and HSV-2 tests at this visit. You will be told whether you are eligible for the study.

If your HIV test result shows that you are infected with HIV, you cannot participate in this study. If you have HIV, the study staff will talk with you about this test result and what this means for you. You will be referred for care and additional counseling and other studies available to you. Sometimes an HIV test result is not clearly positive but is also not negative. This is called an “indeterminate result”. In this case we will draw your blood and test it again until we know for sure whether you are or are not infected with HIV.

Sometimes an HSV-2 test result gives a low positive result. This means the test result is not clearly positive but is also not negative. You will not be eligible at this time to participate in the study if you have a low positive result, unless site staff has confirmed that you have HSV-2 by sending a sample of your blood to a laboratory at the University of Washington in Seattle, USA. Should your HSV-2 test result give a low positive result, and we are unable to confirm your HSV-2 serostatus at the University of Washington, we will ask you to come back for another test in 2 months to determine whether you are or are not infected with HSV-2. You may be eligible for the study at that time, depending on those HSV-2 test results.

If you are eligible, the study staff will fully explain the research study to you and answer any questions that you have. If you decide to participate, you will be asked to sign another consent form to be enrolled in the actual study.

RISKS and/or DISCOMFORTS

Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare.

The counseling about HIV, HSV-2, and other diseases may cause you to worry. If the tests show that you have HIV, knowing your HIV status may cause you anxiety. If you find out you have HSV-2, knowing your HSV status may also cause you anxiety. We will make every effort to protect your confidentiality during the screening tests. However, it is possible that others may learn of your participation here and think you are infected with HIV or HSV-2, or are at high risk for infection with HIV or HSV-2. Because of this, you could have trouble finding or keeping a job. You could also have problems being accepted in your family and community.

POTENTIAL BENEFITS:

You may receive no direct benefit from these tests. However, you will receive information about whether you are infected with HIV and HSV-2, and available resources for care. You will also receive counseling about how to protect yourself and your partner from infection with HIV and STDs. You will be offered free condoms and free treatment for STDs.

COSTS TO YOU:

There is no cost to you for the HIV tests or any of the other tests or exams related to the study.

COMPENSATION FOR YOUR TIME AND TRAVEL:

You will receive [sites insert site-specific amount of money] to pay for your transport costs and time away from work for the screening visits.

CONFIDENTIALITY:

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

Your records may be reviewed by the sponsor of the study (U.S. National Institutes of Health (NIH)) and their representatives, the local government or regulatory agency, **insert name of site** IRB, and the study monitors, supporting this study.

RESEARCH-RELATED INJURY:

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

For questions about your rights as a research subject, contact:

- **[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this screening, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

**APPENDIX V: SAMPLE INFORMED CONSENT FOR SCREENING AT SITES
ENROLLING WOMEN**

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September, 2004

**PRINCIPAL INVESTIGATOR: (US and/or in-country) PHONE:
[Complete with site-specific information]**

INTRODUCTION:

You are being asked to volunteer for screening tests, including blood tests, examinations, and an interview. The purpose of these screening tests is to determine if you are eligible for a research study. This research study is about an approved and widely used drug for genital herpes, called acyclovir. Some people may not be able to join the research study because of information found during the screening visits.

Genital herpes is caused by a virus called “herpes simplex virus 2” or “HSV-2”. HSV-2 is passed from one person to another during sex, so it is called a “sexually transmitted disease” or “STD”. Many people do not realize that they have genital herpes. The purpose of this study is to learn if acyclovir helps prevent infection with the human immunodeficiency virus (HIV) by treating genital herpes infection. HIV is the virus that causes AIDS.

Before you decide whether or not you want to take part in the screening tests, you need to know the purpose of the screening tests, the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form provides information about the screening tests. The study staff will discuss the screening with you, and will answer your questions. After the screening has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the screening, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

Please note that:

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

PROCEDURES:

If you agree to participate in the screening test, you will have two visits here about two weeks apart:

- **The visit today (Screening Visit I)**
 - you will be interviewed;
 - you will receive counseling;
 - you will have blood drawn for HSV-2 and HIV antibody tests; (your HIV antibody test results may be available during this visit; if so, you will receive counseling and your HIV antibody test results).
 - you will give urine for a pregnancy test
- **A visit in about 2 weeks (Screening Visit II)**
 - you will receive counseling and your test results;
- (if you did not receive your HIV antibody test results during Screening Visit I, you will receive these results during this visit);
 - you will find out if you are eligible for the study.

Screening Visit I:

Your first visit will last about one hour and a half. The study staff will ask you where you live and some other questions about yourself. They will ask questions about your sexual history. You may be embarrassed by these questions.

You will be counseled about HIV and other STDs and provided with free condoms. You will also be counseled about getting an HIV and HSV-2 blood tests.

The study staff will draw about 10 ml of blood (less than 1 tablespoon) from you. Your blood will be tested for HIV and HSV-2. You may receive the results of your HIV test as well as further information and counseling at this visit.

If your HIV test result is available today and it shows that you are infected with HIV, you cannot participate in this study. If you have HIV, the study staff will talk with you about this test result and what this means for you. You will be referred for care and additional counseling and other studies available to you. Sometimes an HIV test result is not clearly positive but is also not negative. This is called an “indeterminate result”. In this case we will draw your blood and test it again until we know for sure whether you are or are not infected with HIV.

Your HSV-2 (and HIV if not presented to you today) test result will be available about 14 days later. You will be scheduled to come back here to receive your result at that time.

You will be given a urine pregnancy test. If you are pregnant you will not be able to join the study, and you will be referred for pregnancy services.

Screening Visit II (after 14-60 days):

You will receive counseling, further information about the study, and the results of your HIV (if not presented to you during Screening Visit I) and HSV-2 tests at this visit. You will be told whether you are eligible for the study.

Sometimes an HSV-2 test result gives a low positive result. This means the test result is not clearly positive but is also not negative. You will not be eligible at this time to participate in the study if you have a low positive result, unless site staff have confirmed that you have HSV-2 by sending a sample of your blood to a laboratory at the University of Washington in Seattle, USA. Should your HSV-2 test result give a low positive result, and we are unable to confirm your HSV-2 serostatus at the University of Washington, we will ask you to come back for another test in 2 months to determine whether you are or are not infected with HSV-2. You may be eligible for the study at that time, depending on those HSV-2 test results.

If you are eligible, the study staff will fully explain the research study to you and answer any questions that you have. If you decide to participate, you will be asked to sign another consent form to be enrolled in the actual study.

RISKS and/or DISCOMFORTS

Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare.

The counseling about HIV, HSV-2, and other diseases may cause you to worry. If the tests show that you have HIV, knowing your HIV status may cause you anxiety. If you find out you have HSV-2, knowing your HSV status may also cause you anxiety. We will make every effort to protect your confidentiality during the screening tests. However, it is possible that others may learn of your participation here and think you are infected with HIV or HSV-2, or are at high risk for infection with HIV or HSV-2. Because of this, you could have trouble finding or keeping a job. You could also have problems being accepted in your family and community.

POTENTIAL BENEFITS:

You may receive no direct benefit from these tests. However, you will receive information about whether you are infected with HIV and HSV-2, and available resources for care. You will also receive counseling about how to protect yourself and your partner from infection with HIV and STDs. You will be offered free condoms and free treatment for STDs.

COSTS TO YOU:

There is no cost to you for the HIV tests or any of the other tests or exams related to the study.

COMPENSATION FOR YOUR TIME AND TRAVEL:

You will receive [sites insert site-specific amount of money] to pay for your transport costs and time away from work for the screening visits.

CONFIDENTIALITY:

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

Your records may be reviewed by the sponsor of the study (U.S. National Institutes of Health (NIH)) and their representatives, the local government or regulatory agency, **insert name of site** IRB, and the study monitors, supporting this study.

RESEARCH-RELATED INJURY:

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

For questions about this study or a research-related injury, contact:

- **insert name of the investigator or other study staff**
- **insert telephone number and physical address of above**

For questions about your rights as a research subject, contact:

- **insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site**
- **insert telephone number and physical address of above**

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this screening, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VI: SAMPLE INFORMED CONSENT FOR THE STORAGE OF SPECIMENS OBTAINED WHILE PARTICIPATING IN A RESEARCH TRIAL

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September, 2004

INTRODUCTION

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

HOW WILL YOU GET THE SAMPLES FROM ME?

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

HOW WILL YOU USE MY SAMPLES?

Your samples will only be used to look for additional evidence of infection with HIV or other agents, damage caused by infection, or your body's response to infection (such as examining cells, proteins, and other chemicals in your body).

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that a specific test result would provide important information for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number.

Your samples will not be sold or used directly to produce commercial products. Research studies using your samples will be reviewed by the National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board).

HOW LONG WILL YOU KEEP MY SAMPLES?

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

HOW WILL MY SAMPLES BE STORED?

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

DOES STORAGE OF MY SAMPLES BENEFIT ME?

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

WHAT ARE THE RISKS?

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

WHAT ABOUT CONFIDENTIALITY?

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

We will do everything we can to protect your privacy. Also, any publication of the research will not use your name or identify you personally.

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

In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

WHAT ARE MY RIGHTS?

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

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

WHAT DO I DO IF I HAVE QUESTIONS?

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

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

SIGNATURE PAGE

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

I agree to have my left over blood samples stored and tested for future research related to HIV infection.

_____ Yes

_____ No

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VII: SAMPLE INFORMED CONSENT FOR ENROLLMENT AT SITES ENROLLING MEN

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September, 2004

PRINCIPAL INVESTIGATOR: (US and/or in-country)PHONE: **[Complete with site-specific information]**

INTRODUCTION:

You are being asked to take part in the research study to find out whether suppression of the genital herpes virus makes it less likely to become HIV-infected. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is **[insert name of Principal Investigator]**. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information and the study. We want you to know the purpose of the tests, the possible risks and benefits, and what will be expected of you if you decide to participate. You are free to ask questions about this study at any time. If you agree to take part in this study after the study has been fully explained to you, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy to keep. This process is called informed consent.

Please note that:

- Your participation in this research 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 standard medical care.

PURPOSE OF THE STUDY:

This is a study of a drug called acyclovir that is used to treat genital herpes. Genital herpes is caused by a virus called “herpes simplex virus 2” or “HSV-2”. Acyclovir is approved in the United States, Europe, and **[enter country specific information, if applicable]** for treatment of genital herpes, and has been used in over 40 million people. The HSV-2 virus is passed from one person to another during sex. Your blood test from the screening visit indicates that you have HSV-2. HSV-2 causes genital herpes, but many people who have HSV-2 do not know that they have it. In some people, HSV-2 infection causes sores in the genital area. In all people with HSV-2 infection, the virus can be present in the genital area and the infection can be spread to other sexual partners.

There is no cure for genital herpes, but drugs like acyclovir can help sores heal more quickly. When taken daily, acyclovir can also prevent genital sores among people who have HSV-2.

A number of studies have shown that people with HSV-2 infection have a higher chance to become infected with the human immunodeficiency virus (HIV- the virus that causes AIDS), if they have sex with a person who has HIV. This may be because HSV-2 causes small breaks in the skin or surface in the genital area. It also attracts inflammatory cells to move to the genital area. These are the cells that HIV infects. Acyclovir is not a treatment for HIV. This study is being done to find out if acyclovir helps prevent HIV infection in people who have HSV-2 infection.

To learn this, we will enroll between 2820 and 3012 men and women in Zimbabwe, Zambia, Peru, South Africa, and the United States. It will take about 2 years to enroll all participants at each site. Approximately [X men (**sites in Peru/ United States**)] will be enrolled at this site. Each participant will be followed for either 12 or 18 months after enrollment.

If you agree to participate in the research study, you will be asked to sign or make your mark on this consent form in front of a witness. We will offer you a copy of the form to keep.

PROCEDURES:

You will be assigned to one of two groups. One group will receive acyclovir, the active drug. The other group will receive placebo. A placebo pill looks the same as the acyclovir pill, but does not have any drug or other medicine in it. The kind of pill you will get is called a tablet because of how it looks. Which group you are assigned to will be decided by chance (like tossing a coin). Half the people in the study will receive acyclovir and the other half will receive placebo. Neither you nor the study staff will know which group you are in.

INSTRUCTIONS FOR SITE STAFF: PLEASE READ SECTION A IF THIS PARTICIPANT IS BEING ENROLLED UNDER PROTOCOL VERSION 3.0 OR HIGHER. PLEASE READ SECTION B IF THE PARTICIPANT WAS ENROLLED UNDER A PROTOCOL VERSION EARLIER THAN 3.0 AND IS BEING ASKED TO EXTEND THE LENGTH OF HIS PARTICIPATION. PLEASE READ SECTION C IF THE PARTICIPANT WAS ENROLLED UNDER A PROTOCOL VERSION EARLIER THAN 3.0 BUT IS NOT BEING ASKED TO EXTEND THE LENGTH OF HIS PARTICIPATION.

SECTION A:

You will be in the study for 18 months. During this time you should take one tablet of acyclovir or placebo by mouth every morning and one tablet every evening.

You will be asked to return to the clinic once every month to pick up your next month's supply of tablets, for a total of 18 monthly visits after today.

SECTION B:

You were enrolled prior to the extension of study participation from 12 to 18 months. It would be beneficial to the study if you would agree to remain in the study for a further six months, making your total participation time 18 months following enrollment. Please check and initial below whether you are willing and agree to participate in the study an additional 6 months for a total of 18 months following enrollment. Your choice will not affect the care provided to you by participation in this clinical trial.

YES, I agree to continue to participate in the study up to Month 18.

NO, I wish to end my study participation at Month 12.

SECTION C:

You will be in the study for 12 months. During this time you should take one tablet of acyclovir or placebo by mouth every morning and one tablet every evening.

You will be asked to return to the clinic once every month to pick up your next month's supply of tablets, for a total of 12 monthly visits after today.

Enrollment Visit (Today):

This visit will last about one hour and a half. We will ask you questions about your health and about your sexual history. You may choose not to answer any of the questions if you wish. We will counsel you about protecting yourself and your partner from HIV and other STDs and offer you condoms.

You will also have a genital exam (which means, we will examine your penis and your anus) to see whether you have signs of any infections passed during sex. We will draw 15 ml of blood (about 1 tablespoon) with a needle from you. Your blood will be tested for another STD called syphilis. If we find you have syphilis or any other bacterial STD, we will tell you as soon as possible and give you medicine free of charge or refer you to a clinic where you will be provided free treatment.

A sample of your blood will be sent to the University of Washington for HSV-2 confirmation and potentially be used for future toxicity management.

Should your test results show that you have become HIV positive during your first follow-up HIV test, we will test your enrollment sample to see whether or not you had HIV when you enrolled in the trial. We will communicate this test result to you.

We will also swab your rectum and collect a urine sample from you to test for additional STDs.

We will give you a bottle containing enough study tablets to last you for one month and tell you exactly how and when to take them. Before you leave, we will schedule your next visit for one month later.

Acyclovir For Genital Sores During The Study

If you have ano and/ or genital sores during the study, and you clinician feels that this will be beneficial to your health, you will be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with your study medication. This is the standard dose of acyclovir that is used to treat a recurrence of genital herpes.

Monthly Visits

You will come back to the clinic every month for a study visit. These visits will last about a half hour. You need to bring back your study tablet bottle and any remaining study tablets. The following will happen at each visit:

- We will collect your tablet bottle from the last visit.
- We will ask you questions and talk with you about taking the study tablets.
- You will receive new tablets for the next month.
- We will ask you questions about your health and your sexual activity since the last visit.
- If you have symptoms of STDs or an ano/genital sore, we will examine your genitals and swab the sore to test for STDs. If you have a bacterial STD you will receive treatment (or referral to a local clinic that provides free treatment).
- We will counsel you about protecting yourself and your partner from HIV and other STDs and offer you condoms.
- If you had blood drawn for HIV testing at the previous visit, we will give you your test results and information and counseling about what the results mean.

Every Three Month Visits

Every three months, all monthly procedures will take place, and there will be additional procedures at these visits. Therefore, the visits will last approximately one hour altogether. The following will happen in addition to the monthly procedures:

- You will be counseled about having an HIV test.
- We will draw 15 ml of blood (about 1 tablespoon) with a needle from you. Your blood will be tested for HIV.
- We will examine you for STDs. If you have genital sores, we will swab your genital area.
- We will provide you with all available test results.

Each time we collect blood from you for HIV testing, we will freeze the blood that is left over from your test here at [site/ clinic name]. It may be necessary to re-test these samples for results during the study.

We would also like to keep your frozen blood here after the study is over, and possibly test it in the future. A separate consent form asks for your permission to do this.

You will receive your HIV test result at your next monthly visit, along with information and counseling about what the test results mean. If your HIV test result is positive, we will contact you and ask you to come back to the clinic before the next scheduled date.

Sometimes an HIV test result is not clearly positive but is also not negative. In that case we will test your blood again until we know for sure whether or not you are infected with HIV.

If your HIV test result shows that you are infected with HIV, you will no longer be followed in this study. If you become HIV-infected, the study staff will talk with you about this test result and what this means for you. The staff will obtain a second blood test to confirm the initial positive test and you will be referred for care and additional counseling and other studies and services available to you.

In addition, if your HIV test result shows that you are infected with HIV you will be offered enrollment into a study aimed at determining whether daily acyclovir lowers the amount of HIV virus in your blood during the first six months after you become HIV-infected. This is based on studies that have found that genital herpes may increase HIV levels in early HIV infection. This study will last approximately six additional months and will have its own informed consent forms for you to review and sign should you decide to join this study.

Contact Outside of the Clinic

It may be necessary for site staff members to visit you at your home or another location as or to contact you via telephone as part of the study. The reasons for this include that you have missed visits or indicate that you are not able to make study visits to the research site. Your site counselor and retention specialists can explain the procedures to maintain your confidentiality in greater detail. Please check one of the boxes below as to whether site staff can visit you outside of the clinic. Your choice will not affect the care provided to you by participation in this clinical trial.

Yes, you may visit me outside of the clinic

No, you may not visit me outside of the clinic for any reason

Final Visit

At your last monthly study visit, all procedures listed above will take place. In addition, your blood will be tested for syphilis again. You will then return here about two weeks later to receive all of your final test results and information and counseling about what the results mean.

RISKS and/or DISCOMFORTS:

Acyclovir is highly effective in suppressing HSV-2 virus. It is very safe, based both on clinical trials and treatment of about 40 million people. The most common side effects of acyclovir are nausea, and headache, in rare cases also vomiting and diarrhea. These may go away during treatment. Please tell the study nurse or doctor right away, if you experience these symptoms.

Rarely, people with kidney disease, even those who are not aware that they have it, may have worsening of the kidney disease when given acyclovir. This has been seen also occasionally in healthy elderly persons who received a higher dose of acyclovir that we will be using in this study. Problems with kidneys have not been reported at the dose of acyclovir we are using in more than 70 thousand people who were closely followed after receiving acyclovir at this dose. This does not mean that kidney problems will never occur but that they are likely to occur not more often than four in ten thousand people. Because of that, you will not be tested to see if you have any pre-existing kidney disease before enrolling in this research study. No tests will be done during the study, unless you develop symptoms such as unexplained weight gain and a decrease in how much urine you make. If you report such symptoms, we will draw a blood specimen to test for kidney function (serum creatinine and BUN) and we will also test the blood specimen you gave at the beginning of the study to see if there are any changes in your kidney function since you enrolled in this study. Acyclovir is very safe to take with other medications, except for probenecid, an infrequently used medication in the treatment of gout or as an addition to therapy for syphilis. If you think that you may be taking probenecid at any time during this study, please let the site staff know.

Some people feel discomfort when their genitals are examined. Some people feel discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare.

You will be asked questions about your sexual history. You may be embarrassed by these questions. You may choose not to answer any of the questions if you wish.

The counseling about HIV, genital herpes, and other diseases may cause you to worry. If the tests show that you have HIV, knowing your HIV status may cause you anxiety. We will make every effort to protect your confidentiality during the screening tests.

However, it is possible that others may learn of your participation here and think you are infected with HIV or HSV-2, or are at high risk for infection with HIV or HSV-2.

Because of this, you could have trouble finding or keeping a job. You could also have problems being accepted in your family and community.

POTENTIAL BENEFITS:

There may be no direct benefit to you from this study. No one knows if acyclovir will help prevent HIV infection. Also, you may be in the study group that receives the placebo tablets. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive information about your HIV status and how to protect yourself and your partner(s) from HIV and STDs. You will receive free condoms and treatment for STDs.

If you are in the study group that receives acyclovir, you may have fewer genital sores than you otherwise would. No matter what group you are in, if you come to the study clinic with genital sores at any time during the study, you will be given acyclovir for treatment in addition to your regular study drug. This is the standard treatment for sores caused by genital herpes in many countries. **You should come to the clinic between regular visits or tell the study staff at any of your study visits if you have any genital sores, so you can receive treatment.**

NEW FINDINGS

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this 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:

The study doctor may need to take you off the study drug without your permission if:

- continuing the study drug may be harmful to you
- you are not able to take the study drug as required by the study

If you must stop taking the study drug before the study is over, you will be asked to continue in the study and return for some study visits and procedures.

The study doctor may also need to take you off the study early without your permission if:

- The study is cancelled by the sponsor of the study (U.S. National Institutes of Health (NIH)), the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study.)
- You are not able to attend the study visits or follow the procedures required by the study.

ALTERNATIVES TO PARTICIPATION:

If you choose not to take part in this study, it will have no effect on your regular medical care at this clinic. The local standard of care for treatment of HSV infection and against HSV recurrences where you live will be available to you. You may be able to receive acyclovir treatment for genital herpes from other sources outside of this study, depending on how it is usually treated by doctors in your community.

No drug has been shown to prevent HIV infection. The only known way to prevent sexual spread of HIV infection is to use condoms properly every time you have sex.

COSTS TO YOU:

There will be no cost to you for study-related visits, tablets, examinations, laboratory tests or other procedures.

REIMBURSEMENT:

At each visit you will receive refreshments and **[insert site-specific amount of money]** to pay for your transport costs and time away from work.

CONFIDENTIALITY:

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

Your records may be reviewed by the sponsor of the study (U.S. National Institutes of Health (NIH)) and their representatives, the local government or regulatory agency, **[insert name of site]** IRB, and the study monitors.

RESEARCH-RELATED INJURY:

If you are injured as a result of being in this study, you will be given immediate necessary treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

For questions about your rights as a research subject, contact:

- **[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VIII: SAMPLE INFORMED CONSENT FOR ENROLLMENT AT SITES ENROLLING WOMEN

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September, 2004

PRINCIPAL INVESTIGATOR: (US and/or in-country) PHONE:
[Complete with site-specific information]

INTRODUCTION:

You are being asked to take part in the research study to find out whether suppression of the genital herpes virus makes it less likely to become HIV-infected. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is **insert name of Principal Investigator**. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information and the study. We want you to know the purpose of the tests, the possible risks and benefits, and what will be expected of you if you decide to participate. You are free to ask questions about this study at any time. If you agree to take part in this study after the study has been fully explained to you, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy to keep. This process is called informed consent.

Please note that:

- a. Your participation in this research is entirely voluntary;
- b. You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care.

PURPOSE OF THE STUDY:

This is a study of a drug called acyclovir that is used to treat genital herpes. Genital herpes is caused by a virus called “herpes simplex virus 2” or “HSV-2”. Acyclovir is approved in the United States, Europe, and **enter country specific information, if applicable** for treatment of genital herpes, and has been used in over 40 million people. The HSV-2 virus is passed from one person to another during sex. Your blood test from the screening visit indicates that you have HSV-2. HSV-2 causes genital herpes, but many people who have HSV-2 do not know that they have it. In some people, HSV-2 infection causes sores in the genital area. In all people with HSV-2 infection, the virus can be present in the genital area and the infection can be spread to other sexual partners. There is no cure for genital herpes, but drugs like acyclovir can help sores heal more

quickly. When taken daily, acyclovir can also prevent genital sores among people who have HSV-2.

A number of studies have shown that people with HSV-2 infection have a higher chance to become infected with the human immunodeficiency virus (HIV), if they have sex with a person who has HIV. This may be because HSV-2 causes small breaks in the skin or surface in the genital area. It also attracts inflammatory cells to move to the genital area. These are the cells that HIV infects. HIV is the virus that causes AIDS. Acyclovir is not a treatment for HIV. This study is being done to find out if acyclovir helps prevent HIV infection in people who have HSV-2 infection.

To learn this, we will enroll between 2820 and 3012 men and women in Zimbabwe, Zambia, Peru, and the United States. It will take about 2 years to enroll all participants at each site. Each participant will be followed for 12 or 18 months after enrollment.

If you agree to participate in the research study, you will be asked to sign or make your mark on this consent form in front of a witness. We will offer you a copy of the form to keep.

PROCEDURES:

You will be assigned to one of two groups. One group will receive acyclovir, the active drug. The other group will receive placebo. A placebo pill looks the same as the acyclovir pill, but does not have any drug or other medicine in it. The kind of pill you will get is called a tablet because of how it looks. Which group you are assigned to will be decided by chance (like tossing a coin). Half the people in the study will receive acyclovir and the other half will receive placebo. Neither you nor the study staff will know which group you are in.

INSTRUCTIONS FOR SITE STAFF: PLEASE READ SECTION A IF THIS PARTICIPANT IS BEING ENROLLED UNDER PROTOCOL VERSION 3.0 OR HIGHER. PLEASE READ SECTION B IF THE PARTICIPANT WAS ENROLLED UNDER A PROTOCOL VERSION EARLIER THAN 3.0 AND IS BEING ASKED TO EXTEND THE LENGTH OF PARTICIPATION. PLEASE READ SECTION C IF THE PARTICIPANT WAS ENROLLED UNDER A PROTOCOL VERSION EARLIER THAN 3.0 BUT IS NOT BEING ASKED TO EXTEND THE LENGTH OF HER PARTICIPATION.

SECTION A:

You will be in the study for 18 months. During this time you should take one tablet of acyclovir or placebo by mouth every morning and one tablet every evening.

You will be asked to return to the clinic once every month to pick up your next month's supply of tablets, for a total of 18 monthly visits after today.

SECTION B:

You were enrolled prior to the extension of study participation from 12 to 18 months. It would be beneficial to the study if you would agree to remain in the study for a further six months, making your total participation time 18 months following enrollment. Please check and initial below whether you are willing and agree to participate in the study an additional 6 months for a total of 18 months following enrollment. Your choice will not affect the care provided to you by participation in this clinical trial.

YES, I agree to continue to participate in the study up to Month 18.

NO, I wish to end my study participation at Month 12.

SECTION C:

You will be in the study for 12 months. During this time you should take one tablet of acyclovir or placebo by mouth every morning and one tablet every evening.

You will be asked to return to the clinic once every month to pick up your next month's supply of tablets, for a total of 12 monthly visits after today.

Enrollment Visit (Today):

This visit will last about one hour and a half. We will ask you questions about your health and about your sexual history. You may choose not to answer any of the questions if you wish. We will counsel you about protecting yourself and your partner from HIV and other STDs and offer you condoms.

You will also have an ano/ genital exam, (which means, we will examine your outer genital area and vagina) to see whether you have signs of any infections passed during sex. We will draw 15 ml of blood (about 1 tablespoon) with a needle from you. Your blood will be tested for another STD called syphilis. If we find that you have syphilis or any other bacterial STD, we will tell you as soon as possible and give you medicine free of charge or refer you to a nearby clinic where you will be treated for free.

A sample of your blood will be sent to the University of Washington for HSV-2 confirmation and potentially be used for future toxicity management.

Should your test results show that you have become HIV positive during your first follow-up HIV test, we will test your enrollment sample to see whether or not you had HIV when you enrolled in the trial. We will communicate this test result to you.

We will swab your cervix (opening to the womb) to test for additional STDs. We will collect a urine sample to test if you are pregnant. If you are pregnant you will not be able to join the study.

We will give you a bottle containing enough study tablets to last you for one month and tell you exactly how and when to take them. Before you leave, we will schedule your next visit for one month later.

Acyclovir For Genital Sores During The Study

If you have ano/genital sores during the study, and your clinician feels it would be beneficial to your health, you will be given the standard dose of acyclovir (400 mg three times a day for five days) to take along with your study medication. This is the standard dose of acyclovir that is used to treatment a recurrence of ano/genital herpes.

Monthly Visits

You will come back to the clinic every month for a study visit. These visits will last about a half hour. You need to bring back your study tablet bottle and any remaining study tablets. The following will happen at each visit:

- We will collect your tablet bottle from the last visit.
- We will ask you questions and talk with you about taking the study tablets.
- You will receive new tablets for the next month.
- We will ask you questions about your health and your sexual activity since the last visit.
- If you have symptoms of STDs or an ano/genital sore, we will examine your genitals and swab the sore to test for STDs. If you have a bacterial STD you will receive treatment or be referred to a nearby clinic for free treatment.
- We will counsel you about protecting yourself and your partner from HIV and other STDs and offer you condoms.
- If you had blood drawn for HIV testing at the previous visit and the results were not immediately available, we will give you your test results and information and counseling about what the results mean.
- We will ask you if you have missed or had any late menstrual periods since your last visit.

If we think you may be pregnant, we will collect a urine sample for a pregnancy test. If you are pregnant, you will not be able to continue taking study drug. However, we would still like for you to return for your quarterly visits. After you have given birth, we would also like to ask you questions about the health of your baby.

Every Three Month Visits

Every three months, all monthly procedures will take place, and there will be additional procedures at these visits. Therefore, the visits will last approximately one hour altogether. The following will happen in addition to the monthly procedures:

- You will be counseled about having an HIV test.

- We will draw 15 ml of blood (about 1 tablespoon) with a needle from you. Your blood will be tested for HIV.
- We will examine you for STDs. If you have ano/genital sores, we will swab your genital area.
- We will provide you with all available test results.
- We will collect a urine sample to test if you are pregnant.
If you are pregnant, you will not be able to continue taking study drug. However, we would still like for you to return for your quarterly visits.

Each time we collect blood from you for HIV testing, we will freeze the blood that is left over from your test here at **[site/ clinic name]**. It may be necessary to re-test these samples for results during the study.

We would also like to keep your frozen blood here after the study is over, and possibly test it in the future. A separate consent form asks for your permission to do this.

You will receive your HIV test result during the visit when we draw your blood for the test, along with information and counseling about what the test results mean.

Sometimes an HIV test result is not clearly positive but is also not negative. In that case we will test your blood again until we know for sure whether or not you are infected with HIV.

If your HIV test result shows that you are infected with HIV, you will no longer be followed in this study. If you become HIV-infected, the study staff will talk with you about this test result and what this means for you. The staff will obtain a second blood test to confirm the initial positive test and you will be referred for care and additional counseling and other studies and services available to you.

In addition, if your HIV test result shows that you are infected with HIV you will be offered enrollment into a study aimed at determining whether daily acyclovir lowers the amount of HIV virus is in your blood during the first six months after you become HIV-infected, based on studies that have found that genital herpes may increase HIV levels in early HIV infection. This study will last approximately six additional months and will have its own informed consent forms for you to review and sign should you decide to join this study.

Contact Outside of the Clinic

It may be necessary for site staff members to visit you at your home or another location or to contact you via telephone as part of the study. The reasons for this include that you have missed visits or indicate that you are not able to make study visits to the research site. Your site counselor and retention specialists can explain the procedures to maintain your confidentiality in greater detail. Please check one of the boxes below as to whether site staff can visit you outside of the clinic. Your choice will not affect the care provided to you by participation in this clinical trial.

Yes, you may visit me outside of the clinic

No, you may not visit me outside of the clinic for any reason

Final Visit

At your last monthly study visit, all procedures listed above will take place. In addition, your blood will be tested for syphilis again. You will then return here about two weeks later to receive all of your final test results and information and counseling about what the results mean.

RISKS and/or DISCOMFORTS:

Acyclovir is highly effective in suppressing HSV-2 virus. It is very safe, based both on clinical trials and treatment of about 40 million people. The most common side effects of acyclovir are nausea, and headache, in rare cases also vomiting and diarrhea. These may go away during treatment. Please tell the study nurse or doctor right away, if you experience these symptoms.

Rarely, people with kidney disease, even those who are not aware that they have it, may have worsening of the kidney disease when given acyclovir. This has been seen also occasionally in healthy elderly persons who received a higher dose of acyclovir that we will be using in this study. Problems with kidneys have not been reported at the dose of acyclovir we are using in more than 70 thousand people who were closely followed after receiving acyclovir at this dose. This does not mean that kidney problems will never occur but that they are likely to occur not more often than four in ten thousand people. Because of that, you will not be tested to see if you have any pre-existing kidney disease before enrolling in this research study. No tests will be done during the study, unless you develop symptoms such as unexplained weight gain and a decrease in how much urine you make. If you report such symptoms, we will draw a blood specimen to test for kidney function (serum creatinine and BUN) and we will also test the blood specimen you gave at the beginning of the study to see if there are any changes in your kidney function since you enrolled in this study. Acyclovir is very safe to take with other medications, except for probenecid, an infrequently used medication in the treatment of gout or as an addition to therapy for syphilis. If you think that you may be taking probenecid at any time during this study, please let the site staff know.

Some people feel discomfort when their genitals are examined. Some people feel discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare.

You will be asked questions about your sexual history. You may be embarrassed by these questions. You may choose not to answer any of the questions if you wish.

The counseling about HIV, genital herpes, and other diseases may cause you to worry. If the tests show that you have HIV, knowing your HIV status may cause you anxiety. We will make every effort to protect your confidentiality during the screening tests. However, it is possible that others may learn of your participation here and think you are infected with HIV or HSV-2, or are at high risk for infection with HIV or HSV-2. Because of this, you could have trouble finding or keeping a job. You could also have problems being accepted in your family and community.

PREGNANCY STATEMENT:

You cannot join the research study if you are pregnant. However, acyclovir is not known to cause birth defects. No side effects in newborn babies have been reported, but we do not know for sure how safe acyclovir is for unborn babies. So, if you decide to join the study and become pregnant while you are in the study, you will need to stop taking the study tablets.

The study staff will discuss with you what is known about using the study tablets during pregnancy and the possible effects on you and your baby. We will ask you to continue to come for your quarterly visits for HIV counseling and testing until when you would have finished the study. Once your baby is born, we would also like to ask you questions about the health of your baby.

POTENTIAL BENEFITS:

There may be no direct benefit to you from this study. No one knows if acyclovir will help prevent HIV infection. Also, you may be in the study group that receives the placebo tablets. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive information about your HIV status and how to protect yourself and your partner(s) from HIV and STDs. You will receive free condoms and treatment for STDs.

If you are in the study group that receives acyclovir, you may have fewer genital sores than you otherwise would. No matter what group you are in, if you come to the study clinic with genital sores at any time during the study, you will be given acyclovir for treatment in addition to your regular study drug. This is the standard treatment for sores caused by genital herpes in many countries. **You should come to the clinic between regular visits or tell the study staff at any of your study visits if you have any genital sores, so you can receive treatment.**

NEW FINDINGS

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this 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:

The study doctor may need to take you off the study drug without your permission if:

- continuing the study drug may be harmful to you
- you are not able to take the study drug as required by the study
- if you become pregnant during the study

If you must stop taking the study drug before the study is over, you will be asked to continue in the study and return for some study visits and procedures.

The study doctor may also need to take you off the study early without your permission if:

- The study is cancelled by the sponsor of the study (U.S. National Institutes of Health (NIH)), the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study.)
- You are not able to attend the study visits or follow the procedures required by the study.

ALTERNATIVES TO PARTICIPATION:

If you choose not to take part in this study, it will have no effect on your regular medical care at this clinic. The local standard of care for treatment of HSV infection and against HSV recurrences where you live will be available to you. You may be able to receive acyclovir treatment for genital herpes from other sources outside of this study, depending on how it is usually treated by doctors in your community.

No drug has been shown to prevent HIV infection. The only known way to prevent sexual spread of HIV infection is to use condoms properly every time you have sex.

COSTS TO YOU:

There will be no cost to you for study-related visits, tablets, examinations, laboratory tests or other procedures.

REIMBURSEMENT:

At each visit you will receive refreshments and [insert site-specific amount of money] to pay for your transport costs and time away from work.

CONFIDENTIALITY:

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

Your records may be reviewed by the sponsor of the study (U.S. National Institutes of Health (NIH)) and their representatives, the local government or regulatory agency, (insert name of site) IRB, and the study monitors supporting this study.

RESEARCH-RELATED INJURY:

If you are injured as a result of being in this study, you will be given immediate necessary treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

For questions about your rights as a research subject, contact:

- **[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX IX: AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES (US Sites only)

TITLE OF THE RESEARCH:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals

HPTN 039, Version 3.0

13 September2004

I understand that Federal law requires that researchers, healthcare providers and health plans protect the privacy of information that identifies me. I understand that the privacy law, Health Insurance Portability & Accountability Act (HIPAA) requires that researchers get my permission to be able to use or disclose my protected health information for research purposes in the study entitled “A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Of Acyclovir For The Reduction Of HIV Acquisition Among High-Risk HSV-2 Seropositive, HIV Seronegative Individuals”. By signing this authorization, I am giving that permission.

I authorize [*name of study site and investigator(s)*] and their research staff and business associates (together referred to as the “researchers”) to use and disclose my protected health information for the purposes described below.

My protected health information that may be used and disclosed includes:

- Demographic Information
- Contact Information
- Blood storage
- HIV testing
- HSV-2 Testing
- Syphilis Testing
- Gonorrhea and Chlamydia testing
- Medical History
- Current medications
- Sexual History and Risk Behavior
- Genital symptoms
- Rectal swabs and urine
- Swabs for genital ulcers

My protected health information will be used for:

For Evaluation of acyclovir as per the protocol/informed consent and for which my Protected Health Information, and those of others, is required in order to determine if acyclovir can help prevent HIV acquisition by helping to prevent HSV re-occurrences.

The Researchers may use and share my health information with:

- Family Health International (FHI)
- FHI's Protection of Human Subjects Committee
- **(insert site name)** IRB
- U.S. National Institutes of Health (NIH) and the Division of AIDS (DAIDS)
- Government representatives, when required by law
- Data Safety Monitoring Board
- The study monitors supporting this study

I understand that the researchers agree to protect my health information by using and disclosing it only as permitted by me in this Authorization and as directed by state and federal law.

Once my health information has been disclosed as permitted by this Authorization, the information can no longer be considered protected.

I do not have to sign this Authorization. If I decide not to sign the Authorization:

- It will not affect my treatment, payment or enrollment in any health plans or affect my eligibility for benefits.
- I may not be allowed to participate in the research study.

After signing this Authorization, I can change my mind at any time and:

- Not let the researchers disclose or use my protected health information (revoke this Authorization).
- If I revoke this Authorization, I will send a written letter to: **[name and contact information]** to inform him/her of my decision.
- If I revoke this Authorization, researchers may only use and disclose the protected health information **already** collected about me on this research study. Once I revoke this Authorization no further protected health information will be collected from me for this research study.
- If I change my mind and withdraw this Authorization, I may not be allowed to continue to participate in the study.
- If I revoke this Authorization my protected health information may still be used and disclosed should I have an adverse event (a bad effect).

I understand that I will not be allowed to review the information collected for the research until after the study is completed. When the study is over, I will have the right to access the information.

This Authorization does not have an expiration date.

If I have not already received a copy of the Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights, I should contact the *[Name of Institution's Privacy Officer at Ph: (xxx) xxx-xxxx]*.

I am the study participant or am authorized to act on behalf of the participant. I have read this information, and I will receive a copy of this form after it is signed.

Signature of study participant or *participant's
legal representative

Date

Printed name of participant or
*study participant's legal representative

Representative's relationship to
study participant

*Please explain representative's relationship to participant and include a description of representative's Authority to act on behalf of participant:
