HPTN 039-01-Ancillary

Prospective Cohort Study of HPTN 039 Seroconverters: The Effect of HSV-2 Suppression on HIV-1 Viral Set Point

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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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

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
CDC	Centers for Disease Control and Prevention
CL	(HPTN) Central Laboratory
CORE	(HPTN) Coordinating and Operations Center
CRPMC	(NIAID) Clinical Research Products Management Center
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
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
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

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HPTN 039-01-Ancillary

Prospective Cohort Study of HPTN 039 Seroconverters: The Effect of HSV-2 Suppression on HIV-1 Viral Set Point

SCHEMA

Purpose:	To determine the effect of HSV-2 suppression with twice-daily acyclovir during the first six months after HIV acquisition on HIV viral set point.
Design:	Prospective multi-site cohort study.
Population:	Women and men who have sex with men (WSM, MSM) enrolled in the randomized-controlled trial of acyclovir in the reduction of HIV acquisition (HPTN 039) who are identified as HIV-positive during follow-up.
Study Size:	Estimated 81 seroconverters: 54 on placebo, 27 on acyclovir. (See statistical section for details).
Treatment Regimen:	Study participants identified as HIV positive during HPTN 039 follow-up will continue taking, in blinded manner: ▪ Acyclovir 400 mg po bid, or ▪ Matching placebo po bid for the duration of their participation in this ancillary study.
Study Duration:	Participants who seroconvert will be followed for six months after enrollment; participants who seroconvert will be enrolled within 60 days of when the first HIV positive sample was collected on HPTN 039.
Primary Objective:	To measure the efficacy of twice daily acyclovir suppressive therapy on HIV plasma viral RNA levels during the first 6 months after determination of HIV infection.
Secondary Objectives:	1) To assess the effect of acyclovir suppressive therapy on CD4 counts over the first six months after infection. 2) To describe the incidence and severity of clinical HSV reactivation, as detected during visits or reported by participants, during early HIV infection.
Study Sites:	- Harare, Zimbabwe; - Lusaka , Zambia; - Johannesburg, South Africa; - Lima, Iquitos, and Pucallpa, Peru; - Seattle, WA, USA; - San Francisco, CA, USA.

1 INTRODUCTION

1.1 Background

HSV-2 and HIV interaction

Herpes simplex virus has long been recognized as a significant co-pathogen in individuals infected with HIV. HSV-2 is highly prevalent, accounting for 75% to 80% of genital ulcers in both the developed [1] and developing world [2-4]. Recent population-based studies have also shown high (greater than 70%) prevalence rates in HIV-infected persons, particularly in developing countries and areas of high HIV incidence [5, 6]. The association of HSV-2 with increased risk of HIV acquisition has been well documented by a number of epidemiologic studies [7, 8], but its impact on the natural history of HIV infection, particularly early HIV infection, remains to be delineated.

Both *in vitro* and *in vivo* data support the biologic mechanism that HSV upregulates HIV replication. Several HSV proteins (including ICP-0, ICP-27, Us11) have been shown to increase expression of HIV-1 [9-12]. Both heat-inactivated and infectious HSV-1 and HSV-2 virions can increase HIV-1 expression in macrophages, likely through stimulation of NF-?B activity [13]. HSV can also infect and replicate in activated CD4+ lymphocytes and macrophages [14], and may play a role in the expansion of the HIV target cell population [15]. Investigators have demonstrated by electron microscopy that HIV-1 and HSV-1 co-infect keratinocytes and macrophages in individuals with AIDS [16]. Such co-infected cells were found to harbor a significantly higher number of virions (HSV, HIV, and hybrid virions) compared to cells that were not co-infected with HSV and HIV.

Clinical observations corroborate these in vitro findings; two groups of investigators found a positive correlation ($r=0.24-0.47$, $p=0.05$) between HSV DNA and HIV RNA and HIV DNA, respectively, in cervicovaginal secretions among HIV/HSV-2 coinfected African women [5, 17]. High titers of HIV-1 RNA have also been detected in genital HSV-2 lesions in co-infected men [18].

Longitudinal studies indicate that HSV-2 reactivation is associated not only with higher mucosal HIV levels but also with higher systemic HIV viral burden. Mole et. al. examined the effect of active HSV infection on HIV viral load in plasma [19], and characterized the trend in plasma HIV-1 RNA by obtaining plasma samples one month before an acute herpetic outbreak, during an outbreak, and one month after acyclovir treatment in 16 subjects. Median plasma HIV viral load was 3.4-fold higher during herpes reactivations (range 0-10 fold; $P=0.002$), and was significantly higher than HIV viral levels at baseline and in the treatment period following herpes reactivation in 14 of 16 individuals. Schacker et. al. found similar trends through studying the influence of subclinical HSV reactivation on HIV-1 levels in plasma in 8 men studied during the pre-HAART era. They administered chronic daily suppressive therapy with acyclovir to HIV-1/HSV-2 coinfected persons and measured plasma HIV-1 RNA levels before and

after administration of acyclovir [20]. When adjusted for baseline CD4 counts, acyclovir reduced plasma RNA levels by an average of one-third of a log; a reduction in plasma HIV RNA levels was observed in 11 of 12 persons, and HIV-1 RNA levels returned to previous baseline levels upon discontinuation of therapy. These studies may partially account for the observation in 7 of 8 studies in the era of AZT monotherapy that found increased survival with concomitant acyclovir use [21]. Thus, both clinical and subclinical HSV-2 reactivation have been shown to elevate systemic and genital HIV-1 RNA levels and daily therapy with acyclovir appears to reduce plasma HIV-1 RNA.

Significance of Viral Set Point

In a representative course of early HIV infection, viral load increases sharply during the first few weeks post infection to a peak, and then drops rapidly to a steady state or "set point," after which plasma viral load stays stable for a relatively long period, until progression to AIDS [22-24]. The set point is thought to result from an equilibrium between HIV-1 replication rate and the host immunologic response and typically occurs 4-5 months from the time of acquisition [22, 25]. HIV viral "set point" has been shown to be one of the most important surrogate markers for progression to AIDS [26, 27].

HSV-2 Infection and HIV-1 Viral Set Point

The most compelling epidemiologic evidence favoring an association between HSV-2 infection and HIV-1 viral set point comes from Rakai, Uganda where Gray et. al. identified 256 men and women with incident HIV infection through a community-randomized trial of an STD intervention that included home visits with a standardized interview and blood draw at 10-month intervals [28]. A number of cofactors were identified that may potentially influence HIV viral load in early HIV infection, including gender, age, and stage of HIV disease, as well as HSV-2 serostatus and genital ulcer disease (GUD) in the prior 6 months. At an estimated 5 months after HIV acquisition, serum HIV viral load was significantly higher among persons who reported symptoms of GUD (4.71 v. 4.32 $\log_{10}$ copies/ml, p=.01) than for those who did not and higher among those who were HSV-2 seropositive compared to HSV-2 seronegative individuals (4.56 versus 4.06 $\log_{10}$ copies/ml, $p < .01$). Higher serum viral load among those who reported GUD in the prior 6 months was also observed in a sample of 1293 individuals (592 of whom were a population-based random sample) who were determined to have chronic established HIV infection by WHO provisional staging. In both younger and older individuals, as well as within gender-specific strata, GUD was associated with higher viremia at all stages of HIV infection.

An association between GUD and plasma viral levels was also reported in a cohort study of 161 female commercial sex workers in Mombasa, Kenya who HIV seroconverted during prospective follow-up [29]. During a median of 34 months follow-up with a median of 4 plasma samples, Lavreys et. al. observed a statistically significant greater change in plasma viral load over time (+0.03 $\log_{10}$ copies/mL/month, P=0.001) among those women who presented with a genital ulcer near the time of infection compared to those women who did not, with a

trend toward higher viral set point (+0.47 $\log_{10}$ copies/mL, P=0.09). Comparable data are not yet available from early HIV infection cohort studies outside of these east African settings.

The possibility that GUD is a consequence and thus, a marker of immunosuppression in early HIV infection, rather than a determinant of higher HIV viremia has not been adequately addressed by any observational study to date. However, the observations of increased systemic viral load for HSV-2 seropositivity as well as GUD in the Rakai study may indicate that subclinical as well as clinical HSV reactivation precedes higher HIV viremia. The pattern in plasma HIV-1 viral levels seen during HSV reactivation and acyclovir therapy, described previously, would also support this directionality. A more definitive study, however, would involve an intervention, namely HSV-2 suppression, as a probe to determine whether this relationship is causal.

1.2 Rationale

We hypothesize that acyclovir suppression of HSV-2 during HIV acquisition and peak viremia in the peri-seroconversion period may reduce HIV-1 viral set point. If this hypothesis is correct, suppression of genital herpes may favorably impact both HIV disease progression and infectiousness, and thus, the risk of HIV transmission during a period of high viral load.

As described above, observational data from the Rakai STD intervention trial have shown that HIV seroconverters who were HSV-2 seropositive had higher serum HIV levels at approximately 5 months post-HIV acquisition compared to HSV-2 seronegative seroconverters (4.56 versus 4.06 $\log_{10}$ copies/ml, $p< .01$) [28]. Increased viral load was also observed in those who reported genital ulcer disease (GUD) during the interval of HIV seroconversion compared to those who did not (4.71 v. 4.32 $\log_{10}$ copies/ml, p=.01). These clinical observations are consistent with more than 10 years of *in vitro* data that demonstrate that HSV gene products stimulate HIV replication in lymphocytes and macrophages [12, 30-32]. Thus, both clinical and *in vitro* data support the hypothesis that HSV-2 suppression during early HIV infection may reduce HIV replication and diminish infected target cells in mucosal tissues.

Importance of Follow-up of HPTN 039 Seroconverters

We have the unique opportunity to address this hypothesis directly within HPTN 039, where HIV-negative HSV-2 seropositive MSM and WSM will be randomized to receive daily acyclovir (400 mg bid) or matching placebo and HIV incidence in the two arms will be compared. Comparison of the effects of HSV-2 suppression on plasma HIV levels can be accomplished by maintaining initially assigned treatment (i.e. acyclovir or placebo bid) among HIV seroconverters, which would include the seroconversion period and the first 6 months after HIV infection was identified. We can then determine whether HIV viral set point differs in HPTN 039 seroconverters who continue daily acyclovir suppressive therapy compared to those who continue placebo, analogous to the possibility that

partially effective HIV vaccines may modulate disease progression and is the rationale for follow-up of breakthrough infections in HIV vaccine trials. Because suppressive acyclovir therapy in HIV-infected persons has high safety and minimal side effects and because its impact on HIV viral set point remains unknown, we believe there is sufficient clinical equipoise to maintain study arms after HIV acquisition.

If acyclovir is found to be effective in lowering viral set point, HSV-2 suppression may provide a feasible intervention to ameliorate HIV disease progression, particularly if acyclovir is also found to reduce HIV incidence. Suppression of genital herpes is substantially less costly and associated with fewer short- and long-term side effects than intervention in early HIV-1 infection with antiretrovirals or immunomodulatory treatment. Lastly, HSV-2 suppression during early HIV infection may also offer public health benefits. Genital ulcers and symptoms of herpes are reported frequently in the period of HIV seroconversion and early infection, most likely due to the transient immunosuppression seen at that time [28, 33]. By decreasing the incidence of herpes reactivation during this period of high infectivity, HSV-2 suppression has the potential to diminish the risk of HIV transmission.

Thus, from the perspectives of individual clinical benefit as well as potential public health, there is compelling data to assess the role of HSV-2 suppression during early HIV infection—an opportunity that uniquely exists in HPTN 039.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

- To measure the efficacy of twice daily acyclovir suppressive therapy on HIV plasma viral RNA levels during the first 6 months after determination of HIV infection.

2.2 Secondary Objectives

- To assess the effect of acyclovir suppressive therapy on CD4 counts over the first six months after infection.
- To describe the incidence and severity of clinical HSV reactivation, as detected during visits or reported by participants, during early HIV infection.

2.3 Study Design

HPTN 039 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. WSM will be enrolled at study sites in Lusaka, Zambia, Johannesburg, South Africa, and Harare, Zimbabwe. 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.

HPTN 039 participants who acquire HIV during the course of the study will have been on either acyclovir 400 mg bid or matching placebo during the time of HIV acquisition. We have the opportunity to assess whether herpes suppression may reduce viral set point, potentially ameliorating HIV disease progression in those who become HIV infected.

This ancillary study, HPTN 039-01-Ancillary, will involve the continuation of study drug for the duration of participation after enrollment (up to 6 months after enrollment). All participants of HPTN 039 are expected to be followed at quarterly intervals to test for HIV antibodies. When the initial HIV positive test result is available, and with consent for this ancillary study, participants will be followed with measurement of plasma viral load at Enrollment and months 1, 5, and 6. These sampling points were selected to optimize our ability to detect changes in viral set point while accounting for the heterogeneity in early plasma HIV RNA levels. We estimate we will have sufficient power to detect a clinically significant difference of =0.5 $\log_{10}$ copies/ml in plasma HIV-1 "set point."

As was done in the main HPTN 039 study, 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 (e.g., number of partners, HIV serostatus of partners, if known) and clinical HSV-2 history will be obtained. 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.

Blood will be drawn for $CD4^+$ T-cell counts and plasma HIV RNA at Enrollment and months 1, 5 and 6 after enrollment. Clinical evaluations including an anogenital examination in addition to self-reported anogenital symptoms will also be conducted at Enrollment and months 1, 3, and 6. For female participants: a urine pregnancy test will be performed at Enrollment and months 1, 3, and 6.

The presence of concurrent STDs will be assessed via questionnaire supplemented by directed clinical exam, swab collection and NAAT testing for those with HSV-2 related findings, and by serologic testing for syphilis at the end of study follow-up (last blood draw on participant).

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 unless in the first trimester of pregnancy). Genital lesions and other HSV-2 related genital findings will be swabbed and stored at –20°C or -

70°C to send to the University of Washington Virology laboratory to be evaluated by PCR for pathogens at a later date.

3 STUDY POPULATION

This ancillary study will be drawing its population from the total of 81 anticipated HIV seroconverters from the between 2820 and 3012 high risk HIV-negative, HSV-2 positive heterosexual women and MSM selected for the main HPTN 039 study. These participants will have been selected according to the criteria outlined in Section 3.1, 3.2, and the guidelines in Section 3.4 of the HPTN 039 protocol.

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

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

3.1 Inclusion Criteria

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

- Currently or previously enrolled in HPTN 039.
- HIV-positive during follow-up in HPTN 039.
- Not on HIV antiretroviral therapy.
- 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.
- Continue to take study drug as directed for an additional six months.
- Adhere to study follow-up schedule.
- Provide adequate locator information.

3.2 Exclusion Criteria

As detailed in the HPTN 039 exclusion criteria, men and women who meet **any** of the following criteria are **not eligible** for this study:

- Known history of adverse reaction to acyclovir.
- Known plans for travel away from study site for > 2 months.
- Current use of antiretroviral therapy during the study (at time of enrollment).

- Pregnant as confirmed by a urine pregnancy test at enrollment.
- Found to have been HIV positive at enrollment in HPTN 039, as confirmed by retrospective testing (not all participants will require this testing; this only applies to participants in HPTN 039 who seroconvert at their first HIV test after enrollment).
- More than 60 days of when the first HIV positive sample was collected on HPTN 039
- 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 is allowed).

3.3 Recruitment Process

Enrollment for this ancillary study will take place after the first HIV positive test visit (when the sample was collected). Enrollment must take place within 60 days of when the first HIV positive sample was collected. All required procedures must be completed in one enrollment visit. However, participants may consent for participation on one day, and have all other enrollment procedures performed on a separate day as long as enrollment occurs within 60 days of the first HIV positive test.

During the visit in which HPTN 039 participants first learn of their HIV- positive status (i.e., after the WB results on the first sample are available), potential ancillary study participants will be provided with information about the ancillary study. Participants who remain interested in study participation will undergo the informed consent process at that time. Those participants who want more time to consider their decision have the option of scheduling their enrollment visit at a later time, no later than 60 days from the time of their first HIV positive test (the date on which the sample was collected, not when the result was obtained). Under the HPTN 039 protocol, they will be instructed to continue taking their study medication in the interim and will be provided with refills of medication as necessary. Should they choose not to participate in the Ancillary Study, they will be asked to return any unused medication and will no longer be provided additional medication.

At the Enrollment Visit potential study participants 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 tests of blood obtained from them, and also testing of stored blood samples taken as part of HPTN 039 procedures. They will continue with their assigned study drug, will be provided with supplies of condoms, instructions for study drug use, adherence counseling, and instructions to contact study staff with questions about the study, reports of anogenital symptoms, side effects or other problems.

3.4 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.

Study staff should maintain their HPTN 039 locator databases for participants, updating when necessary.

While study site staff are 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 may 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 (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 research and the importance of completing research study visits.

Site staff should make every effort to have participants report to the clinic for study visits. 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).

3.5 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) of participants who terminate from the study prior to the end of the 6 month period of follow-up, 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 according to the specifications in the package insert.

Study participants will continue their originally randomized assignment 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 symptomatic 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. Participants may also be dispensed open label acyclovir for oral herpes outbreaks, when they occur.

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.

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 have received 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(s) 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 monitored for accuracy. At that time, the study site may destroy medications according to their site specific SOP.

4.3 Adherence Assessment

High adherence to acyclovir or placebo will be important for determining the effect of acyclovir on HIV viral levels 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 anogenital lesions and other anogenital 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. If a female participant becomes pregnant during the study, she will be referred to appropriate services and/or studies to address mother-to-child transmission. She will also 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 or until the end of the pregnancy, whichever comes first. 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.

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 be discontinued from use of study drug, for the duration of her participation in the

study, at the time a woman is determined to be pregnant. 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 Enrollment and months 1, 3 and 6. 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, when possible.

4.6 Concomitant Medications and Opportunistic Infections

Participants will be asked through a structured interview whether they are taking any antiretroviral or prophylactic medication or whether they have had any opportunistic infection since their last study visit.

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 Enrollment Visit Baseline (Day 0)

Eligibility for the ancillary study will have been largely determined over the course of their participation in HPTN 039, based on main study inclusion and exclusion criteria and HIV antibody test results.

Individuals in main study who test HIV-positive will be counseled about the interpretation of the test result. They will be informed of clinical and social services for persons who are HIV-infected and methods to reduce the likelihood of transmitting HIV to others.

If they meet study eligibility criteria, they will be provided information about this ancillary study. If they show interest in participation, a formal enrollment visit can take place. Enrollment procedures can be deferred within a window of 60 days from the time of the HIV positive test visit (the date on which the sample was collected, not when the result was available).

Administrative, Behavioral, And Regulatory Procedures

- Obtain informed consent for study participation.

- Obtain informed consent for storage of blood for future testing and testing of blood stored for HPTN 039 (if consent was obtained for storage) (optional)
- Schedule next visit.

Clinical Procedures

- Partner-specific sexual behavior questionnaire
- Assess presence of HIV-related symptoms
- Administer questionnaire to assess 3-month history of symptomatic STDs, such as genital ulcer disease, vaginal discharge and rectal symptoms.
- Administer questionnaire to assess HIV-related symptoms
- Provide risk reduction counseling.
- Collect blood.
- For female participants, urine pregnancy test.
- Syndromically treat (or refer for treatment) participant-reported symptomatic bacterial STDs.
- Supply study drug, instructions, and adherence counseling

For participants who report genital symptoms:
- Perform anogenital exam and collect swab of genital ulcers or any other HSV-2 related findings

Laboratory Procedures

- HIV viral RNA in plasma using RT-PCR using Amplicor HIV-1 Monitor 1.5 Assay (Roche).
- $CD4^+$ and $CD8^+$ lymphocyte subsets from whole blood.
- For unexplained weight gain greater than 5 pounds (2.3 kilograms) AND unexplained decreased urine output in the past 3 months, perform serum creatinine testing according to the guidelines in the SSP.

5.2 Follow-Up Visits: Monthly (Months 1 To 6)

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

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

For participants who report genital symptoms:

- Perform anogenital exam and collect swab of genital ulcers or any other HSV-2 related findings

For women:

- Obtain urine for pregnancy test

Laboratory Procedures

For swabs from participants with genital ulcers or any other HSV-2 related findings:

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

For women:

- Urine pregnancy test (1, 3, 5, and 6 or at 2 and 4 if indicated)

5.3 Follow-up Visits (Months 1, 3, 5 and 6)

In addition to the monthly visit procedures, the following procedures will be performed at intervals through the six-month follow-up period:

Clinical Procedures

- Perform anogenital exam (**months 1, 3, 6)**.
- Perform urine pregnancy test (**months 1, 3, 6**)
- Collect blood (**months 1, 5, 6**).

The following will occur at **months 1, 3, 5 and 6**:

- Administer questionnaire to assess interval history of symptomatic STDs, such as genital ulcer disease, vaginal discharge and rectal symptoms
- Assess whether there has been an unexplained weight gain greater than 5 pounds (2.3 kilograms), AND unexplained decreased urine output in the past 3 months.

The following will occur at **months 3 and 6**:

- Partner-specific sexual behavior questionnaire

Laboratory Procedures

- HIV viral RNA in plasma using RT-PCR using Amplicor HIV-1 Monitor 1.5 Assay (Roche). (**Months 1, 5, 6**)
- $CD4^+$ and $CD8^+$ lymphocyte subsets from whole blood. (**Months 0, 1, 5, and 6**)
- For unexplained weight gain greater than 5 pounds (2.3 kilograms) AND unexplained decreased urine output in the past 3 months, perform serum creatinine testing according to the guidelines in the SSP.

For women:

- Urine pregnancy test (**Months 1, 3, 6**).

5.4 Exit Visit (Month 6)

The exit visit will be conducted as described above; however, in addition, syphilis serology (including titer if RPR is positive) and treponemal testing will be performed and sites will provide results by telephone, or in person according to when the result is available, ensuring that results are communicated to the participant. Participants with positive serology will be referred for treatment according to local standard of care.

5.5 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;

- HIV-related concerns.

Participants also will be instructed to return to the clinic if they have symptoms of HSV-2 between scheduled study visits (i.e., prodromal symptoms or genital 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-2 related findings will be swabbed and stored at –20°C or –70°C to subsequently assess etiology 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 provided to participants with vaginal and urethral discharge or genital ulcer disease).

6 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. This study is subject to oversight and periodic review by an independent Data Safety Monitoring Board (DSMB) (see section 7.4.3).

6.1 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 comorbidities 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.

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 prospective cohort study of seroconverters identified during follow-up of 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.

A total of 93 participants are anticipated to seroconvert from the total enrollment of 2820 to 3012 high-risk, HIV-negative, HSV-2 seropositive WSM and MSM enrolled in the study. 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, plasma HIV-1 RNA after identification of HIV seropositivity at months 0, 1, 5, 6.

7.2 2 Secondary Endpoints

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

- $CD4^+$ T-cell counts at months 0, 1, 5, 6.
- Occurrence and frequency of genital ulcers.

7.3 Sample Size

Preliminary data from the UW/FHCRC Primary Infection Clinic was used to estimate within and between person components of variance in individuals with early HIV infection. These data are taken from 150 days to 2 years post infection and, therefore, should give reasonable estimates of the variability in viral load around the viral set point. The between person variance component is 0.52 ($\log_{10}$ copies^2/ml^2) and the within person variance component is 0.096 ($\log_{10}$ copies^2/ml^2) [22].

In the HPTN 039 trial we expect 93 seroconverters: 62 in the placebo group and 31 in the acyclovir group. We expect most but not all of these to be available for the proposed follow-up, assuming that some newly-infected persons in domestic sites will elect to initiate antiretroviral treatment after learning they have become HIV-infected. Assuming that 81 seroconverters are available for this trial (54 from the placebo group and 27 from the acyclovir group, assuming acyclovir suppressive therapy reduces HIV acquisition by 50%), the following table gives the power to detect various differences in the viral set point between the acyclovir and placebo groups.

Table 1. Power to detect the indicated difference in $\log_{10}$ HIV RNA (viral set point) between acyclovir and placebo groups assuming 27 and 54 individuals in those groups, respectively. The two-sided α level is 0.05.

	Difference in $\log_{10}$ plasma HIV RNA (viral setpoint) at 6 months between acyclovir and placebo groups		
No. obs/person	.3	.5	.7
1	.37	.77	.96
2	.39	.80	.97
3	.40	.81	.98

Thus, we have about 80% power to detect a difference of 0.5 $\log_{10}$ copies/ml in viral set point. This difference is comparable to what might be expected with nucleoside monotherapy and the minimum change in viral load that could have a measurable effect on HIV disease progression. Due to the relatively low within-person variation in viral load, multiple measurements on an individual do not produce a significant increase in power. If the effect size of acyclovir in the parent trial is smaller than 50%, then our power in this trial would increase since the numbers between the acyclovir and placebo groups would be more balanced. For instance, if the RR in the parent trial were 0.65 instead of 0.5, then we would expect about 32 and 49 individuals in the acyclovir and placebo groups respectively. The power to detect a difference of 0.5 $\log_{10}$ copies/ml in viral setpoint with 2 observations per person would then be 0.83 (compared to 0.80). Alternatively, we could detect a difference of 0.48 $\log_{10}$ copies/ml (compared to 0.5 $\log_{10}$ copies/ml) with 80% power.

7.4 Data Analysis

7.4.1 Primary Analyses

Descriptive analyses of the seroconverters will include calculation of the mean and median viral load by randomization group. A simple t-test can be used to compare log-transformed viral load levels between these two groups. However, caution must be exercised in the interpretation of any difference (or lack of difference) found. Although the overall acyclovir and placebo groups should be comparable at baseline due to randomization, individuals who seroconvert in the acyclovir group may not be comparable to individuals who seroconvert in the placebo group (since they have had different experiences – namely, daily acyclovir therapy – between randomization and seroconversion). Thus, the observed difference between the acyclovir and placebo groups' viral set points may be interpreted as the "net acyclovir effect" (i.e. encompassing the effects of acyclovir both before and after seroconversion) and not exclusively the post-seroconversion effect. Approaches to isolating the effect of an intervention such as acyclovir on post-seroconversion outcomes have been described by Gilbert et al. [34].

Linear regression using the log-transformed viral load levels as the outcome and baseline or other covariates (e.g. CD4) will be use to compute the "adjusted" differences between the acyclovir and placebo groups. The interpretation of these "adjusted" differences is subject to the same cautions noted above.

7.4.2 Secondary Analyses

Secondary analyses of CD4 counts will be virtually identical to those described for viral load levels above, although it is typically not necessary to log-transform CD4 levels to obtain valid inferences. Descriptive statistics will be used to characterize overall CD4 levels and levels within subgroups. T-tests and linear regression will be used to obtain unadjusted and adjusted estimates of the treatment effect.

Secondary analyses of clinical HSV reactivation will be based on the total number of i) patient-reported and ii) clinically observed instances of GUD over follow-up on each subject. Poisson regression with offset equal to the duration of follow-up on each individual (if it varies significantly between individuals) can then be used to assess treatment effect on this endpoint. Robust variances will be used to protect against between-subject variations (i.e. random effects) in the underlying event rates [35].

7.4.3 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. Based on these analyses, the DSMB will make recommendations on whether to continue or halt the study. 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 DSMB[59]. 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 II-IV — and any subsequent modifications — will be reviewed and approved by the same process used in HPTN 039 with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications —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.

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 based on the templates in Appendices II/III, that describe the purpose of 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 IV, and an additional informed consent will be developed to include the new HIPAA regulations (Appendix V, 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 receiving HIV counseling. Trained counselors will be available to help participants deal with these feelings.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial of HSV-infected or HIV-infected individuals). 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 assigned to acyclovir may experience fewer genital ulcers during therapy with the study drug. Regardless of randomization arm, participants will receive acyclovir 400 mg tid for 5 days during episodes of symptomatic genital lesions during the study.

In addition, participants will receive HIV and STD counseling, testing, and genital exams in this study, as well as bacterial STD treatment or referral for free treatment. Participants will be provided with male condoms throughout the study. They will learn how to protect their partners from HIV infection and themselves from becoming infected STDs. They will also be referred for further HIV counseling and treatment. Information about their $CD4^+$ T-cell counts may help them and their clinicians make decisions with respect to their medical care.

There may be no direct benefits to participants in this study. It is not yet known whether acyclovir reduces HIV viral set point. 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 modify the course of HIV disease progression.

8.5 Access to HIV-related Care

8.5.1 Counseling

All 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 post-test HIV counseling, if applicable.

HIV risk reduction and post-test counseling will be provided to all potential study participants and to all enrolled participants. 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 HIV-Infected Participants

Study staff will provide participants with their HIV test results in the context of post-test counseling in the main HPTN 039 study.

8.6 Participant Reimbursement

Participants may 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 in 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 occur in the context of HPTN 039.

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):

- Whole blood for $CD4^+$ and $CD8^+$ lymphocyte subsets (LL).
- Urine for pregnancy testing (LL).

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). Local laboratories may choose to test the samples for HIV RNA; these results will not be included in the data analysis but will be used for participant care.

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 (UW):

- Plasma for HIV RNA testing (UW).
- Swabs of genital lesions, frozen at –20°C, for PCR (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. Local regulations may prohibit shipping of specimens for archive outside of the country; in such a case, local regulations should be observed. All specimens will be shipped in accordance with IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS. All specimens will be shipped initially to the CL; CL will forward the appropriate specimens on a regular basis to UW for testing.

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.

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.

CL staff will follow-up directly with site staff to resolve any quality assurance problems identified through this process.

9.4 Specimen Storage And Possible Future Research Testing

Study site staff will ship samples to the CL on a regular basis, and 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 HPTN 039 procedures. Included in this step will be CORE review of each site-specific study informed consent form.

Pending successful 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 039-01-Ancillary

VISITS / PROCEDURES	Enrollment Visit (Day 0)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6 (or Exit)
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES							
Obtain/ update locator information		X	X	X	X	X	X
Administer eligibility checklist	X						
Obtain informed consent for enrollment (and optional storage of blood if pt. agrees)	X						
Provide condom counseling and distribute condoms		X	X	X	X	X	X
CLINICAL PROCEDURES							
Provide test results and counseling (as applicable)	X	X	X	X	X	X	X
Collect unused study drug and/or bottle from previous visit		X	X	X	X	X	X
Provide adherence counseling	X	X	X	X	X	X	X
Administer brief sexual behavior questionnaire		X	X	X	X	X	X
Administer partner-specific sexual behavior questionnaire	X			X			X
Assess genital symptoms and STD history (including unexpected weight gain AND decreased urine output)	X	X		X		X	X
Administer current genital symptoms questionnaire		X	X	X	X	X	X
Administer questionnaire to assess HIV-related symptoms	X						
Assess presence of HIV-related symptoms	X						
Administer questionnaire to assess opportunistic infections		X	X	X	X	X	X
Record ART taken since last visit	X	X	X	X	X	X	X
Provide risk reduction counseling	X	X	X	X	X	X	X
Obtain medical history		X	X	X	X	X	X
Perform anogenital exam for STDs	X[1]	X	X[1]	X	X[1]	X[1]	X
Collect Blood	X	X				X	X
Collect swabs for participants with genital ulcers	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Treat bacterial STD (if clinically indicated)/syndromic management or refer for free treatment	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Dispense study product and instructions for use	X	X	X	X	X	X	X
LAB PROCEDURES							
HIV viral load from plasma	X	X				X	X
CD4/CD8 count (whole blood)	X	X				X	X
Syphilis RPR							X
For WSM Urine for pregnancy	X	X	X[1]	X	X[1]	X	X

1. If indicated.

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

TITLE OF THE RESEARCH:

A Prospective Cohort Study of Recent Seroconverters in HPTN 039: the Effect of HSV-2 Suppression on HIV-1 Viral Set Point

HPTN 039-01-Ancillary, Version 2.0 November 5, 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?

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 and will be destroyed.

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.

_____	_____
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 III: SAMPLE INFORMED CONSENT FOR ENROLLMENT AT SITES ENROLLING MEN

TITLE OF THE RESEARCH:

A Prospective Cohort Study of Recent Seroconverters in HPTN 039: the Effect of HSV-2 Suppression on HIV-1 Viral Set Point

HPTN 039-01-Ancillary, Version 2.0 November 5, 2004

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

INVESTIGATOR'S STATEMENT

Introduction

You are being asked to take part in a research study to find out whether suppression of the genital herpes virus changes the HIV viral level of someone who has just become infected with HIV. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study is **[Insert name of Principle 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 for treatment of genital herpes, and has been used in over 40 million people. 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.

The specific purpose of this study is to determine whether suppression of genital herpes (HSV-2) in the early period of HIV infection can lower the amount of HIV in the blood in the first 6 months after a person becomes infected with HIV. Several studies have shown that people with HSV-2 infection who are also infected with human immunodeficiency virus (HIV) may have

higher levels of HIV virus in their blood. This may be because HSV-2 attracts inflammatory cells to the genital area and those cells can be infected with HIV. HIV is the virus that causes AIDS. Acyclovir does not specifically treat HIV. However, given the interaction between HSV-2 and HIV from prior studies, it is important to see if suppressing HSV-2 will lower the amount of HIV. Thus, this study is being done to find out if acyclovir used in the early months of HIV infection has any effect on HIV viral levels.

To learn this, we will enroll approximately 40 newly HIV-infected men in Peru and the United States who were participants in the HPTN 039 study. It will take about 18 months to enroll all participants. Approximately **{X}** men will be enrolled at this site. Each participant will be followed for 6 months after enrollment.

You have become HIV infected during the main HPTN 039 study. In this follow-up study, you will be tested to monitor the status of your HIV infection. We will measure the amount of HIV virus in your blood and your CD4 cell counts at Enrollment and months 1, 5, and 6 in this study, at no expense to you. We will provide you with your CD4 results approximately 2 weeks after each test. You will also continue to take your blinded study medication throughout this time; this means that you will continue taking the treatment to which you were originally assigned in the main study (acyclovir or placebo). While acyclovir is not a treatment for HIV, there are research studies that have shown that people whose HSV-2 infection is suppressed by daily acyclovir may have lower levels of HIV virus in their blood.

We will inform you about current guidelines for the use of antiretroviral drugs in treating HIV infected adults and adolescents. We will give you a copy of these recommendations. Your clinician will have an opportunity to consult with the study clincian, as desired, regarding your treatment options. TREATMENTS FOR HIV INFECTION WILL NOT BE PROVIDED THROUGH THIS STUDY. Should you decide to begin antiretroviral treatment while enrolled in this study, you will continue to be followed as described in this consent form.

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 continue receiving the same pills that you received in the main HPTN 039 study. 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. Neither you nor the study staff will know which group you are in.

You will be in the study for 6 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 6 visits after today. At every visit, we will continue to ask you to update your locator information.

Enrollment visit:

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. In addition, the following will happen at this 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 draw approximately 10 ml of blood (about a tablespoon) with a needle from you. This blood will be measured for the amount of HIV virus in your blood. It will also be tested to see how your immune system is doing (by a "CD4 and CD8 count").

- If you have symptoms of STDs, or an anogenital sore, we will examine your genital and anal area 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).

Each time we collect blood from you, we will freeze the blood that is left over from your test here and store it **[site/clinic]**.

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.

If you have a reaction to the acyclovir, we may run additional tests on this blood sample to help us make recommendations regarding your health care.

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

Acyclovir For Herpes Outbreaks During the Study

If you have herpes outbreaks (either genital or oral) during the study, 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. This is the standard dose of acyclovir that is used to treat an outbreak of herpes.

Monthly Visits

You will come back to the clinic every month for a study visit. These visits will last about a half hour and are similar to the ones in the main study. 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, including any antiretroviral medication you may have taken.
- If you have symptoms of STDs or a genital sore, we will examine your genital and anal area and swab the sore. 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.
- We will give you your test results from your last blood draw and give you information and counseling about what the results mean.

Months 1, 3, 5 and 6 Visits
These visits will be about one hour long. The following will happen in addition to the monthly procedures:

- We will draw approximately 10 ml of blood (about a tablespoon) with a needle from you. This blood will be measured for the amount of HIV virus in your blood. It will also be tested to see how your immune system is doing (by a "CD4 and CD8 count"). **(Months 1, 5 and 6)**
- We will provide you with all available test results.
- We will examine your genital and anal area (**Months 1, 3 and 6**, and if you have symptoms of STDs or a genital sore). If there are any sores present, we will swab the sores. If you have a bacterial STD, you will receive treatment (or referral to a local clinic that provides free treatment). .
- In the event of unexplained weight gain > 5 lbs (2.3 kg) AND unexplained decreased urine output in the past 3 months, we will perform serum creatinine testing.

Under the law, all cases of gonorrhea, syphilis, and chlamydia must be reported to **[as relevant to site]**. This reporting requires giving your name and contact information. If you test positive for gonorrhea, syphilis, or chlamydia while you are in the study, we will report your name to **[as relevant to site]**.

Final Exit Visit
At your last study visit, all procedures listed in the Month 1 visit will take place. In addition, we will test your blood for syphilis. At this visit, we will draw approximately 15 ml of blood (about a tablespoon) with a needle from you.

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. You may choose not to be visited outside of the clinic at any time, and your choice will not affect the care provided to you by participation in this clinical trial.

Test Results and Other Information
We will provide you with your test results during the study if they become available. After the study, you will be provided with your syphilis test results either over the telephone or in person. Finally, when all of the data from this study have been analyzed, you may be able to obtain other information at the clinic.

It may be necessary to test your samples or refer to the previous data collected from you from the main HPTN 039 protocol for the purposes of this protocol. By signing this Informed Consent Form, you are granting permission for this.

Risks, Stresses and Discomfort
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 than 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 the how much urine you make. If you report such symptoms, we will draw a blood specimen to test for kidney function (serum creatinine) 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. 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 lower HIV viral levels. Also, you may be in the study group that receives the placebo capsules. Information learned from this study may help in finding new ways to make people with HIV disease live longer. You will receive information about your HIV infection and how to protect your partner(s) from HIV and yourself from STDs. You will receive free condoms and treatment for STDs. You will receive information about your CD4 and CD8 cell counts that may help you and your doctor make decisions about your medical care. You will also receive information about where you can go for necessary medical care, emotional support, counseling and other services you may need.

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 time 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 U.S. Food and Drug Administration (FDA), 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.)
- 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 HIV care and treatment of HSV infection 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.

Costs to You
There will be no cost to you for study-related visits, tablets, examinations, laboratory tests or other procedures. You will pay for any other medical costs not related to this study. You will be responsible for costs of care related to medical treatment resulting from HIV infection, except treatment for genital herpes.

Compensation for Your Time and Travel
You will receive **X** for today's visit, **X** for each monthly visit to pay for your transportation costs and time away from work for the study visits.

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 IV: SAMPLE INFORMED CONSENT FOR ENROLLMENT AT SITES ENROLLING WOMEN

TITLE OF THE RESEARCH:

A Prospective Cohort Study of Recent Seroconverters in HPTN 039: the Effect of HSV-2 Suppression on HIV-1 Viral Set Point

HPTN 039-01-A, Version 2.0 November 5, 2004

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

INVESTIGATOR'S STATEMENT

Introduction
You are being asked to take part in a research study to find out whether suppression of the genital herpes virus changes the HIV viral levelof someone who has just become infected with HIV. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study is **[Insert name of Principle 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 for treatment of genital herpes, and has been used in over 40 million people. 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.

The specific purpose of this study is to determine whether suppression of genital herpes (HSV-2) in the early period of HIV infection can lower the amount of HIV in the blood in the first 6 months after a person becomes infected with HIV. Several studies have shown that people with HSV-2 infection who are also infected with human immunodeficiency virus (HIV) may have higher levels of HIV virus in their blood. This may be because HSV-2 attracts inflammatory cells

to the genital area and those cells can be infected with HIV. HIV is the virus that causes AIDS. Acyclovir does not specifically treat HIV. However, given the interaction between HSV-2 and HIV from prior studies, it is important to see if suppressing HSV-2 will lower the amount of HIV. Thus, this study is being done to find out if acyclovir used in the early months of HIV infection has any effect on HIV viral levels.

To learn this, we will enroll a total of **[XX]** newly HIV-infected women in Africa who were participants in the HPTN 039 study. It will take about 18 months to enroll all participants. Approximately **[XX]** women will be enrolled at this site. Each participant will be followed for 6 months after enrollment.

You have become HIV infected during the main HPTN 039 study. In this follow-up study, you will be tested to monitor the status of your HIV infection. We will measure the amount of HIV virus in your blood and your CD4 cell counts at Enrollment and months 1, 5, and 6 in this study, at no expense to you. We will provide you with your CD4 results approximately 2 weeks after each test. You will also continue to take your blinded study medication throughout this time; this means that you will continue taking the treatment to which you were originally assigned in the main study (acyclovir or placebo). While acyclovir is not a treatment for HIV, there are research studies that have shown that people whose HSV-2 infection is suppressed by daily acyclovir may have lower levels of HIV virus in their blood.

We will inform you about current guidelines for the use of antiretroviral drugs in treating HIV infected adults and adolescents. We will give you a copy of these recommendations. Your clinician will have an opportunity to consult with the study clincian, as desired, regarding your treatment options. TREATMENTS FOR HIV INFECTION WILL NOT BE PROVIDED THROUGH THIS STUDY. Should you decide to begin antiretroviral treatment while enrolled in this study, you will continue to be followed as described in this consent form.

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 continue receiving the same pills that you received in the main HPTN 039 study. 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. Neither you nor the study staff will know which group you are in.

You will be in the study for 6 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 6 visits after today. At every visit, we will continue to ask you to update your locator information.

Enrollment visit:
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. In addition, the following will happen at this 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 draw approximately 10 ml of blood (about a tablespoon) with a needle from you. This blood will be measured for the amount of HIV virus in your blood. It will also be tested to see how your immune system is doing (by a "CD4 and CD8 count").

- If you have symptoms of STDs, or an anogenital sore, we will examine your genital and anal area 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 collect a urine sample from you to test for pregnancy. If you are pregnant, you will not be able to continue taking study medication. However, we would like you to continue to participate in the study. We may offer you acyclovir for the treatment of genital sores during the second and third trimesters of your pregnancy, while you are enrolled in the study.

Each time we collect blood from you, we will freeze the blood that is left over from your test here and store it **[site/clinic]**.

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.

If you have a reaction to the acyclovir, we may run additional tests on this blood sample to help us make recommendations regarding your health care.

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

Acyclovir For Herpes Outbreaks During the Study
If you have herpes outbreaks (either genital or oral) during the study, 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. This is the standard dose of acyclovir that is used to treat an outbreak 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 and are similar to the ones in the main study. 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, including any antiretroviral medication you may have taken.
- If you have symptoms of STDs or a genital sore, we will examine your genital and anal area and swab the sore. If you have a bacterial STD, you will receive treatment (or referral to a local clinic that provides free treatment).
- If you or study staff feel that you may be pregnant, we will collect your urine and test for pregnancy. If you are pregnant, you will not be able to continue taking study medication. However, we would like you to continue to participate in the study. We may offer you

acyclovir for the treatment of genital sores during the second and third trimesters of your pregnancy, while you are enrolled in the study.
- We will counsel you about protecting yourself and your partner from HIV and other STDs and offer you condoms.
- We will give you your test results from your last blood draw and give you information and counseling about what the results mean.

Months 1, 3, 5 and 6 Visits
These visits will be about one hour long. The following will happen in addition to the monthly procedures:

- We will draw approximately 10 ml of blood (about a tablespoon) with a needle from you. This blood will be measured for the amount of HIV virus in your blood. It will also be tested to see how your immune system is doing (by a "CD4 and CD8 count"). **(Months 1, 5 and 6)**
- We will provide you with all available test results.
- We will examine your genital and anal area (**Months 1, 3 and 6**, and if you have symptoms of STDs or a genital sore). If there are any sores present, we will swab the sores. If you have a bacterial STD, you will receive treatment (or referral to a local clinic that provides free treatment).
- We will collect a urine sample from you to test for pregnancy (**Months 1, 3 and 6**). If you are pregnant, you will not be able to continue taking study medication. However, we would like you to continue to participate in the study. We may offer you acyclovir for the treatment of genital sores during the second and third trimesters of your pregnancy, while you are enrolled in the study.
- In the event of unexplained weight gain > 5 lbs (2.3 kg) AND unexplained decreased urine output in the past 3 months, we will perform serum creatinine testing.

Final Exit Visit
At your last study visit, all procedures listed in the Month 1 visit will take place. In addition, we will test your blood for syphilis. At this visit, we will draw approximately 15 ml of blood (about a tablespoon) with a needle from you.

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. You may choose not to be visited outside of the clinic at any time, and your choice will not affect the care provided to you by participation in this clinical trial.

Test Results and Other Information
We will provide you with your test results during the study when they become available. After the study, you will be provided with your syphilis test results either over the telephone or in person. Finally, when all of the data from this study have been analyzed, you may be able to obtain other information at the clinic.

It may be necessary to test your samples or refer to the previous data collected from you from the main HPTN 039 protocol for the purposes of this protocol. By signing this Informed Consent Form, you are granting permission for this.

Under the law, all cases of gonorrhea, syphilis, and chlamydia must be reported to **[as relevant to site]**. This reporting requires giving your name and contact information. If you test positive for gonorrhea, syphilis, or chlamydia while you are in the study, we will report your name to **[as relevant to site]**.

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.

If you become pregnant, you must notify the study doctor immediately. 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 also discuss with you the chance of giving HIV to your baby and will refer you to services where they can provide anti-HIV medicines help reduce this risk. We cannot provide these medicines in this study. We will ask you to continue to come for your follow-up visits for 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.

Risks, Stresses and Discomfort

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 than 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 the how much urine you make. If you report such symptoms, we will draw a blood specimen to test for kidney function (serum creatinine) 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. 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 lower HIV viral levels. Also, you may be in the study group that receives the placebo capsules. Information learned from this study may help in finding new ways to make people with HIV disease live longer. You will receive information about your HIV infection and how to protect your partner(s) from HIV and yourself from STDs. You will receive free condoms and treatment for STDs. You will receive information about your CD4 and CD8 cell counts that may help you and your doctor make decisions about your medical care. You will also receive information about where you can go for necessary medical care, emotional support, counseling and other services you may need.

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 time 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 U.S. Food and Drug Administration (FDA), 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.)
- 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 HIV care and treatment of HSV infection 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.

Costs to You
There will be no cost to you for study-related visits, tablets, examinations, laboratory tests or other procedures. You will pay for any other medical costs not related to this study. You will be responsible for costs of care related to medical treatment resulting from HIV infection, except treatment for genital herpes.

Compensation for Your Time and Travel
You will receive **X** for today's visit, **X** for each monthly visit to pay for your transportation costs and time away from work for the study visits.

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

TITLE OF THE RESEARCH:

A Prospective Cohort Study of Recent Seroconverters in HPTN 039: the Effect of HSV-2 Suppression on HIV-1 Viral Set Point

HPTN 039-01-A, Version 2.0 November 5, 2004

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 Prospective Cohort Study of Recent Seroconverters in HPTN 039: the Effect of HSV-2 Suppression on HIV-1 Viral Set Point". 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
- Plasma HIV viral level testing
- CD4 and CD8 cell count testing
- Syphilis Testing
- STD testing
- Medical History
- Current medications
- Sexual History and Risk Behavior
- Genital symptoms
- 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 lowers the amount of HIV virus in my blood.

The Researchers may use and share my health information with:

- Family Health International (FHI)
- Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
- FHI's Regulatory Affairs and Quality Assurance
- **(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: