

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-
INFECTED INDIVIDUALS IN CARE SETTINGS**

DAIDS ID: 10668

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, U.S. National Institute of Allergy and Infectious Diseases
U.S. National Institute on Drug Abuse
U.S. National Institute of Mental Health
U.S. National Institutes of Health

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PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV- INFECTED INDIVIDUALS IN CARE SETTINGS

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LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	audio-computer assisted self interviewing
ACTG	AIDS Clinical Trials Group
AC2	Aptima Combo 2
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ASI	addiction severity index
ATN	Adolescent Medicine Trials Network
AUDIT	Alcohol Disorder Identification Test
CAB	Community Advisory Board
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression Scale
CI	confidence interval
CORE	(HPTN) Coordinating and Operations Center
CT	chlamydia
CTN	clinical trial network
CTU	clinical trials unit
DAIDS	Division of AIDS
EC	ethics committee
FCH	Fenway Community Health
GC	gonorrhea
GEE	generalized estimation equations
HAART	highly active anti-retroviral therapy
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HRSA	Health Resources and Services Administration
HSV	Herpes simplex virus
IATA	international air transport association
ICH	International Conference on Harmonisation
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IOM	Institute of Medicine
IPEC	Instituto de Pesquisa Clinica Evandro Chagas
IRB	institutional review board
LDMS	Laboratory Data Management System
LL	local laboratory
MOP	(HPTN) Manual of Operations
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NGO	Non-governmental organization

NIDA	National Institute of Drug Abuse
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NL	(HPTN) Network Lab
OHRP	(NIH) Office of Human Research Protection
OR	odds ratio
PCR	polymerase chain reaction
PI	principle investigator
PEP	post-exposure prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief
PrEP	pre-exposure prophylaxis
QA	quality assurance
RSC	Regulatory Support Center
SAE	serious adverse event
SDA	strand displacement amplification
SDMC	(HPTN) Statistical and Data Management Center
SHAS	Supplement to HIV/AIDS Surveillance
SMC	(HPTN) study monitoring committee
SSP	study specific procedures (manual)
STAI	state-trait anxiety inventory
STD	sexually transmitted disease
STI	sexually transmitted infection
VCT	voluntary counseling and testing

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INVESTIGATOR OF RECORD PROTOCOL SIGNATURE PAGE

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Version 2.0 / 01 November 2011

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Sponsored by:

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U.S. National Institutes of Health

I, the Investigator of Record, 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 after submission of the site's final Financial Status Report to the Division of AIDS (DAIDS), unless otherwise specified by DAIDS or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

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

Name of Site Principal Investigator

Signature of Site Principal Investigator

Date

HPTN 063

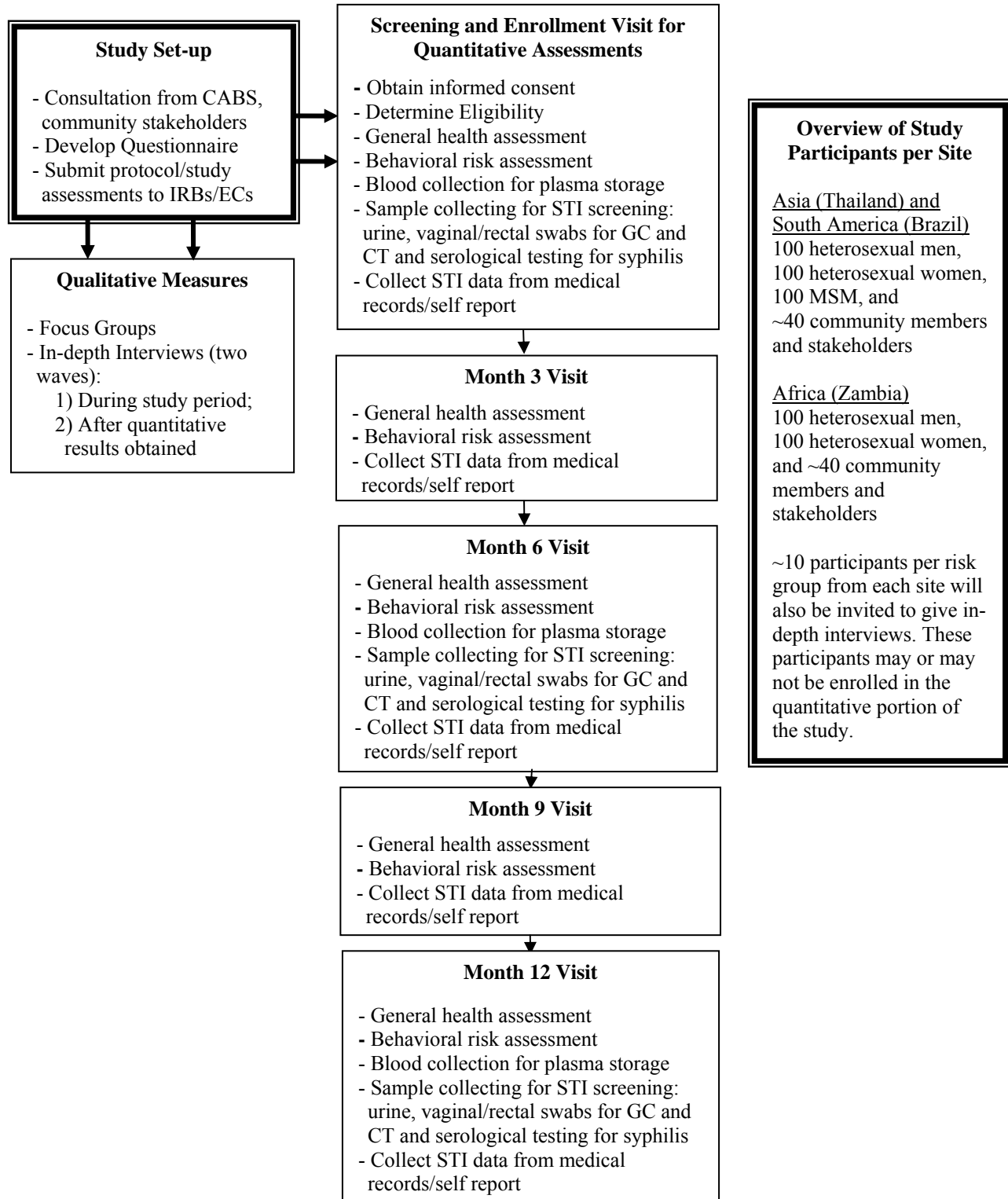
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SCHEMA

Purpose:	To conduct preparatory research needed to design a behavioral intervention to decrease sexual transmission risk behaviors in HIV-infected individuals in care and to determine whether a similar intervention structure can be used across various sexual risk groups and cultural settings.
Design:	Multi-site, observational, cohort study (quantitative component). In-depth interviews and focus groups (qualitative component).
Study Population:	HIV-infected men and women in Africa (Zambia), Asia (Thailand), and South America (Brazil), who have reported recent (within 3 months) HIV sexual transmission risk behavior.
Study Size:	800 quantitative (HIV-infected) participants: 300 heterosexual men (100 per site), 300 heterosexual women (100 per site), 200 MSM (100 per site in Asia and South American sites only); approximately 120 qualitative participants (community members/stakeholders; 40 from each site, a subset of the HIV-infected participants will also participate in qualitative individual interviews).
Study Duration:	Approximately two years total: Approximately one year for participant accrual – participants will be followed for one year with interviews and assessments quarterly. Qualitative assessment will occur during this 2 year time frame.
Primary Objectives:	<ol style="list-style-type: none">1) To establish baseline rates of sexual HIV transmission risk behavior in high-risk, HIV-infected individuals, and to observe the rates and patterns of behavioral change over time.2) To gather formative data on the potential structure and content of a behavioral intervention for individuals with HIV in care in international settings and to determine the best, culturally appropriate model for the intervention that will link prevention to care for HIV-infected individuals.3) To examine potential psychosocial and sociodemographic correlates of sexual risk taking in these individuals in order to help shape the content of an individualized behavioral intervention.
Secondary Objectives:	Evaluate STI prevalence and incidence and investigate whether these biomarkers may be used to corroborate self-reported sexual behavior associated with potential transmission risks
Study Sites:	<ul style="list-style-type: none">• Matero Clinic CRS; Lusaka, Zambia• Chiang Mai University. AIDS Prevention CRS; Chiang Mai, Thailand• Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS; Rio de Janeiro, Brazil

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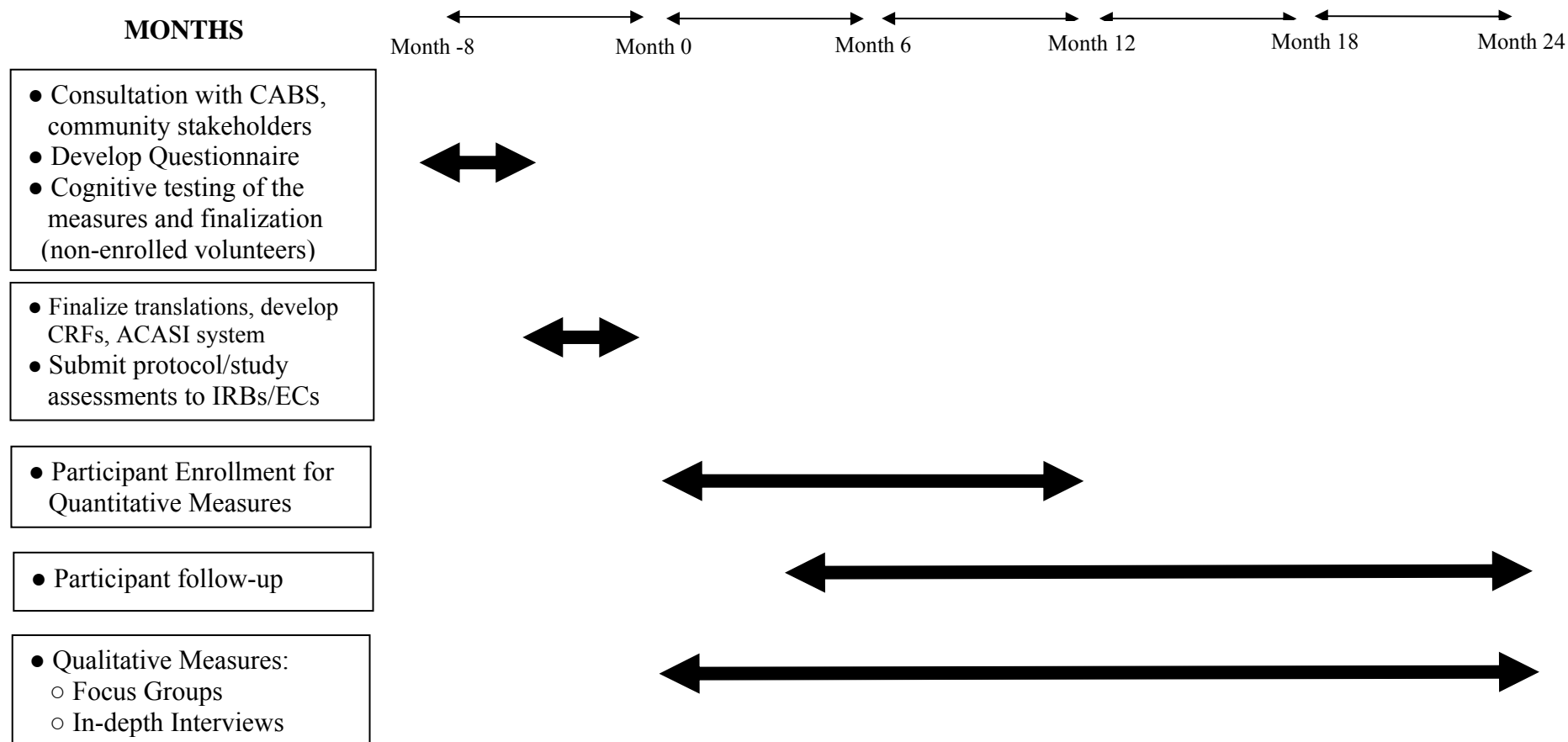
OVERVIEW OF STUDY DESIGN



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STUDY TIMELINE



1.0 INTRODUCTION

1.1 Background and Prior Research

This project will allow for the collection of necessary preparedness data to design and implement a multi-site human immune-deficiency syndrome (HIV) prevention trial with HIV-infected participants that links HIV prevention with HIV care in diverse international settings. In the context of this study, we define the term “secondary prevention trial” as a study that examines a behavioral risk reduction intervention with HIV-infected individuals. The eventual trial will use the existing infrastructure of the HIV Prevention Trials Network (HPTN), and it is expected that it will utilize other National Institutes of Health (NIH) Acquire Immune Deficiency Syndrome (AIDS) clinical trial networks (i.e. AIDS Clinical Trial Group [ACTG], International Maternal Pediatric Adolescent AIDS Clinical Trials Group [IMPAACT], International Network for Strategic Initiatives in Global HIV Trials [INSIGHT], Adolescent Medicine Trials Network [ATN]) to test an intervention that links HIV prevention with HIV care in NIH-funded HIV care settings across the world.

To date, although there has been recent attention to secondary HIV prevention in the U.S., secondary prevention efforts in international settings are limited. Effective behavioral interventions in diverse settings require careful preparedness work in order to maximize the chances of success and to assure that theory-based interventions are appropriate to the relevant cultural setting’s populations. Behavioral interventions also require preparedness work to estimate baseline outcomes in the group that would, in an eventual randomized trial, be assigned to a comparison condition. This estimate is important because of the trend in HIV prevention studies for comparison arm participants to also improve as part of study participation. This trend has had the effect of limiting the degree to which an intervention can demonstrate statistically significant effects.

Using the existing infrastructure of the NIH-sponsored clinical trials networks, including an experienced statistical and operations center that already works in the study settings, greatly increases the feasibility of rapidly conducting preparedness research for secondary prevention trials, as well as decreases the cost of doing so in any other mechanism (e.g. a multi-site R01). The proposed preparatory work will be used in the design of a multi-center international secondary HIV prevention efficacy trial, which, if successful, will document the feasibility and utility of an intervention that could be widely utilized in HIV care clinics throughout the world. The ultimate intervention could become part of standard of care for HIV, become part of an overall HIV prevention package for a community, and could become part of anti-retroviral treatment (ART) programs such as those provided by the President’s Emergency Plan for AIDS Relief (PEPFAR).

Validated secondary behavioral HIV prevention interventions are an important component of a repertoire of potential approaches to prevent HIV on a global scale. Currently there is no biomedical cure, vaccine, or definitive primary prevention intervention for HIV. Given the complexity of HIV transmission, both biomedically and behaviorally, it is likely that a combination of approaches is needed. Capitalizing on the

ability to identify large numbers of individuals with HIV who present for HIV care, may be a highly effective way to decrease transmissions.

1.2 Rationale for a Preparedness Study Linking HIV Prevention with HIV Care through HPTN

1.2.1 ART Access is Expanding across the Globe, Allowing for the Identification of Large Numbers of Individuals with HIV in Care.

The roll out of ART in diverse parts of the world through the Clinical Trials Networks, PEPFAR, and government and non-governmental (NGO) - sponsored initiatives provides a timely and unique opportunity to identify large numbers of individuals with HIV who are in care in diverse parts of the world.

The ACTG has numerous international clinical trials units that conduct translational and therapeutic research across the world. The ACTG's stated research priorities are translational research and drug development and optimization of clinical management, including co-infection and co-morbidities. These clinical trials units are typically situated in settings where both research clinical trials and HIV clinical care are delivered. Hence, these settings have both research infrastructure and provide care, facilitating enrollment into studies of HIV transmission risk behaviors and into a prevention trial that links HIV prevention with HIV care. One study, ACTG 5175, for example, has completed stage 1 enrollment of patients in the following international sites: Johannesburg and Durban, South Africa; Chiang Mai, Thailand; Lilongwe and Blantyre, Malawi; Pune and Chennai, India; Harare, Zimbabwe; Port-Au-Prince, Haiti; Rio de Janeiro and Porto Alegre, Brazil; and Lima, Peru. Members of the current protocol team trained these sites in providing safer sex counseling as part of the trials, as well as oversaw translations and back translations of behavioral assessment measures.

PEPFAR is a five-year, \$15 billion American Government initiative to combat the global HIV/AIDS epidemic and focuses on the following 14 countries: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda and Zambia. This comprehensive plan aims to "prevent 7 million new AIDS infections, treat at least 2 million people with life-extending drugs, and provide humane care for millions of people suffering from AIDS, and for children orphaned by AIDS." In September 2005, approximately 401,000 people were receiving treatment with PEPFAR support in the focus countries, and around 70,000 were benefiting in other countries through U.S. bilateral programs (U.S. Department of State, 2006). By the end of September 2007, approximately 1.45 million people were receiving PEPFAR-supported treatment, of which 94% were in the 14 focus countries (U.S. Department of State, 2007). PEPFAR provided HIV care for over 1.7 million people through March 2005; by the end of September 2007, this number had risen to nearly 6.7 million. These numbers present a timely and unique opportunity to identify vast numbers of HIV-infected individuals in care around the world. Notably, only 20% of PEPFAR dollars are spent for HIV/AIDS prevention, with a principal focus on primary prevention (at least 33% of this is to be spent on abstinence-until-marriage programs) suggesting the need for evidenced-based secondary prevention efforts. The preparedness research articulated in this current protocol would also be of great benefits to initiatives such as PEPFAR should there be a plan to add secondary prevention to that program.

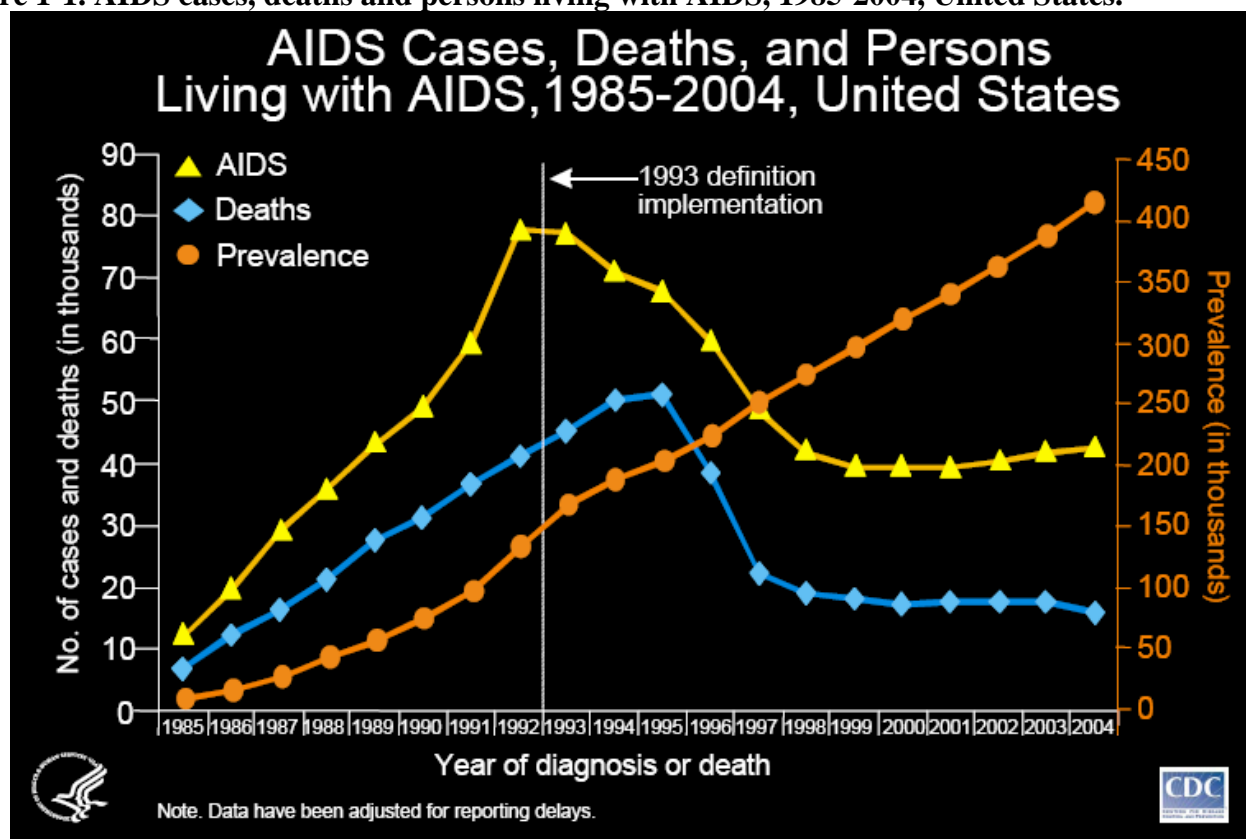
1.2.2 The Expansion of ART Means that More Individuals with HIV Will Live Longer Lives Creating the Need for Secondary Prevention Efforts in Larger Numbers of Individuals.

The availability of treatment for HIV is rapidly growing, with ART becoming more and more available in the diverse areas of the world where it is needed. This accomplishment will extend the lives of large numbers of individuals in places where the HIV burden is exceptional. The consequence of HIV treatment in diverse settings, however, on sexual behavior, its correlates, and long term quality of life, is poorly understood and conflicting, and there is a dearth of intervention studies that link prevention and care in such settings.

As the prevalence of HIV in the population increases due to greater treatment success, and decreased deaths associated with HIV disease, there are more and more individuals who will need to maintain self-care and risk-reduction practices. During the 1980s when the HIV/AIDS epidemic started in the U.S., people with an AIDS diagnosis were not likely to live longer than a few years. However, with the advent of HIV treatment success, HIV-infected individuals in the U.S. now have longer and healthier lives. As of November 2007, there were 30 antiretroviral drugs approved by the U.S. Food and Drug Administration to treat people infected with HIV (U.S. Department of Health and Human Services, 2007). The complex dynamic here is that the use of antiretroviral therapy has greatly reduced the number of deaths associated with AIDS, but to date cannot suppress HIV viral replication completely, and therefore, people infected with HIV who take antiretroviral drugs may be still able to transmit HIV to others. Additionally, excellent adherence over long periods of time is required to maintain a suppressed viral load.^{6;10;40;47} Noncompliance with combination therapy can result in increased HIV replication and the development of viral mutations, which can lead to medication resistance.^{3;10;11;34;80}

Due to the decline in HIV-associated deaths, the prevalence of people living with AIDS in the U.S. more than doubled from 1993 (173,772) to 2001 (362,827) (CDC, 2001), and at the end of 2003, an estimated 1,039,000 to 1,185,000 persons in the U.S. were living with HIV/AIDS. In 2005, the estimated number of deaths of persons with AIDS in the United States was 17,011, a dramatic decrease from the number of AIDS associated deaths in 1993 (CDC, 2005). Table 1-1 below depicts AIDS cases, deaths and persons living with AIDS in the U.S. from 1985 through 2004.

Figure 1-1. AIDS cases, deaths and persons living with AIDS, 1985-2004, United States.



Source: Centers for Disease Control and Prevention, 2005.

A similar pattern of increased prevalence and decreased deaths is expected to occur, over time, in diverse settings, and hence, implementable, culturally-relevant, and empirically-supported HIV-risk reductions that link HIV prevention and HIV care are needed. In order to develop the best interventions that link HIV prevention into HIV care, research is needed to determine whether a similar structure of an intervention can be done in multiple risk groups and multiple settings, as well as the most important culturally relevant topical content areas for the intervention to address.

1.2.3 Integrating HIV Prevention Into HIV Care Will Be a Particularly Cost-Effective Means to Prevent or Decrease Continued HIV Risk Behavior and Transmission by Infected Individuals.

Significantly reducing HIV transmission will require new strategies, including increased emphasis on preventing transmission by HIV-infected persons.^{12;17;41} As stated in the Institute of Medicine's (IOM), *No Time To Lose: Getting More From HIV Prevention*, "... the clinical care setting provides opportunities for integrating prevention into the standard of care for those who are infected or at high risk".¹⁷ Clinicians providing medical care to HIV-infected persons can play a key role in helping their patients reduce risk behaviors and maintain safer practices.^{12;14;25;26;41;48;56} There is a paucity of research on how to effectively do this, particularly in resource poor settings where the burden of HIV is disproportionate and where access to ART is rapidly expanding. By gathering baseline data on HIV transmission risk behavior, sexual partners, and psychosocial and structural variables related to HIV transmission risk behavior, the present study is meant

to inform the development of a standard practice, easy-to-implement, but effective intervention that can link prevention to care in diverse settings for diverse populations and risk groups.

Although cost information on HIV-prevention services is limited and generally restricted to studies of the cost-benefit or cost-effectiveness of certain types and locations of HIV counseling and testing services and other interventions,^{36;38;42;66} estimates suggest that U.S. prevention activities averted 204,000-1,585,000 infections at a cost of between U.S.\$49,700 and U.S.\$6,400 per infection prevented (less than the medical costs of treating a person with HIV).³⁵ Systematic reviews examining the cost-effectiveness of public health interventions for primary HIV prevention programs suggests substantial cost benefits of HIV prevention.^{39;75;81} For example, a review of cost-effectiveness studies found costs between U.S.\$460 and U.S.\$1.2 million per case of previously unknown HIV infection prevented, strongly depending on prevalence; studies on sexual and vertical transmission demonstrated lower costs when the benefits of treatment were included.⁷⁵

Effective ART regimens have substantially improved survival for HIV-infected persons and have increased the lifetime cost of HIV-related medical care in the U.S. From the time of entering HIV care, per person projected life expectancy is 24.2 years, discounted lifetime cost is U.S.\$385,200, and undiscounted cost is U.S.\$618,900 for adults who initiate ART with CD4 cell count < 350/microL.⁷³ Lifetime cost of HIV medical care has grown from about U.S.\$55,000 to more than U.S.\$155,000, while the number of quality of life years lost per case of HIV infection has decreased from 9.26 to 7.10, when discounted at a 5% annual rate.³⁷ The net effect of these increases in the medical costs of care and treatment saved by averting an HIV infection and in quality of life years makes HIV prevention a relatively more cost-effective strategy than other, non-HIV health-related programs.³⁷

1.2.4 HIV-Infected Individuals Continue to Engage in Sexual Behaviors That Place Their Partners at Risk for HIV Acquisition or Themselves at Risk for Other Sexually Transmitted Infections (STIs).

A number of studies conducted in the U.S. and western Europe have documented that a substantial proportion of HIV-infected individuals engage in high-risk sexual practices with HIV-negative or unknown-serostatus partners.^{21;23;29;43;44;46;58;83;84;86} Reviews suggest that one in three HIV-infected individuals continue to engage in unprotected anal and vaginal intercourse (i.e. without a condom) after knowing that they are HIV-infected, and unprotected sex often occurs with unknown serostatus or known HIV-negative partners.^{22;45;57} In addition, prior research has documented increased rates of STIs among HIV-infected men and women compared to the general U.S. population, with a varying incidence of 11% to 25%,^{5;45;52;65} suggesting continued sexual risk taking among individuals infected with HIV. A study by Kalichman⁴⁵ of 223 men, 112 women, and five transsexuals living with HIV infection found that (263) 78% of participants had been sexually active in the previous 3 months. For the entire sample, 42 (12%) participants reported an STI in the past 3 months and 40 (11%) experienced symptoms of an STI without indicating a specific diagnosis in that time. In a large, 16-site study of U.S. men who have sex with men (MSM), conducted during May 2000 to December 2002, a total of 2,491 HIV-infected MSM were interviewed as part of the Supplement to HIV Surveillance (SHAS) project.¹³ Of 1,923 (77%) MSM who had HIV diagnosed for greater

or equal to 12 months, 1,177 (61%) reported having sex (i.e., any oral or anal intercourse) with a man during the preceding 12 months; overall, 40% of sexually active MSM reported insertive anal intercourse at last sexual encounter; of these, 25% did not use a condom. Taken together, these findings provide strong evidence for continued sexual risk taking among HIV-infected men and women in a variety of settings, and under a variety of circumstances indicating that sexually active HIV-infected individuals are at risk for transmitting HIV to their sexual partners as well as acquiring new STIs. Because the majority of these findings have come from U.S. and western European countries, there is a need to do the current study to get a sense of this in international sites, particularly in those that would join a secondary HIV prevention trial.

1.2.5 Newer STI Screening Tests, Using Nucleic Acid Amplification Testing (NAAT) Identify Substantial Levels of Untreated Gonorrhea and Chlamydia in High Risk Individuals

Based on a total of 1,110 MSM enrolled, for oropharyngeal gonorrhea (GC) samples (89 infections detected), sensitivities were 41% for culture, 72% for strand displacement amplification (SDA), and 84% for Aptima Combo 2 (AC2). For rectal GC samples (88 infections detected), sensitivities were 43% for culture, 78% for SDA and 93% for AC2. For oropharyngeal CT samples (9 infections detected), sensitivities were 44% for culture, 67% for SDA, and 100% for AC2. For rectal chlamydia (CT) specimens, (68 infections detected), sensitivities were 27% for culture, 63% for SDA, and 93% for AC2. Specificities of SDA and AC2 were >99.4% for both organisms and anatomical sites. However, based on initial findings on 205 MSM, polymerase chain reaction (PCR) had a 78.9% GC specificity with oropharyngeal swabs and PCR testing was discontinued for the rest of the study. Therefore, AC2 and SDA were far superior to culture for the detection of CT or GC from the oropharynx and rectum, with AC2 detecting twice as many infections as culture. NAATs can improve the ability to diagnose rectal and oropharyngeal infection with CT or GC in MSM.⁷²

Over a 1-month period asymptomatic MSM in care at a Boston community health center (n = 114) were screened for GC and CT using the BD ProbeTec technique. Eleven percent of the sample tested positive for one of the 2 STIs (GC or CT) from at least one mucosal site, but more positives were detected in the anal sites specimens. No positives were detected as positive by culture for either organism. Urine chlamydia (NAAT), 2.6%; Urine gonorrhea (NAAT), 1.0%; Amplified anal swab chlamydia (NAAT), 6.1%; Amplified anal swab gonorrhea (NAAT), 1.7%. Thus it is important to test rectal swabs in addition to urethral sites in MSM. Individuals who were infected with an STI were considerably more likely to have a prior history of one or more STI infections when compared with those without an STI infection (odds ratio (OR) = 3.69; $P < 0.02$).⁶³

1.2.6 Linking HIV Prevention into HIV Care in an Ongoing Way Can Allow for an Intervention to Continue, Resulting in Long-Term Benefit.

In both primary and secondary HIV prevention, when risk reduction interventions are effective, typically benefits wane with time.^{27;32;33;69} Because behavior change often occurs in incremental steps, a behavioral intervention that is routinely conducted during ongoing clinic visits could result, over time, in patients adopting and maintaining safer practices.¹² The present preparedness work will allow, through the HPTN platform, the

development of the structure and content of a behavioral intervention that links HIV prevention with HIV care that can be done in an ongoing way to maximize the chances of sustained behavioral change.

1.3 Rationale for Examining Behavioral and Biological Endpoints.

The focus of the present study is to gather formative data on HIV-infected individuals in care in order to develop a behavioral intervention and to understand what will be the best endpoint for an eventual intervention trial. The final endpoints used in an efficacy trial will depend on the sexual behaviors and partnership patterns of the various risk groups and settings. We will therefore gain an understanding of partner types in the context of risky sex. Accordingly we will ask about whether partners were casual but someone who the person knows, who can therefore be tracked, or an anonymous contact with a person who could potentially be found (e.g. because they met at specific venue, like a brothel), or totally anonymous and untraceable. We will ask these types of questions regarding the most recent incidents of unprotected sex with negative or unknown status partners. Depending on the answers to these types of questions, we see two potential options regarding having an HIV-incidence outcome.

1) The data obtained here may show that most risky behavior with HIV-infected individuals in care, occurs in the context of primary sexual partnerships, and/or sexual partnerships where the partner can be tracked. In this scenario, a sero-discordant partner study with an HIV incidence endpoint would be appropriate.

2) The data obtained may show that much of the risky behavior with HIV-infected individuals in care occur in the context of multiple and unstable sexual partnerships, and the ability to track sexual partners is compromised. In this scenario an HIV-incidence endpoint with a secondary prevention intervention for individuals in care would likely need to be part of an overall HIV prevention package that might include both primary and secondary prevention in a larger social setting, requiring community randomization in order to demonstrate changes in HIV incidence in populations exposed to a combined intervention. Using the infrastructure of the HPTN to develop a culturally appropriate and feasible intervention could then be implemented in settings where ART is being rolled out (e.g. PEPFAR), and include enough intervention components to reduce community incidence.

The present study will sample HIV-infected individuals who are in HIV care and are at risk for sexually transmitting HIV to their sexual partners. Despite HIV prevention and educational efforts, increased risk-taking behavior among HIV-infected individuals has been reported in several settings in the U.S., further evidenced by an increase in incidence rates of STIs.^{2;7;68;74} In contrast, HIV-infected individuals in Côte d'Ivoire reported abstinence as the most common HIV prevention strategy; patients receiving ART did not report increased coital frequency or risky behavior.⁶⁴ One study in Uganda found that providing ART and counseling was associated with reduced sexual HIV transmission risk behavior.⁸ We will build on these studies by using up-to-date assessment methods, as well as by understanding the behavioral patterns exhibited by various subpopulations in care at various international settings.

1.4 Rationale for Evaluating Bacterial STI Incidence as a Secondary Endpoint in an Eventual Behavioral Intervention

Gonorrhea and chlamydia have been shown to enhance potential infectivity of HIV in co-infected patients in studies in Malawi^{15;16} and Kenya⁵⁰. Moreover, incident bacterial STI can serve to corroborate self-reported sexual risk behaviors. The purpose of assessing the prevalence of urethral and rectal gonorrhea and chlamydia, as well as syphilis, at baseline and to assess their incidence at 12 months after the treatment of the prevalent infections in this feasibility study will be to determine if any of these potential biomarkers are sufficiently commonly detected to warrant their inclusion in an efficacy trial.

Comparisons can be made between self-reported behaviors and STI prevalence and incidence, as well as the difference in prevalence and incidence of each infection between HIV-infected persons from different countries, different genders, and different sexual orientations. The present study will collect sufficient samples (see Section 2.3.6) for a nested case control study to examine the utility of STI endpoints and their association with self-reported risk behavior.

1.5 The Importance of Conducting Preparedness Work Prior to a Full-Scale Trial in Order to Estimate Study Outcomes.

There is a body of literature suggesting that individual behaviors may be altered as a result of being in a research study.^{30;77} Because research participants randomized to receive the control/comparison condition in prevention trials often reduce their HIV transmission risk behavior concurrent to being a part of a study, conducting preparedness work in the framework of a real life investigation is both necessary and essential to estimating actual outcomes in the context of prevention trials. Accordingly, the current study will provide a more accurate portrait of what participants' outcomes (e.g. sexual behaviors) in the comparison arm of an eventual trial would look like. This estimate is particularly important to the success of an eventual prevention efficacy trial, as other studies have been unsuccessful at showing a benefit of the intervention on study outcomes because the comparison group derived benefit as well, therefore limiting the degree to which these interventions were able to demonstrate effects. Because of this, it is important to power a full-scale trial relative to these estimates, so that determination of statistical significance is feasible.

1.6 Existing Secondary Prevention Studies that Will Inform the Eventual Randomized Controlled Secondary HIV Prevention Trial.

Several randomized controlled trials or quasi-experiments using a variety of behavioral interventions have been conducted in the U.S. with HIV-infected individuals using reported sexual behavior as the primary outcome⁴.

A meta-analytic review of 12 HIV interventions for people living with HIV was conducted to determine overall efficacy in reducing HIV risk behaviors and identify intervention characteristics associated with efficacy.¹⁹ The 12 studies that met inclusion criteria were published from 1995-2005. Overall, interventions significantly reduced unprotected sex [OR, 0.57; 95% confidence interval (CI) 0.40-0.82] and decreased acquisition of sexually transmitted infections (OR, 0.20; 95% CI, 0.05-0.73). As a whole,

this meta-analysis revealed that interventions with the following characteristics significantly reduced sexual risk behaviors:

- (1) those based on behavioral theory;
- (2) interventions designed to specifically change HIV transmission risk behaviors;
- (3) interventions that were delivered by health-care providers or counselors of HIV-infected patients;
- (4) interventions that were individualized and delivered to individuals;
- (5) interventions that were intensively delivered;
- (6) interventions that were implemented in care settings where people living with HIV/AIDS received routine services or medical care;
- (7) interventions that promoted and provided skills building, and
- (8) interventions that addressed a myriad of issues related to mental health, medication adherence, and HIV risk behavior, such that the intervention took a multi-pronged approach to reducing risk.

The authors concluded that interventions targeting people living with HIV/AIDS are efficacious in reducing unprotected sex and acquisition of sexually transmitted infections (based on studies conducted in the U.S.). Efficacious strategies identified in this review will be used and incorporated into the formative phase of this study to assess the acceptability of such intervention approaches across cultural settings. In particular, our formative work will focus on an intervention that will be in the context of routine care (point 6), and one that addresses a myriad of culturally-relevant issues (point 8). Those that are culturally appropriate will be integrated into the eventual randomized controlled trial.

Specifically, two provider-based interventions have demonstrated success using reported sexual behavior as the outcome. The Options Project, a brief clinician-delivered intervention carried out during regular care, has shown prior success of a quasi-experimental, clinic-assigned trial.²⁸ This study is currently being tested in replication studies, including South Africa. Richardson et al. (included in the meta-analysis above), in the Partnership for Health study found evidence supporting brief safer sex counseling by medical providers using a clinic-randomized design (N=585) across six clinics.⁶⁷ These are only two provider-based interventions, but they lend support for potentially having a provider component in the eventual trial. The reductions in HIV risk taking in both the Options Project and the Partnership for Health, however, were modest, and hence we anticipate that the eventual trial will employ client-centered, individualized interventions to maximize substantial and durable behavioral changes.

So far, only one secondary prevention trial-The Willow Program - has used STI outcomes (included in the meta-analysis above).⁸⁵ This study was a randomized controlled trial (N=366 HIV-infected women) of a women-centered intervention and demonstrated both reductions in sexual behavior and incident STIs. The Willow Program intervention emphasized gender pride, maintaining current and identifying new network members, HIV transmission knowledge, communication and condom use skills, and healthy

relationships. Primary findings showed that over the 12-month follow-up period, women in the Willow intervention, relative to the comparison, reported:

- 1) Fewer episodes of unprotected vaginal intercourse (1.8 vs. 2.5; $P = 0.022$).
- 2) Were less likely to report never using condoms (OR = 0.27; $P = 0.008$).
- 3) Had a lower incidence of bacterial infections (Chlamydia and gonorrhea) (OR = 0.19; $P = 0.006$).
- 4) Reported greater HIV knowledge and condom use self-efficacy, more network members, fewer beliefs that condoms interfere with sex, and fewer partner-related barriers to condom use.
- 5) Demonstrated greater skill in using condoms.

It is anticipated that the ultimate intervention informed from the current proposed study will incorporate components taken from The Willow Program, such as HIV and STI transmission knowledge, education and communication skills related to condom use, negotiating sexual safety, and how to seek out healthy relationships. Additionally, Willow, as a women-centered intervention, with an emphasis on gender pride, is an example of an intervention that incorporated additional psychosocial issues into HIV risk reduction. Learning from the success of that study, the present study will attempt to delineate the salient and important relevant psychosocial issues to address in an ultimate intervention to be implemented in multiple settings across multiple risk groups. Finally, a multi-site ($N = 3,818$), intensive intervention (15 - 90 minute sessions), delivered to a diverse sample of individuals living with HIV found a 36% reduction in sexual risk taking comparing the intervention to the control group.³³

It is important to note that we fully plan to use the formative work to determine the model for the eventual intervention, which may or may not be cognitive behavioral in nature. Another major advantage of this feasibility study is the ability to determine whether the overall public health model – integrating HIV prevention with HIV care – is a valid one. While we do anticipate enrolling across various cultural settings, the formative study will determine the feasibility of that approach. The eventual intervention may be a modular based intervention that will guide a general approach, but also allow for within-participant, or potentially, within- setting variability where modules are delivered based on participant need. This will maximize the exportability of the results across various risk groups and settings. The formative work will allow us to determine if such an approach is feasible. As members of this protocol team are testing a similar approach (with a modular intervention) in a single-site domestic study (Mayer, Safren, NIMH grant number 068746). By doing formative work in international settings, we will be able to conduct a trial that is internally valid, but that tests an intervention that will be maximally applicable across settings. Hence, we anticipate that the eventual trial will be a hybrid efficacy/effectiveness study.⁷⁰

1.7 Eventual Endpoint of an Efficacy Trial.

The primary focus of the present study is to use the data collected to determine the best fitting behavioral intervention for this population. We will also obtain information about whether an HIV incidence endpoint is feasible in the ultimate prevention with positives trial, and will work the Central Lab on the development of optimal algorithms for serodiagnosis. The final endpoints used in an efficacy trial will depend on the sexual behaviors and partnership patterns of the various risk groups and settings as described above in Section 1.3.

The types of information that will be collected in HPTN 063 that will be essential to the development of a robust, culturally-appropriate intervention will need to address the following types of questions:

1. What are the types of relationships that are most common among HIV-infected individuals that may expose their partner(s) to HIV transmitting behaviors?
2. What types of individuals are engaging in the greatest level of transmitting behaviors?
3. What are the types of knowledge, attitudes and beliefs that inform the behaviors of HIV-infected persons in care in international settings?
4. Is the STI burden among some groups of HIV-infected persons in care of sufficient magnitude to consider aggressive STI diagnosis and treatment as a part of a future combination modality prevention intervention?

The most powerful eventual prevention trial would have an HIV-incidence endpoint. Enrolling individuals into a trial that links HIV prevention into HIV care, where the target participants are already HIV-infected, limits the degree to which one can have HIV incidence as the primary endpoint. Considering a future trial, HIV-incidence endpoints could occur in a sero-discordant couples study, or could be part of a larger HIV prevention package in a community that might include both primary prevention and secondary prevention. If future, comprehensive HIV prevention trials are proposed that include a mix of behavioral interventions for primary and secondary prevention, biologic or barrier methods (i.e. post-exposure prophylaxis / pre-exposure prophylaxis [PEP / PrEP]), partially effective vaccines, and/or public health awareness campaigns, we would need the preparedness information being collected in the present study to form the secondary prevention intervention techniques.

Summary

NIH-funded clinical trials units (CTUs) are in a unique position to develop a secondary HIV prevention intervention that could be widely implemented in diverse cultural settings. Though the present study is a preparedness study, it will answer important questions about the ability to administer an intervention with a similar structure across various risk groups and settings. The mix of qualitative research to examine the necessary components of the intervention, and quantitative research on the variables related to HIV-risk behavior in various risk groups and settings will allow for the development of a culturally-relevant, adaptable intervention that can link HIV prevention

with HIV care on a large scale basis. The public health significance of this is largely due to the increasing availability of ART in diverse areas of the world, where it is greatly needed.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objectives of this study are:

- To establish baseline rates of sexual HIV transmission risk behavior in high risk HIV-infected individuals, and to observe the rates and patterns of behavior change over time.
- To gather formative data on the potential structure and content of a behavioral intervention for individuals with HIV in care in international settings and to determine the best, culturally appropriate model for the intervention that will link prevention to care for HIV-infected individuals.
- To examine potential psychosocial and sociodemographic correlates of sexual risk-taking in these individuals in order to help shape the content of an individualized behavioral intervention.

2.2 Secondary Objectives

The secondary objective of this study is to:

Evaluate STI prevalence and incidence and investigate whether these biomarkers may be used to corroborate self-reported sexual behavior associated with potential transmission risks

2.3 Study Design

2.3.1 Study Type

This will be a one-year observational cohort study (approximately two years to complete after institutional review board (IRB) approval, participants will be enrolled over the course of approximately one year, and followed for one year) of individuals living with HIV who are in care in selected CTU sites. Individuals who are already enrolled in trials that involve protocolized HIV risk reduction counseling and adherence counseling (e.g. ACTG 5175 and HPTN 052 protocols were developed by the investigators from the present study), will not be eligible. Following participants for one year was selected to gather formative intervention data, STI data, and behavioral risk data to estimate incidence and determine the length of follow-up in an ultimate randomized controlled trial. Qualitative information will also be gathered concurrently through focus groups and in-depth interviews with a subset of quantitative study participants, CAB members, clinic workers and other community stakeholders.

2.3.2 Behavioral Risk, Sociodemographic, and Psychosocial Assessment Battery

During this one-year period, participants will complete a behavioral risk battery (including interview guided questions as well as confidential/ACASI questions), which will assess self-reported sexual risk-taking and the variables associated with self-reported sexual risk-taking in these settings. These behavioral risk factors may be targets of an eventual intervention, and the longitudinal observational study will allow for collection of baseline data that will also inform study power calculations and the appropriateness of the proximal behavioral targets of the intervention. The battery will build upon the ones currently used in HPTN 052 and ACTG 5175, which was shaped through extensive consensus work across the study sites and across HPTN and ACTG investigator teams, subcommittees, and other stakeholders (current principal investigator (PI), Safren, and co-investigator, Celentano, lead this effort). This battery has been translated and back translated to local languages in Brazil, Haiti, India (both Chennai and Pune), Malawi, Peru, S. Africa, and Thailand and includes questions on sexual risk-taking behavior, ART adherence, quality of life, social support, substance use, and HIV-transmission related information. The ACTG 5175 and HPTN 052 measure can be seen at <https://www.fstrf.org/apps/cfmx/apps/actg/html/QOLForms/index.html>, form 0060. We will, however, adapt the sexual risk-taking measures so that they can be assessed anonymously to the study sites, using audio-computer assisted self-interviewing (ACASI).

With consultative input from local community advisory boards (CAB) and other stakeholders, a culturally appropriate assessment will also be developed and include variables of eventual interest for the intervention trial and/or potential effect moderators. This will include questions about their patterns of sexual partners (e.g. MSM behavior, monogamous seroconcordant partner, monogamous serodiscordant partner, serial monogamous, sex work), attitudes and beliefs about safe sex, ART use, HIV transmission (e.g. self-efficacy, viral load beliefs, treatment optimism), community violence, intimate partner violence, access to food and shelter, alcohol/drug use, etc. Partner related variables are of interest because partner choice could differentially affect STI acquisition and HIV transmission. For example, having sex with only one other HIV-infected person would put you at risk for STI acquisition and/or HIV super-infection, but not transmitting HIV to an uninfected person. We will spend considerable time developing and adapting questions about ART and viral load beliefs, as these have been robust indicators of risk in U.S. studies.^{18;59} Standard demographic information will also be collected..

Sensitive questions will be assessed via an ACASI mechanism where answers are anonymous to the study staff – with participants' information not being provided to the study site in a linked way (and participants will be told of this to minimize, as much as possible, response bias).

2.3.3 Quantitative Behavioral Measures; Development and Validation

The final list of measures will be developed with site input and initial formative work at the site level. Hence, there will be constructs of relevance at the site level that are not listed below, and a more parsimonious assessment battery will ensue as the protocol is developed. Accordingly, we will be particularly sensitive to participant burden when finalizing the behavioral assessment battery. A preliminary list is below.

During the development period, we will time the assessment battery, and utilize the shortest possible measures that will yield reliable, valid responses. Although the measures for HPTN 052 and ACTG 5175 are being used in these large scale studies, the measures per se have not been subject to formal empirical validity. Hence, as part of the finalization of the measures, we will conduct comprehensive “cognitive testing” of the measures. Briefly, this involves conducting the assessment battery with a subset of (non-enrolled) individuals at the sites. After each item, the interviewer then asks questions about the degree to which the respondent understands the questions. The interviewer asks the respondent how they chose their response and requests that the respondent restate the question in their own words to gauge understanding. In doing so, the team is able to determine the validity, reliability, and cultural applicability of these measures. This will be done in an iterative process while the assessment battery is revised in order to ensure that the correct domains are being assessed. The team will use the process of cognitive testing to examine issues such as participant burden, and whether the length of the assessment battery is acceptable to participants at the local sites.

Sexual Risk Taking: The measure for ACTG 5175 and HPTN 052 asks about vaginal and anal sex with primary and other partners over the past three months. As sexual risk taking is one of the primary outcomes of this study, and was not for either ACTG 5175 or HPTN 052, we will likely need to add more detailed questions to this measure, using the measure from Health Resources and Services Administration (HRSA) prevention for positives cross-site study as a base. This measure asks about insertive and receptive vaginal/anal intercourse by partner type (HIV-infected, HIV-uninfected, HIV status unknown), as well as unprotected (i.e. without a condom or dental dam) oral sex. Number of partners and acts will be assessed both with and without protection. This will be done via an ACASI system to maximize the chances of disclosing sensitive information, as it can be done confidentially and anonymous to the site staff.

Substance and Alcohol Use: The ACTG 5175 and HPTN 052 measure asks a series of yes/no questions about substance use, as well as a frequency scale regarding the number of times a person drank five or more drinks at a time. We will expand on this, using a frequency-quantity assessment of alcohol use^{20;82} following the Alcohol Use Disorders Identification Test (AUDIT).¹ We will also develop a list of locally used substances at the sites. The NIDA-Clinical Trials Network Addictions Severity Index Lite (CTN, ASI-Lite) is a clinical-research oriented, briefer version of the ASI^{60;61} being used across all CTN studies, and we will ask these questions regarding the culturally relevant substances. The ASI measures the severity of problems in seven areas of functioning that are frequently affected in patients with substance use disorders. We will administer portions of the Drug and Alcohol sections of the ASI using the Time Line Follow Back⁷⁶ calendar methodology, so that all calendar days in the last month are covered. We will use this methodology to determine the number of days in a month that drugs are used, as an additional secondary outcome measure for drug use. We will specifically ask Alcohol and drug use questions within the context of sexual risk-taking so that it will be possible to know if the risky episodes occurred when using. The site’s standard of care for substance abuse will also be tracked to see if it has any affect on risky sexual behavior.

HIV Medication Adherence: We will use the visual analog scale, which assesses adherence over a 30-day period for each medication.^{9;31} This measure has been validated in both international and domestic settings. Consideration will be given to also utilizing

unannounced pill counts.⁴⁵ The HIV medication adherence assessment is informed by formative work on the acceptability of adherence measures conducted by Safren and HPTN investigators in India and Malawi.⁷¹

Quality of Life and Role Impairment: Role Impairment will be assessed with a modified version (ACTG-SF 21)⁸⁷ of the SF-21, which is the quality of life measure used in ACTG clinical trials, including HPTN 052 and ACTG 5175. This measure has specific application, reliability, and predictive and construct validity in assessing general quality of life for people living with HIV, and has subscales for psychological and medical quality of life.

Social Support: The team will assess social support using the items from the ACTG outcomes committee assessment that assesses general social support as well as social support related to adherence.

Beliefs/Attitudes/Motivations: Following initial work at each site, we will adapt measures of beliefs, attitudes, and motivations regarding safe sex. This will be an assessment of issues such as motivations for protecting self versus protecting others, viral load beliefs, HIV treatment optimism, strategic positioning, partner selection, and beliefs about superinfection. This assessment will be initially based on ongoing work by the principal investigator (PI; Safren) and Co-PI (Mayer), with MSM,⁵⁹ and will be expanded upon to the appropriate risk groups and cultural settings. We will utilize the CAB to help develop a comprehensive list.

Culturally relevant barriers to and facilitators of sexual risk-taking: Each setting and risk group will have culturally specific issues related to sexual risk taking. For example, a married woman whose primary risk may be her husband may have issues distinct from an MSM with multiple partners. Hence, specific quantitative questions will be developed for the various sites regarding additional barriers and benefits to sexual risk-taking. We will develop these questions based on a prior successful technique used in ACTG 5175 and HPTN 052, where individual site investigators were queried (who in turn, queried their staff and key informants at their sites) regarding culturally relevant barriers and benefits to HIV Medication Adherence. These items were then included in the adherence assessment for those large scale international studies. This assessment will also involve assessing the relevant motivational and behavioral skills regarding safer sex. We will utilize CABs at each site to help develop a comprehensive list of these barriers and facilitators.

Mood and anxiety (mental health/distress): The expression of anxiety and depression are culturally determined. Hence, we anticipate that we will use the CES-D²⁴ to assess depressed mood. This measure has been used in international settings. We will ask about anxiety, and we anticipate using the State-Trait Anxiety Inventory (state version; STAI)⁷⁸ which is the most frequently used scale internationally, with many foreign language adaptations.

Feelings about care received at the clinic: We will gather information on whether patients are satisfied with the care received at the clinic e.g. engagement of staff, accessibility of the clinic staff, understanding of their concerns, compassion/sympathy, etc.

Exposures to secondary prevention messages: Participants will be asked about the frequency and content of counseling procedures received at the clinic or elsewhere. Study staff will assess the extent of exposure to prevention messages as well as the efficacy of counseling procedures with respect to how well they relay adequate information and how efficacious they are in eliciting behavioral modifications.

Structural, sociocultural factors that may drive risk behavior. These issues will be articulated by the CAB and other consultations to be relevant to the risk group and setting. Potential variables include exposure to community violence, intimate partner violence, access to jobs, food insufficiency. These issues will also be assessed in the qualitative interviews discussed below to ensure we obtain the necessary information to determine whether an individual level intervention is feasible, and/or what types of structural level interventions would be best suited to the various risk groups and settings.

2.3.4 Qualitative Formative Data on Eventual Intervention Development

There will be two parts of formative development in the current study:

1) During the first 8 months (see Study Timeline month -8 to month 0), all study sites will gather insights related to the quantitative assessment battery to be used during the quantitative phase of this study. This will not require obtaining IRB approval as this will be done on a consultant/advisory basis with key informants such as CAB members at each of the sites. No data is being collected about these individuals, but rather consultation with them about the domains of assessment that we need to ask about. Input is being solicited from them about the study design and study instruments. See Appendix VII for details on this consultation phase.

2) Portions of the second part of formative development will be subject to IRB review, and will initiate during month 0, concurrent to the other parts of the present proposal. These data will be used to shape the ultimate intervention model. This will consist of conducting in-depth, semi-structured qualitative interviews and focus groups. Details of these interviews can be found in Sections 4.5 and 4.6.

The investigators will develop a qualitative interview guide for the focus groups (when possible, focus groups will be used because of the ease of transcription and coding) and individual in-depth interviews that will allow for feedback about the intervention content. The responses will be collated and interpreted for re-occurring themes (see qualitative data analysis below). These data will answer questions about the content of intervention material, the format of intervention delivery, timing of intervention, and other feasibility and acceptability issues. It will also ensure that intervention targets the most relevant cultural determinants of HIV risk behavior.

The qualitative interview guide will be based, in part, on an interview guide developed by the PI (S. Safren) and administered in Chennai, India. Results of 30 in-depth individual interviews of HIV-infected participants across the 6 most relevant risk groups in Chennai (men who have sex with men, sex workers, injection drug users, married men, married women, truck drivers and men who travel for work) have recently been reported.⁵¹ Perceived benefits of risk reduction included motivation to protect others from infection and one's self from further infection. Barriers to reduced risk included complexity,

stigma, perception of HIV-infected peers being less concerned about protecting others, condom use being linked to sexual and gender roles, and condom use being inconvenient or unappealing.

Questions will be asked in open-ended ways, in order to elicit information without guiding a particular response. They will be followed up with probes to ensure completeness of qualitative data. Staff will be trained prior to conducting any qualitative interviewing. Generally, similar questions will be asked to key informants and to focus group participants. Topics will include the following, but may expand after finalization with site PIs, their team, and relevant CAB input.

- 1) Anticipated issues with the feasibility of the approach at the various sites and across the three risk groups (MSM, heterosexual men, heterosexual women).
- 2) Important topics to cover in the intervention across settings and participant demographics.
- 3) Individual versus structural variables that drive sexual transmission risk behavior across the various risk groups at each site.
- 4) How to best assess sexual risk taking in a valid confidential way (e.g. to use or not use ACASI, an interviewer who is trained versus a peer, how to phrase lead in questions).
- 5) Ways to best recruit and retain participants.
- 6) Suggestions for improving the chances of success.
- 7) Who would be the best interventionist (e.g. peer, provider, counselor, or a combination).
- 8) The pros and cons of a group versus individual approach to the intervention.
- 9) How we can best assess whether an eventual intervention is feasible and acceptable to participants, the community, and other stakeholders.

For individuals living with HIV, we will also ask about the following:

- 1) Perceptions of general knowledge about HIV among individuals living with HIV who are in care, and how HIV is spread.
- 2) Barriers and facilitators of safe sex.
- 3) Sexual communication between partners.
- 4) Questions specific to each risk group (e.g. heterosexual women, MSM, heterosexual men), their sexual networks, and additional essential elements of an intervention.

- 5) Individual versus structural variables that drive sexual transmission risk behavior across the various risk groups at each site.
- 6) How can we best assess whether an eventual intervention is feasible and acceptable to participants, the community, and other stakeholders.

The study team will review the general notes from these interviews with the interviewers as they occur in real time, allowing for intervention development to occur concurrent to data collection and analysis. In addition to copious note taking, the qualitative interviews will be transcribed for content and thematic analysis using NVivo software (see qualitative analysis section below). The protocol chair and members of the protocol team have experience using this technique in HPTN preparedness studies for HPTN 052. The themes will be coded and systematically reviewed to ensure informed decisions are made about the intervention content. A member of the protocol team will be present to the extent possible during focus groups, to ensure consistency among the various sites with regards to the data collected as this will help inform the topics to be covered in the intervention that will be used in an eventual controlled trial.

Intervention manual development will occur in an iterative way. After all of the qualitative work is done and as the quantitative data are being collected, an outline of an intervention manual will be developed. This will likely include provider components and counselor components. The protocol chair for HPTN 052 and ACTG 5175 took a similar approach for the adherence counseling piece of that protocol as well as by members of the study team for a single-site U.S. based positive-prevention trial.⁴⁹ After this manual is developed, we will once again present the manual to the CABs and key-informants for additional feedback. This feedback will be reviewed by the study team, and adjustments to the manual will be made.

The quantitative data will also be used toward intervention development. Variables that are most predictive of sexual risk taking in the various demographic groups will be highlighted in the eventual intervention manual.

Finally, at the end of the data analysis of the quantitative phase, we will conduct additional qualitative research as needed to clarify the findings. For this, we will ask the individuals who consented and participated in the qualitative interviews to return for a second interview (if individuals from the original interviews are not available, additional participants may be enrolled in order to gather sufficient data). This interview will focus on their interpretations of the key study findings, and clarifications as to any issues that emerge in the data.

2.3.5 From HPTN 063 to an Efficacy Study

The present study has the goal of collecting the necessary data to determine the best structure and content of a behavioral intervention to reduce HIV sexual transmission risk-taking behavior in individuals in care in diverse settings.

By “structure” of the intervention we seek to determine answers to logistical and potential feasibility and acceptability issues such as whether it would be delivered individually or in group format, the number of sessions, whether it would be delivered by

a counselor, an HIV care provider, a peer, or a combination of one or more of these individuals.

By “content” of the intervention we seek to determine whether there are specific topical areas that will be administered as an intervention for all risk groups in all settings or whether there would be modules that reflect particular topics that are delivered depending on risk group, setting, or participant need.

Because the purpose of this current project is to determine these issues, we are not able to, in advance, plan for or budget for a pilot, run-in of the intervention. Hence, we plan that piloting of the intervention would need to occur after this information is collected. This may occur as a preliminary phase of an efficacy study or part of an interim-stage efficacy trial depending on the results and lessons learned from the present study.

2.3.6 Specimen Collection and Storage

Blood will be drawn from participants at enrollment, and 6 and 12 month (termination) visits and processed for plasma storage. This plasma will be stored to potentially test for HIV plasma RNA, if resources are subsequently available. Plasma HIV RNA measures could be used to assess the correlation between potential infectivity and risk behavior. Stored specimens may be used in future studies characterizing viral resistance, cytotropism, or other relevant assays.

Urine, vaginal/rectal swabs, and blood will also be collected to test for bacterial STIs as well (at enrollment, 6 and 12 months). Syphilis testing will be done in real time on blood samples. Urine and swabs will be collected and stored for a future nested analysis to evaluate the incidence of STI infection in high-risk participants (see Section 4.4, below).

2.3.7 Current Medical Condition of Participants

Participants will be evaluated at each study visit for their current medical condition (including new STIs and their subsequent treatment) in order to identify any correlates between medical status and risk behavior and also to evaluate the extent to which STIs are diagnosed and treated during the course of the study. A limited physical exam will be done by the medical staff at the sites including a symptoms directed physical exam, a review of the participant’s medical history since the last visit, and a review of their medical records. Current medications will also be noted. STI data that will be collected for statistical analysis will include laboratory diagnosed genitourinary chlamydia, gonorrhea and syphilis. Descriptions of other STIs or those diagnosed empirically (i.e. syndromic management of urethral or vaginal discharges, pelvic inflammatory disease and/or genital tract ulcers) will also be recorded on the case report forms. Site staff will undergo training as a part of study activation activities to ensure that recognition and diagnosis of STIs is uniform across sites.

3.0 STUDY POPULATION

High risk HIV-infected men and women in Africa (Zambia), Asia (Thailand), and South America (Brazil), who have reported recent (within 3 months) HIV transmission risk behavior including unprotected insertive anal or vaginal intercourse (i.e. without a condom)

with a person who is HIV uninfected or of unknown HIV status, will be enrolled. This will include heterosexual men, heterosexual women, and MSM.

For the MSM population, we will enroll men who have sex with men, regardless of whether or not they also have sex with women. We will use the study data to find out whether there are different classifications/risk profiles for MSM, and whether they will need different intervention approaches.

Clinic workers, CAB members, and other community stakeholders will participate on a consultant basis in order to provide additional data to inform the study assessments and eventual intervention.

3.1 Inclusion Criteria (Quantitative Assessment/Qualitative Measures)

Participation in this study is completely voluntary.

- Men and women at least 18 years of age (Note: Pregnant and breast feeding women are allowed to enroll into the study)
- Documented evidence of HIV infection (HIV diagnosis performed outside of the trial is acceptable so long as local/country guidelines were followed in the testing)
- Receiving HIV/AIDS care (defined as at least two visits within 9 months of enrollment) in a formal health care setting (clinic or hospital)
- Reported history of sexual risk behavior in the previous 12 months, including: acquisition of a sexually transmitted infection, vaginal or anal intercourse without a condom, difficulty negotiating condom use, or non-disclosure of HIV status to an HIV-uninfected partner or partner of unknown HIV serostatus.
- **NOTE:** For the MSM population, we will enroll men who have sex with men, regardless of whether or not they also have sex with women

3.2 Exclusion Criteria (Quantitative Assessment/Qualitative Measures)

- Anyone currently enrolled in another study that involves protocolized HIV risk reduction counseling (e.g. ACTG 5175 or HPTN 052) or any other prevention study
- Anyone having unprotected (i.e. without a condom) sex for the expressed purpose of conceiving
- Planning to relocate out of the area in the next year
- Any condition that, in the opinion of the Investigator of Record or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Rationale for inclusion and exclusion criteria.

Previously, we considered excluding individuals newly initiating ART, including only those with a detectable viral load. A meta-analysis by Crepaz et al (2004)¹⁸ pooled data from 25 studies comparing people receiving and not receiving ART, comparing those with and without an undetectable viral load, and examining the impact of beliefs about ART and viral load. Aggregating data using random-effects models, the study showed that beliefs about ART (e.g. that being on ART prevents you from spreading the disease) were significantly associated with elevated sexual risk. However, being on ART versus not, and having an undetectable viral load versus not were not associated with increased sexual risk. For this study, we seek to maximize the generalizability of the eventual trial, and, for a preparedness study, we are seeking to be as inclusive as possible to answer empirically, questions about inclusion criteria of the eventual trial (i.e. for the eventual trial, after determining if group differences are vast, we can make the inclusion criteria more circumscribed). Hence, the present study will select for individuals engaging in sexual risk-taking behaviors, but not stratify based on whether or not they are receiving ART.

Consideration was also given to only enrolling one risk group in the present study (i.e. only heterosexual men, heterosexual women, or MSM). This would be to maximize the internal validity of the study. Because this is a formative preparedness study, it is important to have information about all three sexual risk groups for HIV transmission because we need to learn whether we can mount a similarly structured intervention for each group. It is possible that this preparedness trial will yield data indicating a need for different interventions for different risk groups or different cultural settings. It is also possible that this preparedness trial will yield data pointing to the feasibility of a similar approach across risk groups and settings. The qualitative data will be used to examine feasibility and acceptability concerns regarding an intervention, and the quantitative data will yield data to examine the frequency of HIV sexual transmission risk behavior across the risk groups, as well as the correlates. The power analysis, site selection, and sample size were done to maximize the chances of answering these key questions. The overarching goal of this preparedness study is to develop an intervention that can be as generalizable as possible, with the goal of wide-scale implementation should it prove to be efficacious.

3.3 Recruitment Process (Quantitative Assessment)

Recruitment for this study will take place from the pool of HIV-infected patients receiving HIV/AIDS care (defined as at least two visits over the past 9 months) in a formal international health care setting (clinic or hospital). Details on patient recruitment and recruitment strategies will be outlined in the study specific Standard Operating Procedures (SOPs) and follow the guidelines specified in the Study Specific Procedures (SSP) Manual and the HPTN Manual of Operations (MOP; http://www.hptn.org/network_information/policies_procedures.htm).

Participants who come to the clinic for HIV care will be invited by the study coordinator to participate in the study, this will happen while they are waiting for their clinic appointments. If recruitment is problematic based on patients' unwillingness to divulge sexual risk taking behavior during screening visits, the protocol team will assess

alternative measures for identifying recent risk behavior such as new acquisition of STIs. If recruitment of a particular risk group is problematic, the protocol team will work with the individual sites to develop targeted recruitment strategies – however, the participants need to be an established patient at the clinic to participate in the study. Each participating site has well established strategies for identifying HIV patients for care and recruitment into clinical studies as briefly outlined below.

3.3.1 Matero Clinic CRS – Lusaka, Zambia

The site identifies catchment areas such as ARV clinics, out patient departments, maternal child health centers, TB Corner and centers where voluntary counseling and testing are offered as well as other institutions where HIV care is offered e.g. home-based care.

Community sensitization to these types of studies occurs through meetings with CABs, health workers, health community workers and stakeholders as well as drama performances, door-to-door sensitization and community sensitization.

3.3.2 Chiang Mai Univ. AIDS Prevention CRS - Chiang Mai, Thailand

Recruitment occurs through the coordination with the following voluntary counseling and testing (VCT) centers:

- District/provincial hospital in upper-north of Thailand
- Anonymous clinics
- Private laboratory/ hospital/ clinic
- Blood banks

Recruitment will also be targeted through mass media with the productions of materials such as posters, brochures, leaflets, and clinic name-cards. These will be distributed through VCT units, radio broadcast, local newspapers, Research Institute for Health Sciences/Chiang Mai University website, CAB newsletters, and magazine

3.3.3 Instituto de Pesquisa Clinica Evandro Chagas CRS (IPEC CRS) - Rio de Janeiro, Brazil

Recruitment occurs through health services such as VCTs HIV/AIDS clinics (including IPEC's HIV/AIDS Clinic), general clinics, and blood banks. Collaborations with health professionals have been established for recruitment in these health services. In addition, recruitment efforts will target communities through qualified community leaders that broadcast information about the studies and refer patients to the site. There will also be direct recruitment through posters, audio-visual media and also through the study subjects, their friends and family.

3.4 Co-Enrollment Guidelines

Participants will only be enrolled from sites that may have conducted other NIH AIDS clinical trial network studies. However, individuals who are currently enrolled in these studies would **not** be eligible for the current study because they have already undergone rigorous HIV prevention and safe sex counseling. During follow-up, co-enrollment in

another study will be discouraged. However, decisions about whether or not a participant who enrolls in another trial will continue participation in HPTN 063 (if willing) will be made on a case-by-case basis by the Protocol Team, depending on the nature and timing of the other study.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain him/her for 12 months of follow-up in order to minimize possible bias associated with loss-to-follow-up. Optimally, participant retention procedures will be established such that loss rates do not exceed the incidence rate of the primary study outcome. Study site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures include:

- Scheduling the assessments to coincide with a patient's already scheduled HIV care visits at the clinic.
- Explanation of the study visit schedule (quarterly, similar to HIV care visits) and procedural requirements during the informed consent process, and re-emphasis at each study visit.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes and/or other participant-identified community locations.

3.6 Participant Withdrawal

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason and at any time. The 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 Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and Coordinating and Operations Center (CORE) Protocol Specialist.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, Office for Human Research Protection (OHRP), or site IRBs / ethics committees (ECs) terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 4.3) of participants who terminate from the study prior to the planned termination time period and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

Participants will be informed that withdrawal from the study will not affect their continued receipt of HIV care at the clinic in any way.

4.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Appendices I and II. Presented below is additional information 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.

4.1 Screening/Enrollment Visit (Quantitative Assessment)

Screening and enrollment may occur on the same day or separate days depending on the availability of the participant and the clinic staff. During the screening, participants will be administered a combined screening and enrollment informed consent. If they consent to the screening and enrollment procedures, they will first undergo screening. As a part of the screening procedures, participants will provide demographic and locator information. They will also be asked about their sexual activities and partners. If a participant meets the eligibility criteria for the study and the study staff agree that they can fulfill the study requirements, they will be asked to enroll. The point of enrollment will be when the participant is first logged into ACASI. Screening and enrollment can happen during the same visit. If this is not possible based on time/schedule conflicts, enrollment can take place at a later date but must occur within 30 days of screening.

During the enrollment visit, participants will update their locator information. They will then be administered a sexual risk and behavior questionnaire. Some of the questions will be administered by study staff. Questions containing sensitive sexual content will be administered via an ACASI or other confidential (and anonymous to the site staff) electronic system.

Participants will provide up to 10 ml of blood during this visit and STI information will also be collected from participant medical records and self-report. Study staff will also evaluate the current medical condition of the participants (e.g. limited physical exam, symptom directed physical exam, medical history since last visit, and review of medical records) and any medications they are taking for HIV/AIDS related treatment (e.g. anti-retrovirals, medications for opportunistic infections, etc.). In Brazil and Thailand specimens will be collected for STI analysis involving real-time syphilis testing and potential future testing of gonorrhea, chlamydia, and HSV-2. In Zambia, samples will undergo real-time syphilis, gonorrhea, and chlamydia testing and will be stored for potential future testing of HSV-2 and possible shipment to the NL for gonorrhea and chlamydia QA testing and other STIs. Social harm information (any untoward social occurrences that happens to a participant as a result of their participation in the study, described below in Section 5) will also be recorded.

4.2 Follow-Up Visits (3, 6, and 9 Month Visits)

Follow-up visits will occur at any routine clinic visit at 3, 6, and 9 months from enrollment. Visit windows will be specified in the SSP manual (similarly for the termination visit, below). During these visits, participants will update their locator information and complete a sexual risk and behavior questionnaire, similar to the enrollment visit. STI information will be collected from participant medical records as well as based on self report and study staff will evaluate the participant's current medical condition and any medications they are taking for HIV/AIDS related treatment (as described above). Specimens will be collected for STI analysis at the enrollment, 6 and 12 month visit only, including blood, urine, and vaginal/rectal secretions. Social harm information will also be recorded.

4.3 Termination Visit (12 Month Visit)

During the termination visit, participants will complete a sexual risk and behavior questionnaire, similar to the previous visits. STI information will be collected from participant medical records and self report and study staff will evaluate the current medical condition of the participants and any medications they are taking. Participants will also provide up to 10 ml of blood as well as other biological specimens during this visit for specific STI testing (see Section 4.4 below for details). Social harm information will be recorded. Exit interviews and termination activities will also take place at this visit. As with the follow-up visits, visit windows will be specified in the SSP manual.

4.4 Specimen Collection and STI Evaluation

Specimens will be collected at the enrollment, 6 and 12 months visits for STI analysis. Some testing will occur in real time. Others will occur at the end of the study or in potential future analysis:

4.4.1. Brazil and Thailand Site-Specific

- a) Urine, vaginal swab, and rectal specimens will be stored for a future nested analysis based on behavioral indicators of risk. Genitourinary gonorrhea and chlamydia will be assessed using urine (MSM and heterosexual men) and self-collected or clinically-collected rectal swabs (MSM), and self-collected or clinically-collected vaginal swabs for women. A subset of collected specimens will be tested at the local sites using nucleic acid amplification tests, using kits approved by national health authorities at each site and test performance will be validated by quality assurance assessment with the guidance of the Network Laboratory. Rectal and vaginal swabs and urine for gonorrhea and chlamydia will be sent to the Network Lab for storage and processing. (**Note:** The informed consent will explain to participants that these samples may or may not be used to test for these STIs in future studies, and that if they have symptoms of an STI they should discuss this with their doctor. In the event that an STI is discovered in these analyses, participants will be called back into the clinic for re-testing and treatment, as indicated in the consent form.)

- b) Syphilis serological testing will be performed at the local laboratories in real time using blood samples and a screening assay (either RPR or VDRL), and confirmed at the local site, by a confirmatory assay (using MHA-TP or FTA-ABS), with quality assurance reviewed by the Central Laboratory.
- c) Plasma will be stored for potential future testing for HIV viral load and HSV-2 serologies. Viral load data may be used in studies modeling the potential infectiousness of high risk participants. If HSV testing is done, all month 12 samples will be tested for HSV-2; all participants who test positive will also have their 6 month and enrollment samples tested as well. Samples may also be used for future viral characterization, including resistance and cytotropism assays.
- d) Information collected about interim STI diagnoses will be obtained through medical chart review and participant interviews at the sites to determine if incident STIs are diagnosed between study visits, and to understand local clinical practices regarding syndromic management of STI.
- e) All syndromic STIs that participants report during the study visits, will be diagnosed and treated at the study visits, or interim visits, and the data will be captured in CRFs.

4.4.2. Zambia Site-Specific

Specimens will be collected at the enrollment, 6 and 12 months visits for STI analysis. Testing will occur in real time.

- a) Genitourinary gonorrhea and chlamydia will be assessed using urine (men) or vaginal swabs for women. The collected specimens will be tested real time at the local sites using nucleic acid amplification tests, using kits approved by national health authorities at each site and test performance will be validated by quality assurance assessment with the guidance of the Network Laboratory. (Note: The informed consent will explain to participants that these samples may or may not be stored for quality assurance purposes. In the event that an STI is discovered in the quality assurance assessment, participants will be called back into the clinic for re-testing and treatment, as indicated in the consent form.) Urine and vaginal swabs will also be stored for quality assurance purposes using in-country facilities.
- b) Syphilis serological testing will be performed at the local laboratories in real time using blood samples and a screening assay (either RPR or VDRL), and confirmed at the local site, by a confirmatory assay (using MHA-TP or FTA-ABS), with quality assurance reviewed on site by the Network Laboratory.
- c) Plasma will be stored for potential future testing for HIV viral load and HSV-2 serologies. Viral load data may be used in studies modeling the potential infectiousness of high risk participants. If HSV testing is done, all month 12 samples will be tested for HSV-2; all participants who test positive will also have their 6 month and enrollment samples tested as well. Samples may also

be used for future viral characterization, including resistance and cytotropism assays.

- d) Information collected about interim STI diagnoses will be obtained through medical chart review and participant interviews at the sites to determine if incident STIs are diagnosed between study visits, and to understand local clinical practices regarding syndromic management of STI.
- e) All syndromic STIs that participants report during the study visits, will be diagnosed and treated at the study visits, or interim visits, and the data will be captured in CRFs. Patients who have not been treated syndromically will be recalled if positive results are received on any specimen.

4.5 In-Depth Interviews (Qualitative Assessment)

For the qualitative interviews, we will enroll approximately 10 participants from each of the three risk groups (heterosexual women, heterosexual men, and MSM) following the same inclusion/exclusion criteria for participation in the quantitative assessments. The number of participants for interviews is likely to range between 8 and 12 or until redundant themes emerge, as is typical in qualitative research.⁶² Prior to participating in the qualitative interview, each eligible HIV-infected patient in care will complete a separate informed consent process. Interviews will be recorded and transcribed.

Individual in-depth interviews will also happen at each site with key informants. This will be with relevant NGO leaders and other community stakeholders at the sites who are not part of the site's CAB. In these instances, we will rely on the sites to identify key-informants and interview them about the topics below. We anticipate at least five key-informants per site. These participants will also complete an informed consent process. These interviews will also be recorded and transcribed.

At the end of the quantitative study, when data are collated and analyzed, we will conduct a second wave of qualitative interviews. This will be done to assist us with the interpretation of the results. It will allow the team to ask additional open-ended questions that may clarify the quantitative results. We will attempt to interview the same individuals who completed the first set of qualitative interviews. However, if this is not feasible, or depending on the results of the quantitative study and the questions to be asked, not scientifically appropriate, we will interview new individuals. As with the first wave of qualitative interviews, we expect to enroll 8-12 per risk group per site, or until redundancy occurs.

4.6 Group Consultative Input

CAB members and provider teams will have multiple meetings to provide input about the eventual intervention. We will not audio record these meetings with CAB members and members of the provider team. Instead, we will take comprehensive notes about their suggestions and use these to help shape the eventual intervention. As noted above, these individuals are part of community groups designed to give feedback and advice for studies and programmatic activities on a consultant basis, hence they are not considered research subjects and will not be subject to guidelines regarding informed consent.

Qualitative interviewing will be done by trained ethnographers at the study sites. The training will be done by the behavioral scientist investigators (Safren and Celentano). This will involve attention to probing, asking open-ended questions, and grounded theory.

With respect to intervention development, we envision at least two CAB and provider meetings, one of which can happen at the same meetings as the meetings regarding shaping the assessments. The second will be after the other qualitative and quantitative data are collected, and will involve helping shape the structure and content of the intervention based on this data

4.7 Risk Reduction Counseling

All participants in the current study will only be allowed to enter the trial if they are receiving primary care at the study site which includes risk reduction counseling and prevention messages from their primary providers. Appendix VI contains information about the standards for HIV-risk reduction counseling at each of the three study sites. These standards are consistent with UNAIDS and WHO standards. Study operations procedures will be developed to ensure that participants are exposed to this as part of clinical care at the visits. Although the clinical care and accompanying standard of care (that includes HIV counseling) will occur during the study visits (as study visits will be tied to clinical visits) the providers will not necessarily be study staff. As part of their routine study visits, participants will be asked if they have any questions about HIV transmission, sexual practices, and how to protect their partners, and counseling will be provided in response to specific participant questions. Study staff, however, will not be delivering a protocol specified risk reduction intervention as part of the study because this is what we are seeking to develop as part of the formative work for the eventual trial.

5.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

Because this study includes no biomedical intervention or study product, standard adverse event reporting will not be undertaken and no adverse event data will be collected on case report forms for entry into the study database. However, in accordance with 45 CFR 46, unanticipated problems or serious adverse events that are judged to be related or possibly related to study participation will be documented and reported to the IRB/ECs according to their individual requirements and to the DAIDS Medical Officer and the Office of Human Research Protections (OHRP). This reporting will be performed according to the timelines and definitions included in pre-established written procedures, such as the SSP manual and SOPs, and the guidelines provided at www.hhs.gov/ohrp/policy/AdvEvtGuid.htm. Serious adverse events will not be reported to the DAIDS Regulatory Compliance Center (RSC).

In order to prevent adverse social events related to study participation, social harms will be monitored throughout the study. Social harms are any untoward social occurrences that happen to a participant as a result of their participation in the study. Examples include loss of employment, harassment by neighbors, shunned by family, rejection by partner, etc. Although social harms due to this study are expected to be negligible, they will be monitored closely throughout the study. Information on social harms will be actively solicited from participants at follow-up visits and recorded on case report forms

and captured in the study database. Participants will also be encouraged to report any social harm on an ad hoc basis when it occurs. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to responsible site's IRB/EC at least annually, or according to their individual requirements. The nature and frequency of these social impact reports will be monitored by the protocol team on a regular basis. In addition, these data will be reviewed by the HPTN (SMC).

6.0 STATISTICAL CONSIDERATIONS

6.1 Review of Study Design

This is a multi-site, observational, cohort study to gather preparatory data needed to design and implement prevention trials for HIV-infected individuals in HIV care in diverse international settings. Heterosexual men, heterosexual women and MSM are being recruited from international health care settings and will be followed for 12 months, with quarterly visit at month 3, 6, 9, 12. Two study sites (Thailand and Brazil) will recruit all three risk groups (heterosexual men, women, and MSM) and one site (Zambia) will recruit only heterosexual men and women. Longitudinal data will be collected in order to estimate the prevalence of sexually risky behaviors, to discover potential psychosocial and socio-demographic correlates, and to explore the relationship between clinically-diagnosed/self-reported STI and sexual risk-taking. While STI specimen will be collected at enrollment and at the month 6 and 12 visit, a nested case-control sampling scheme based on the behavior risk taking will be employed to test genitourinary gonorrhea and chlamydia in a subset of the study cohort.

The study will also include qualitative assessments gathered from in-depth interviews and focus groups comprised of a subset of the qualitative study participants, study staff, community groups, and CAB members.

6.2 Endpoints

6.2.1 Primary Endpoints

Consistent with the primary study objective to establish baseline rates of sexual risk-taking in high risk HIV-infected individuals, and to observe the rates and patterns of behavioral change over time, without a focused intervention, the following endpoint(s) will be assessed:

- Number of self reported unprotected (i.e. without a condom) sex acts with serodiscordant partners (partners of negative or unknown HIV status)
- Number of sexual partners (main and/or casual, new)
- Frequency of condom use

Consistent with the primary study objective to gather formative data on the potential structure and content of a behavioral intervention for individuals with HIV in care in international settings to determine the best, culturally appropriate model for the intervention that will link HIV prevention to HIV care, the following endpoint(s) (potentially modified after CAB input) will be assessed:

- HIV-associated medication adherence
- Substance and alcohol use
- Quality of life and role impairment
- Social support
- Beliefs, attitudes and motivations toward safer sex
- Barriers to safer sexual behavior
- Mood and anxiety

6.2.2 Secondary Endpoints

Consistent with the secondary study objective to evaluate STI incidence rates, the following endpoint(s) will be assessed:

- Laboratory diagnosis of an STI (chlamydia or gonorrhea) in participant medical records
- Self-reported STI (empirically diagnosed or diagnosed outside of the clinic; treated or untreated)
- Laboratory diagnosis of an STI at enrollment, 6 and the 12 months

6.3 Sample Size

6.3.1 Quantitative Assessments

Approximately 800 (300 heterosexual men, 300 heterosexual women, 200 MSM) participants will be recruited for this study: all three risk groups will be represented in Brazil and Thailand, with 100 individuals per risk group at these sites; 100 high-risk HIV-infected heterosexual men and 100 high-risk HIV-infected heterosexual women will be represented from Zambia. Table 6-1, 6-2, and 6-3 show the relationship between the power, effect size and a range of sample sizes. Note that this study is powered to estimate the prevalence of risk factors, not to evaluate the efficacy of a treatment/intervention effect. Furthermore, these tables assume a single observation for each participant; narrower confidence intervals and increased power likely will result from the longitudinal data being collected in this study. Table 6-1 gives the half-width of a 95% CI for the estimated prevalence as a function of the observed prevalence and the sample size per risk group. If the observed proportion of a particular risky behavior or a targeted STI prevalence at enrollment and month 12 is unique to one risk group in one site, the half-

width of a 95% CI for the proportion can be found in the column with sample size 100. On the other hand, if the observed proportions for one risk group are similar across different sites, the sample sizes can be aggregated across sites and thus yields a narrower half-width.

Table 6-1. Half-width of a 95% CI for sample proportion as a function of observed proportion and sample size e.g. 95% CI if $p = .3$ and $n = 100$ is $0.3 \pm .09$					
		Sample size per risk group			
		50	100	200	300
Observed proportion	0.1	0.083	0.059	0.042	0.034
	0.2	0.111	0.078	0.055	0.045
	0.3	0.127	0.090	0.064	0.052
	0.4	0.136	0.096	0.068	0.055
	0.5	0.139	0.098	0.069	0.057

Table 6-2 demonstrates the powers of detecting an association between a risky behavior and a psychosocial or social-demographic factor given a range of sample sizes. In this table we assume the prevalence of the risk behavior is 0.3 and the prevalence of the social-demographic factor is 0.5. Suppose we have a cross-sectional sample of 100 subjects in a risk group, and observed odds ratio between the two factors is 2.0, the power to rule out the null hypothesis that there is no association is 0.35. If the same risk groups across 3 sites can be pooled, greater power can be achieved (0.78 if pooling 300 subjects across 3 sites, 0.60 if pooling 200 subjects across 2 sites).

Table 6-2. The power to detect a significant association between a risky behavior and a psychosocial or social-demographic factor at type I error 0.05 for a range of odds ratios and sample sizes, assuming the prevalence of the risky behavior is 0.3 and the prevalence social-demographic factor is 0.5.					
		Total sample size per risk group			
		50	100	200	300
Odds ratio (effect size)	1.5	0.09	0.15	0.25	0.35
	2.0	0.19	0.35	0.60	0.78
	2.5	0.27	0.48	0.78	0.92
	3.0	0.41	0.69	0.94	0.99

Table 6-3 shows the power to detect a significant interaction effect between the psychosocial or social-demographic factor and risk groups, i.e., whether there is a difference between odds ratios observed in different risk groups. It is assumed that the prevalence of the risky behavior is 0.3, the prevalence if social-demographic factor is 0.5, the odds ratio in the first group is 1.5, and equal sample sizes in two risk groups. For example, if the odds ratio in the second group is $1.5 \times 1.5 = 2.25$ and there are 100 subjects in each risk group, the power to detect a significant interaction will be approximately 0.10. As compared to Table 6-2, the powers in Table 6-3 are generally lower because of the increased variance of estimated interaction parameters. These calculations assume categorical variables. An increased power would result if variables are continuous.

The final choice of 100 participants per each risk group per site is largely driven by the observation that a smaller sample size than 100, for example 50 in Table 6-1, would render too wide a confidence interval (less precision) for estimating the prevalence, particularly for STI with low prevalence. In addition, one of the primary objectives of this study is to examine potential psychosocial or sociodemographic correlates of sexual risk taking in these individuals in order to help shape the content of a behavioral intervention. Although the study is not fully powered to detect significant associations between psychosocial or social-demographic factors and risky behaviors within each risk group at each site, if the same risk groups across different sites can be pooled, a sample size of 300 participants (100×3) would yield approximately 80% power to detect a significant association with odds ratio 2.0 (Table 6-2). Furthermore, if the odds of a risk behavior varies by less than a factor to 2.0 between two risk groups then it may make sense to use a common intervention that targets that risk behavior for both groups. If the odds of the risk behavior varies by more than a factor of two then this may suggest that any intervention should be focused differently for the risk groups. A smaller sample size in each risk group at each site, for instance 50 or 75, would yield a much lower power in detecting aforementioned correlates or variation.

Table 6-3. The power to detect a significant difference in associations between a psychosocial or social-demographic factor and a risky behavior among two risk groups. The type I error was set at 0.05 for a two-sided test, assuming the prevalence of the risky behavior is 0.3, the prevalence if the social-demographic factor is 0.5, the odds ratio in the first group is 1.5, and equal sample sizes in two risk groups.					
		Total sample size per risk group			
		50	100	200	300
The ratio of Odds ratios in two groups (effect size)	1.5	0.07	0.10	0.15	0.20
	2.0	0.12	0.20	0.35	0.49
	2.5	0.17	0.31	0.55	0.72
	3.0	0.22	0.42	0.70	0.8

In the nested case-control sample for STI testing, 100 high behavioral risk participants and 100 low behavior risk participants will be identified at month 6 and at month 12 for each of three sexual risk groups (MSM, heterosexual man, and heterosexual women). Their rectal swabs (MSM), urine (MSM and heterosexual men) and vaginal swabs (women) will be tested for gonorrhea and chlamydia. The total number of specimen being processed will be 1,200 with 400 in each sexual risk group. Table 6-4 shows the sample sizes needed to establish the association between behavior risk taking and STI incidence with power 0.8 and type I error 0.05 for a range of odds ratios. Equal sample size is assumed for two behavior risk groups (high versus low). The prevalence of STI in the low risk group is assumed to be 0.05. With the targeted 400 samples for each of the sexual risk groups, the study has 80% power to detect an association with odds ratio 3. Note that this calculation is based on 400 independent samples across month 6 and month 12. When considering the potential correlation between two STI tests for the same subject the samples are no longer independent and therefore a slightly increased sample size is required.

Table 6-4. The sample size per group required to detect a significant association between STI and high behavior risk with various odds ratios with power 0.8 and type I error 0.05.				
	Odds ratio			
	2.0	2.5	3.0	3.5
The number of samples per group (high or low risk)	512	268	174	126

6.3.2 Qualitative Assessments

As stated in Section 4.5, the number of participants for interviews (from the pool of quantitative assessments) is likely to range between 8 and 12 or until redundant themes emerge. Ten participants per risk group per site are anticipated. In addition, at least 5 community stakeholders will also be interviewed from each site.

There will be approximately 8-12 participants in each focus group and 3-4 focus group sessions per site. They will be led by an experienced focus group moderator at each site. It is anticipated that there will be approximately 120 qualitative participants (40 from each site) from the community.

6.4 Data Analysis of Quantitative Assessments

Descriptive statistics and graphics will be used to summarize the characteristics of endpoints of interest among risk groups over a 12-month follow-up period. For categorical variables, the numbers and the proportions will be tabulated; for continuous variables, the mean, median, standard deviation, and quantiles will be reported. To assess the association of two categorical variables in cross-sectional analyses, chi-square tests will be used with exact p-values if the expected cell count in some stratum is small. To assess the association of a continuous variable and a categorical variable from cross-sectional data, t-test or linear regression will be used; nonparametric method such

spearman's rank test may be used if sample size is small and data are non-normal. Interactions will be evaluated in a generalized linear regression. The details of endpoint measurement and statistical analysis will be provided in a separate document as statistical analysis plan. The longitudinal data will be analyzed using generalized estimation equations (GEE)⁵³ with robust variance estimates.

6.4.1 Primary Analyses

Corresponding to the primary objective, the prevalence of sexually risky behaviors will be estimated quarterly during the course of follow-up, both overall and within subgroups. The association of a potential predictor with a risky behavior will be assessed in generalized estimation equations, in which logistic regression will be used for binary endpoints and linear regression will be used for continuous endpoints (possibly transformed). For instance, does frequency of unprotected sex (i.e. sex without a condom) differ between the heterosexual men and heterosexual women and MSM? The results of these analyses will be used to suggest which factors may be suitable targets for intervention. For example, modifiable psychosocial factors showing a strong association with risky behavior may be suitable targets for intervention. Regression models will also be used to evaluate whether or not the strength of the association between the psychosocial factor and the risky behavior varies by risk groups or sites (i.e. interaction or effect modification). For instance, does the odds ratio between optimism about ART and frequency of unprotected sex differ between subgroups? A significant interaction may suggest that the intervention must be modified for the different risk groups or sites.

6.4.2 Secondary Analyses

Corresponding to the secondary objective, the incidence rates of STIs will be estimated based on a nested case controlled study of STI testing. Incidence will be estimated as the number of new cases of STIs (individual STIs as well as any STI) divided by the number of person years at risk for the disease. The incidence rates of STIs will be compared between subgroups of interest using a proportional hazard regression. A robust variance estimator⁵⁴ will be used to correct for correlated observations if participants experience multiple STIs over the course of follow-up. The relationship between acquisition of an STI with sexual risk-taking will be assessed using generalized estimating equations, in which the endpoint will be new STIs reported in each quarterly visit and the predictors are qualitative measures of sexual risk taking, such as the number of unprotected sex acts (i.e. sex without a condom) in each quarterly visit.

6.4.3 Missing Data Due to Loss to Follow-up

While sites will make every reasonable effort to retain the study participants, missing data due to loss to follow-up will occur as in any longitudinal observation study. It is anticipated, however, that missing data should not be a serious issue toward bias and power in our study for the following reasons: 1) HPTN studies historically have high retention rates (>90%) for 12 months follow-up and all three sites are experienced in study management and patient retention; 2) the study participants are HIV-infected individuals in care and the study visits will be coupled with their routine clinic visits. Therefore participants will likely be more motivated to come back to study visits than

HIV negative individuals in a primary prevention trial; 3) the main primary objective is to establish baseline rates of sexual risk taking.

Even if a participant is loss to follow-up, the information on his/her available visits still contributes to the rate estimation. That said, we will examine the impact and the patterns of missing data in the data analysis stage, e.g., the proportion of missing data, whether certain baseline characteristics can predict what is missing, etc. If the missing data appear insignificant, we will consider analysis only using complete data. If the amount of missing data is significant, we will employ multiple imputations⁵⁵ based on predictors and available follow-up data. We acknowledge the validity of such imputation relies on the assumption that the missing data only depends on the observed data, not on missing data nor on unmeasured predictors.

6.5 Data Analysis of Qualitative Assessments

The qualitative interview data will be analyzed using content analysis.⁷⁹ Transcripts will be back translated into English and sent securely to protocol staff at Fenway Community Health (FCH), where members of the protocol team have extensive experience analyzing qualitative research data. After transcripts are reviewed for errors and omissions, study staff at FCH will use NVivo software to thematically organize transcripts. Two different coders will enter all data to account for variations in coding, and the team will be in consultation with English speaking staff at the study site for clarification of interpretation and content analysis. Research staff will review the coded transcripts and agree on the final overarching themes. Data will be reexamined and ongoing discussion between coders and study investigators will allow for further theorizing and making interconnections between research questions and raw data.

7.0 HUMAN SUBJECTS CONSIDERATIONS

This is an observational study and participation is completely voluntary. The information gained from this study will inform a future trial, and hence no biomedical or behavioral intervention or investigational product will be tested. Participants will be high-risk patients living with HIV and receiving care at HIV care facilities. Participants will receive treatment as usual in the clinic. Some of the ethical considerations involve learning about HIV transmission risk behaviors in HIV-infected individuals. Hence, this study can only take place in settings where confidentiality can be maintained. Specific risk assessment data as assessed via ACASI (or another confidential electronic device) will remain anonymous to the study site personnel. All study procedures will be approved by local and appropriate IRBs before implementation. All study staff will receive the appropriate human subjects and good clinical practice training before they participate in any of the human subjects research aspects of the project. Any definitely, probably, or possibly related SAE will be reported to the DAIDS Medical Officer, and to the site's IRB/EC, per their requirements and pre-established written procedures.

The team would be interested in reporting significant public health concerns back to the clinics. However, the team is doubtful that significant findings will be identified that are not already known by the clinic staff and counselors. In addition, based on the number of people who will be enrolling in the study in total, statistically significant trends would be highly difficult to detect with just a subset of enrollees (i.e. cells include site and risk

group). Based on previous studies, the most significant issues resulted from social harms, particularly, people who are “outed” as HIV positive because of their participation in the study. In the present study we do not expect this to be a problem because it is taking place in the context of HIV care clinics.

At all three sites, there is standard counseling which is detailed in Appendix VI. If significant issues arise that are not already addressed by the sites standard of care (counseling, availability of medications, etc.), and the team learns of it, the team will notify the sites of these issues and make the appropriate referrals for how to address them. Although we do not anticipate this to be the case, the most likely way this would happen would be through the qualitative interviews, as the quantitative data only assesses sexual risk taking and substance use. Other constructs are assessed via interviewer / self-report. If issues emerge in any of the other constructs, the sites would necessarily know about it because the interviewers will be site staff.

In addition, the HPTN Study Monitoring Committee also evaluates the data approximately twice yearly and can also serve as a mechanism to identify trends that may indicate issues with patient safety and provide the team with direction.

7.1 Ethical Review

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

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

Subsequent to initial review and approval, the responsible 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. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, via the HPTN CORE, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

7.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing a study-specific informed consent form for local use, based on the template in Appendices III through V, that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The HPTN CORE will work closely with the study site to

ensure that the informed consent forms are translated into local languages, and that the accuracy of the translation is verified by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party, impartial witness. (Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*.) Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their informed consent forms if they are willing to receive them.

7.3 Risks

As this is an observational/epidemiological study, there is minimal risk to participants. Participants are asked, however, to give blood samples at the enrollment, 6-month and the final (month-12) visits for STI analysis, viral load determination, and/or viral characterization. As a result of this blood draw, some participants may feel discomfort, dizziness, or even faint when their blood is drawn. Redness, pain, swelling, bruising, or rarely an infection may occur where the blood is taken.

Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or discussing issues related to HIV. 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 (e.g., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

7.4 Benefits

Information learned in this study may lead to the development of an effective prevention plan that may help reduce the spread of HIV infection. In addition, participants will receive some STI testing and as part of the study and will also receive free condoms throughout the study.

7.5 Incentives

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

7.6 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited only 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. The use of participant identifiers on study records will comply with the DAIDS policies for Source Documentation and Essential Documents. 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 secured files in an area with limited access.

Participants' study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; representatives of the HPTN CORE, SDMC, and/or Network lab (NL); government and regulatory authorities, and/or site IRBs/ECs.

Sensitive information that is collected via an ACASI or similar mechanism will be anonymous to the study staff. The only link between these data and the participant identification will be with the SDMC for data management purposes. These data will not be reported back to or stored at the site.

7.7 Communicable Disease Reporting Requirements

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

7.8 Study Discontinuation

The study may be discontinued at any time by National Institute of Allergy and Infectious Disease (NIAID), the HPTN, OHRP, government or regulatory authorities, and/or site IRBs/ECs.

8.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

8.1 Local Laboratory Specimens

As described in Section 4, the following types of specimens will be collected for testing and storage at the local laboratory (LL):

Brazil and Thailand:

- EDTA Whole Blood for plasma processing, storage, and shipment to the NL (below)
- No Additive Whole blood (for real time syphilis testing)
- Urine (for storage and shipping to the NL for possible future chlamydia and gonorrhea testing)

- Rectal/Vaginal swabs (for short-term storage and shipping to the NL for possible future chlamydia and gonorrhea testing)

Zambia:

- EDTA Whole Blood for plasma processing, and storage and possible future shipment to the NL
- No Additive Whole blood (for real time syphilis testing)
- Urine (for chlamydia and gonorrhea testing and for storage for quality assurance purposes) and possible future shipment to the NL.
- Vaginal swabs (for chlamydia and gonorrhea testing and for storage for quality assurance purposes) and possible future shipment to the NL.

Each study site will adhere to standards of good clinical laboratory practice, HPTN Manual of Operations Section 13, and local standard operating procedures for proper collection, processing, labeling, transport, and storage at the LL. Specimen collection, testing and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual. All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations.

8.2 Network Laboratory Specimens

As described in Section 4, the following types of specimens from Brazil and Thailand will be stored for future testing at the HPTN NL:

- Vaginal/Rectal swabs (for possible future chlamydia and gonorrhea testing)
- Plasma (for possible HSV-2 testing)
- Urine (for possible future Chlamydia and gonorrhea testing)

For Zambia, the above specimens will be stored at the LL for quality assurance testing and possible shipment to the NL.

8.3 Quality Control and Quality Assurance Procedures

The international CTU must participate in the DAIDS External quality assurance (QA) proficiency programs for HIV diagnosis, STI, Viral load and CD4 if you want to access this data from the medical records) NL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures.

HIV QA testing will be performed according to the HPTN NL Manual of Operations. For the Brazil and Thailand study sites, this will occur at the NL; for Zambia this will occur on-site at the LL or the HPTN NL. The HPTN NL will repeat HIV WB testing on 10% of

participant samples. NL staff will follow-up directly with site staff to resolve any QA problems identified through this process.

CT/NG QA testing will occur at the LL for all Zambia samples with potential future testing on stored samples at the NL. This will be done with the guidance of the Network Laboratory and in accordance with guidelines for quality assessment for external laboratories in the HPTN NL Manual of Operations.

Shipping of Specimens for QA Testing:

All specimens will be shipped in accordance with the HPTN Manual of Laboratory Operations and International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

8.4 Specimen Storage and Possible Future Research Testing

Study site staff will store all plasma and urine, and vaginal/rectal swabs collected in this study at least through the end of the study. The Brazil and Thailand sites (and possibly the Zambia site) will periodically ship urine, rectal and vaginal swabs and plasma to the NL. Study participants will be asked to provide written informed consent for their samples 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 after all protocol-related testing is complete.

8.5 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. All infectious specimens shipped from sites that will be transported to the NL will be shipped in accordance with United States regulations (42 CFR 72).

9.0 ADMINISTRATIVE PROCEDURES

9.1 Study Activation

Prior to implementation of this protocol and any subsequent full version amendments, sites must have the protocol and protocol consent form approved by their local IRB/EC. Protocol documents must be registered with and approved by the DAIDS Regulatory Support Center (RSC) Protocol Registration Office.

Following ethical review and approval, each participating site will complete the DAIDS protocol registration process as described in the DAIDS Protocol Registration Manual (<http://rsc.tech-res.com/forms.htm>). Protocol Registration must occur before the site can enroll any subjects into the study. The HPTN CORE, SDMC and NL staff will work closely with each site to ensure completion of this and all other study-specific site activation requirements as detailed in the HPTN MOP and the SSP Manual. Upon successful protocol registration and completion of all other study-specific site activation

requirements, the CORE will issue a study activation notice to the site. Implementation of the study may not proceed prior to receipt of this written notification.

9.2 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 reporting, 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 data management system. Quality control reports and queries will routinely be sent back to the site for verification and resolution.

Close cooperation between the study Investigator, NIAID Medical Officer, Protocol Specialist, Biostatistician, SDMC Project 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.

Qualitative data gained through in-depth interviews and focus groups will be managed and analyzed by members of the protocol team at Fenway Community Health (see Section 6.5 for details).

9.3 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 participants and other research regulations and guidelines.
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices.
- 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, NL, NIAID, and U.S. 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.

9.4 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, rights or welfare of participants, or to eliminate apparent immediate hazards to participants.

9.5 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 DAIDS. Study records include administrative documentation, including site registration documents and all reports and correspondence reSouthg 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. Qualitative data gained from in-depth interviews and focus groups, including recordings, original transcripts and English translations, will also be maintained along with other study records.

9.6 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.

Findings from the study will be presented to the CABs in each community. The study teams will work with the CABs to decide on the best method for disseminating information about the study. This can occur, for example, via a community meeting, radio broadcast, etc. Slides will also be posted on the HPTN website which can be used as presentation materials in the various communities.

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APPENDICES

**APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR THE
QUALITATIVE ASSESSMENT (IN-DEPTH INTERVIEWS AND FOCUS GROUPS)**

**APPENDIX I: Schedule of Study Visits and Procedures for the Qualitative Assessment
(In-Depth Interviews and Focus Groups)**

<u>FOCUS GROUP</u>	Session 1	Session 2
Target Day	Day 0	Day xx
Administrative and Behavioral Procedures to be Performed at the Clinical Site		
General demographic information	X	X ¹
Participation in Focus Group	X	X ¹

¹ Participants may be called back to participate in a second focus group session following analysis of the data.

<u>IN-DEPTH INTERVIEW</u>	Session 1	Session 2
Target Day	Day 0	Day xx
Administrative and Behavioral Procedures to be Performed at the Clinical Site		
Participation consent	X	
Demographic information	X	X ¹
Participation in In-Depth interview	X	X ¹

¹ Participants may be called back to participate in a second interview following analysis of the data.

APPENDIX II: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR THE QUANTITATIVE ASSESSMENT

APPENDIX II: Schedule of Study Visits and Procedures for the Quantitative Assessment

	Screening	Enrollment	Month 3 Follow-Up Visit	Month 6 Follow-Up Visit	Month 9 Follow-Up Visit	Termination Visit (Month 12 Visit)
Target Day	≤-30 days	Day 0	Day 91	Day 182	Day 274	Day 365
Administrative and Behavioral Procedures to be Performed at the Clinical Site						
Screening/Enrollment consent	X					
Locator information	X	X	X	X	X	
Eligibility determination	X					
Demographic information		X				
Social harm data		X	X	X	X	X
Administration of questionnaire		X	X	X	X	X
Self reported STIs		X	X	X	X	X
Clinical Procedures to be Performed at the Clinical Site						
Specimen collection (blood, urine, vaginal/rectal swabs)		X		X		X
Medical history		X	X	X	X	X
Survey of medications including adherence		X	X	X	X	X
STI abstraction from medical charts		X	X	X	X	X
BLOOD VOLUME (ml)		up to 10ml		up to 10ml		up to 10ml

**APPENDIX III: SAMPLE INFORMED CONSENT FORM –STUDY PARTICIPANT
(QUANTITATIVE)**

SAMPLE INFORMED CONSENT FORM –STUDY PARTICIPANT (QUANTITATIVE)

DIVISION OF AIDS, NIAID, NIH

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED
INDIVIDUALS IN CARE SETTINGS**

Version [X.X]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]

INTRODUCTION:

You are being asked to volunteer for screening to find out if you are eligible for the investigational research study named above. If you meet the screening criteria, you may be invited to enroll in the study today. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This is a study for men and women who are HIV-infected. The study will consist of approximately 800 participants (500 men and 300 women). Participants will come from Africa, Asia, and South America.

Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to review the following information. If you wish, discuss it with others, ask questions, or ask us for more information. Once you understand this study, and if you agree to take part, you will be asked to sign this form or make your mark in front of someone. We will give you a copy of this form to keep.

Please note that:

- Your participation in this study 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 health care.
- Even if you agree to have the screening procedures, you do not have to join the research study.

DESCRIPTION OF THE STUDY:

The purpose of this study is to gather information needed to design and put into practice future programs related to HIV research and care. These programs will help HIV-infected individuals protect their own health, and reduce the chances that they will spread HIV to others.

No HIV medication will be provided as a part of this study.

STUDY VISITS:

Screening/Enrollment Procedures:

If you agree to participate in the screening process, and you are found to be eligible for the study, then you may be enrolled today. The screening process will last up to 1 hour. Some people may not be able to join the research study because of information found during the screening. If you are eligible, and you decide to enroll, the enrollment process will last up to 2 hours.

During the screening process:

- We will ask you where you live and how to find you.
- We will ask you questions about you (like your age), your sexual activities, and your sexual partners.
- We will provide you information about how to prevent the spread of HIV.

If you are eligible for this study and agree to participate, you will have time to ask questions and discuss any concerns you may have with the study staff. If you agree to join this study, you will be asked to come back to the clinic every 3 months for one year (5 visits all together including this visit).

The following activities will take place after you enroll:

You will be asked to confirm detailed information about where you live and how we can find you, including whether there are any people that we may contact when we are looking for you. This information is very important because we may need to contact you to give you new information or we may need to find you if you miss an appointment. If you miss an appointment during the study, we will try to reach you through the contact information you provide. If we contact any of the people that you give us permission to contact, we will not tell them why we are trying to reach you. If you are not willing to give us contact information to reach you, you should not agree to be in this study.

We will ask you additional questions about HIV, your health, your sexual activities, and your feelings and beliefs. You will be able to answer some of the more sensitive questions in private. Study staff will not review these answers. They will be sent directly to a database through a phone or computer and will not have your name attached. We will also review your medical records.

We will draw 10 ml of blood (around 2 teaspoons) to test for Herpes Simplex virus and your HIV viral load. We will also collect blood, urine and/or vaginal/rectal swabs to test for other sexually transmitted infections such as chlamydia, gonorrhea and syphilis. We will test for some of those infections today. Others we may test for at a later date using your frozen samples if you agree. Participants will receive the results of these tests through their clinician. If a sexually transmitted infection is discovered in these samples, you will be called back to the clinic for re-testing and treatment. You will also have a brief physical exam.

At every visit, we will ask you if you have had any bad social experiences because of your participation in this study. These are called Social Harms.

Quarterly Study Visits (Every Three Months):

The quarterly visits will last about 1 and 1/2 hours. During these visits, we will do the following:

- We will update the information on where you live and how to find you.

- We will ask you questions about HIV, your health and sexual activities, similar to the first visit.
- We will ask you if you have had any bad social experiences because of your participation in this study.
- We will review your medical records.
- We will draw 10 ml of blood (around 2 teaspoons) at your **6 month visit and last visit only**.
- We will collect urine and/or vaginal/rectal swabs at your **6 month visit and last visit only**.

RISKS and/or DISCOMFORTS:

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may become embarrassed, worried, or anxious when discussing your sexual practices and HIV. A trained staff member will help you deal with any feelings or questions you have. There may also be social risks such as stigma that may result from being involved with the study or having your HIV status known.

POTENTIAL BENEFITS:

You may get no direct benefit from the study. However, during the study, you will receive information related to HIV and other sexually transmitted infections you may have. You will also be able to ask questions about your health and feelings. You will receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help reduce the spread of HIV in the future and may help develop programs to assist people with HIV with their sexual health.

NEW FINDINGS:

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Other administrative reasons.

COSTS AND COMPENSATION:

There is no cost to you for participating in this study. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

ALTERNATIVES TO PARTICIPATION:

If you choose not to take part in this study, it will have no effect on your regular health care at this clinic.

This clinic *[can or cannot – site specific]* provide you with drugs to prevent or treat infections related to HIV. However, the clinic *[can or cannot]* provide anti-HIV drugs. In order to receive anti-HIV drugs, you would have to buy the drugs from a private doctor or local pharmacy. *[This paragraph should be changed to be site-specific, indicating what kind of HIV-care can be normally provided by the clinic to the HIV-infected individual.]*

CONFIDENTIALITY:

Your study records and test results will be kept strictly confidential to the extent permitted by law, but absolute confidentiality cannot be guaranteed. You and your blood samples will be identified by a code number only, and personal information from your records will not be released without your written permission. All sensitive information collected about your sexual practices will go directly to the database through a computer or telephone and will not be seen by the clinic staff. You will not be personally identified in any publication about this study. However, your records may be reviewed by the sponsor of the study (United States NIH), HIV Prevention Trials Network (HPTN) *[insert name of site]* Institutional Review Board, *[insert name of site]* Ethics Committee, study staff and study monitors and *[insert applicable local authorities]*.

If during the course of these screening tests, we find out that you have *[insert all applicable reportable diseases (e.g., HIV)]*, we must report it to *[insert the name(s) of the local health authorities]*. Although we must report that we have treated someone with *[insert all applicable reportable diseases]*, your name will not be reported to the agency. *[Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]*

SAMPLES LEFTOVER AT THE END OF THE STUDY

Once all the testing in the study is done, if there are samples that are left we would like to use them for future research that is not a part of this study, but would be used for HIV-related research only. An Institutional Review Board or Ethics Committee, which watches over the safety and rights of research participants, must approve any research study using your samples. There is no time limit on how long these samples will be stored, and they may be stored outside of your country. At the end of this consent form you will indicate whether you agree to this future testing, which may include genetic tests. Genetic testing is testing on the information that you inherit from your parents. If you do not agree to future testing of your samples, they will be destroyed at the end of the study.

RESEARCH-RELATED INJURY:

[Site-specific: insert institutional policy] If you are injured as a result of this study, the study clinic will give you immediate necessary treatment for your injuries. You will then be told where you may receive additional treatment for your injuries. The cost of this treatment may be charged to you. There is no program to pay for the treatment of such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS or QUESTIONS:

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

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

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

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

**SIGNATURE PAGE: SCREENING AND ENROLLMENT (STUDY PARTICIPANT -
QUANTITATIVE)**

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED
INDIVIDUALS IN CARE SETTINGS**

Version [X.X]

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to participate in this research study, please sign your name or make your mark in the signature area at the bottom of this page. By providing your initials in the spaces below you may also agree to additional storage and testing of any left-over blood samples.

Specimens Stored for Future Testing

_____ My initials indicate that any left-over blood samples may be stored for future testing:

_____ I do not agree to allow leftover samples to be saved for long term storage and future testing after the study

Notification of Future Test Result

My initials below indicate if I want to be contacted in the future if test results on frozen samples show that I may have a sexually transmitted infection

_____ **YES**

_____ **NO**

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date

**APPENDIX IV: SAMPLE INFORMED CONSENT FORM – IN-DEPTH INTERVIEWS
(QUANTITATIVE STUDY PARTICIPANTS)**

**SAMPLE INFORMED CONSENT FORM – IN-DEPTH INTERVIEWS
(QUANTITATIVE STUDY PARTICIPANTS)**

DIVISION OF AIDS, NIAID, NIH

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED
INDIVIDUALS IN CARE SETTINGS**

Version [X.X]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]

INTRODUCTION

You are being asked to participate in an interview to help us learn more about HIV in your community. This information will be used to help develop a large international HIV prevention study that may help reduce the spread of HIV in communities in Africa, Asia, and South America. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

The information you give in this interview will be combined with the rest of the information that is collected during this research. We will interview approximately 100 people. We will use all of that information to learn more about the people affected by HIV in these communities. In the future we hope this information will help to reduce HIV rates in people who live in these communities.

PROCEDURES

The interview will be given by a member of the research team. They will ask you where you live and how to contact you. The interview questions will cover many issues, including topics such as education, income, cultural norms, mental health, substance use, and domestic and sexual violence.

To help make sure that we fully understand your answers, **the interviews will be audio-recorded**. The information on the audio-recording will then be typed by an individual who works with the research team. Your name will not be included in that typed record. After this research study has been completed all of the interview recordings will be destroyed.

- The interview **will take about 1 hour** to complete.
- There will be **no cost to you** to participate in the focus groups.
- **You will receive** [insert local compensation amount] for your time and effort.
- We may contact you again in the next few months to ask you some follow-up questions. We will use the information you provided at the beginning of the interview to contact you.

RISK

The risk to you in participating in this interview is that some of the questions may be uncomfortable and may make you feel embarrassed. If any of the questions make you very upset the interviewer may go to another question or totally stop the interview. You will also be provided with contact and referral information if any of the questions raise issues that you would like to address at this or some later time. There may also be social risks such as stigma that may result from being involved with the study or having your HIV status known.

BENEFITS

There are no direct benefits to you for participating in this interview. We hope that the benefit from this interview will be the information that might help reduce the risk of HIV among people in your community.

VOLUNTARY PARTICIPATION

Your participation in this interview is voluntary. You can decide to not participate in this interview and still remain in the other part of this study. Although we hope that you will be comfortable answering all of the questions openly and honestly, please remember that you may refuse to answer any of the questions, or stop participating in the interview completely, at any time.

CONFIDENTIALITY

The research team will protect your confidentiality by not putting your name on any of the transcripts. These items will be kept in a secure location that can only be accessed by the study staff. These records may be reviewed by the sponsor of the study (United States NIH), *[insert name of site]* Institutional Review Board, study staff and study monitors and *[insert applicable local authorities]*. *[Sites will fill in any information regarding the legal limits of confidentiality and when or if some information would have to be disclosed, e.g. if a participant reported that they had intentions on hurting someone.]* Your personal information may also be disclosed if required by law.

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 participant, 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: IN-DEPTH INTERVIEWS (QUANTITATIVE STUDY PARTICIPANTS)

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED
INDIVIDUALS IN CARE SETTINGS**

Version [X.X]

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the focus group, please sign your name on the line below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(*As appropriate*)

Witness's Signature and Date

**APPENDIX V: SAMPLE INFORMED CONSENT FORM – IN-DEPTH INTERVIEWS
(STAKEHOLDERS)**

SAMPLE INFORMED CONSENT FORM – IN-DEPTH INTERVIEWS (STAKEHOLDERS)

DIVISION OF AIDS, NIAID, NIH

HPTN 063

PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED INDIVIDUALS IN CARE SETTINGS

Version [X.X]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]

INTRODUCTION

You are being asked to participate in an interview to help us learn more about HIV in your community. This information will be used to help develop a large international HIV prevention study that may help reduce the spread of HIV in communities in Africa, Asia, and South America. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

The information you give in this interview will be combined with the rest of the information that is collected during this research. We will use all of that information to learn more about the people affected by HIV in these communities. In the future we hope this information will help to reduce HIV rates in people who live in these communities.

PROCEDURES

The interview will be given by a member of the research team. They will ask you where you live and how to contact you. The interview questions will cover many issues, including topics such as education, income, cultural norms, mental health, substance use, and domestic and sexual violence.

To help make sure that we fully understand your answers, **the interviews will be audio-recorded**. The information on the audio-recording will then be typed by an individual who works with the research team. Your name will not be included in that typed record. After this research study has been completed all of the interview recordings will be destroyed.

- The interview **will take about 1 hour** to complete.
- There will be **no cost to you** to participate in the focus groups.
- **You will receive** [insert local compensation amount] for your time and effort.
- We may contact you again in the next few months to ask you some follow-up questions. We will use the information you provided at the beginning of the interview to contact you.

RISK

The risk to you in participating in this interview is that some of the questions may be uncomfortable and may make you feel embarrassed. If any of the questions make you very upset the interviewer may go to another question or totally stop the interview. You will also be provided with contact and referral information if any of the questions raise issues that you would like to address at this or some later time. There may also be social risks such as stigma that may result from being involved with an HIV study or having people assume that you are HIV-infected.

BENEFITS

There are no direct benefits to you for participating in this interview. We hope that the benefit from this interview will be the information that might help reduce the risk of HIV among people in your community.

VOLUNTARY PARTICIPATION

Your participation in this interview is voluntary. Although we hope that you will be comfortable answering all of the questions openly and honestly, please remember that you may refuse to answer any of the questions, or stop participating in the interview completely, at any time.

CONFIDENTIALITY

The research team will protect your confidentiality by not putting your name on any of the transcripts. These items will be kept in a secure location that can only be accessed by the study staff. These records may be reviewed by the sponsor of the study (United States NIH), *[insert name of site]* Institutional Review Board, study staff and study monitors and *[insert applicable local authorities]*. *[Sites will fill in any information regarding the legal limits of confidentiality and when or if some information would have to be disclosed, e.g. if a participant reported that they had intentions on hurting someone.]* Your personal information may also be disclosed if required by law.

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 participant, 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: IN-DEPTH INTERVIEWS (STAKEHOLDERS)

HPTN 063

**PREPARING FOR INTERNATIONAL PREVENTION TRIALS INVOLVING HIV-INFECTED
INDIVIDUALS IN CARE SETTINGS**

Version [X.X]

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the focus group, please sign your name on the line below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(*As appropriate*)

Witness's Signature and Date

APPENDIX VI: OVERVIEW OF SITES' STANDARD HIV/AIDS COUNSELING PROCEDURE

APPENDIX VI: Overview of Sites' Standard HIV/AIDS Counseling Procedures

Chiang Mai

A. HIV/AIDS counseling and education provided to HIV positive participants:

1. Discuss about confidentiality and revealing the HIV status to family/ friend, and he/she concerns about telling others.
2. HIV education
 - modes of transmission and methods of sexual protection.
 - difference between HIV and AIDS
 - correct any misinformation or myths
 - discuss about CD4, Viral load
3. Risk reduction
 - review condom use; consistency, frequency, technique, barriers to use etc.
 - demonstrate condom use on a model
 - discuss ways to overcome barriers to condom use
 - discuss health maintenance; nutrition, exercise, sleep/rest, hygiene
 - discuss alcohol, tobacco, drug use and relation to health
 - discuss contraception, pregnancy and breast feeding (female participant)
4. Partner Notification
 - discuss reveal HIV status to partner; why and how, (role-play, if necessary)
5. Discuss on ART adherence
 - concept of ART adherence, and discuss about adherence and resistance
 - discuss on side effects, eliminating or reducing side effects, consult physician if necessary
 - determine the usefulness of the various components of the participant's adherence Plan
 - address how to handle missed doses
 - reminder strategies, including partner support, role of family, community, social support and privacy
 - pill dispensing and accounting

B. Frequency: HIV/AIDS patients receive HIV/AIDS counseling/education during routine visits which occurs, in general, every 2-3 months.

C. Length of time: 30-45 minutes.

D. Resources:

- Human resource: Nurse, Physician, People living with HIV/AIDS group
- Place: VCT unit, counseling room
- Material: brochure, flyer, model (demonstrate condom use)

E. Derivation: Standard care from Ministry of Public Health, Faculty of Medicine, Chiang Mai University, HPTN 052 study.

IPEC

Purpose: To provide HIV/AIDS counseling related to adherence, safer sex, risk reduction plan, partner notification, create a Positive Living Plan, pre-conception and contraception.

Frequency: HIV/AIDS patients receive HIV/AIDS counseling/education during routine visits which occurs, in general, every 3 months.

Length of time: 40-60 minutes.

Resources: Handout visual materials about pills taking and adherence tools (diary cards, note cards, etc.); material to demonstrate the proper use of condoms and provide free condoms; folders that explain about contraceptive methods; folders and posters made for recruitment to studies.

Derivation: Recruitment sources are disclosed below.

1. Counseling adherence procedures: providing accurate information about treatment and medication:

- 1.1. Knowledge of HIV pathogenesis, overview of HAART, drug interaction, side effects, managing and treatment.
- 1.2. Explain the difference between HIV and AIDS. Meaning of undetectable Viral Load. (VL).
- 1.3. The meaning of adherence, including barriers to adherence, and the relationship between adherence and drug resistance.
- 1.4. Emphasize the importance of client's engaging. Facilitate the dispensing medication, create and negotiate a tailored treatment plan that suits client's work schedule. Strategies to handle non-adherence.
- 1.5. Explain times of drug administration, the importance of continuity of medication, about handling with the missed and/or slip up doses.
- 1.6. Pill dispensing and accounting.
- 1.7. Sharing of medication and changing of medication schema, if necessary.

2. Counseling on safer sex:

- 2.1. Focus on issues surrounding the safer sex practices.
- 2.2. Assessing the knowledge of HIV/AIDS and providing appropriate information about the transmission and prevention of HIV infection.
- 2.3. Demonstrate the proper use of condoms and provide free condoms. Role-Play the demonstration and ask patients to demonstrate condom use on a model together, if necessary.
- 2.4. The ways to consistently protect the uninfected person from infection.
- 2.5. Emphasize on building good communication between the partners. Discuss family and community pressures and conflicts.
- 2.6. Discuss violence or abuse, drug and alcohol abuse and the ways to address these problems, if necessary.
- 2.7. Discuss social support and privacy.

3. Counseling on Risk Reduction Plan:

- 3.1. Encourage client's self-esteem and trust.
- 3.2. Discourage stigma, prejudice and myths related with STD/HIV/AIDS.
- 3.3. Providing accurate information about STD/HIV/AIDS common signs & symptoms transmission, prevention and treatment. Emphasize the relationship between STD and HIV/AIDS.
- 3.4. Explain the benefits and the correct condom use, demonstrate the correct way of use on a model of a penis. Ask the client to demonstrate on a model.
- 3.5. If client is an injecting drug user, explain the importance of using clean equipments and not sharing.

4. Counseling about partner notification:

- 4.1. Discuss the importance of confidentiality.
- 4.2. Discuss why partner should be notified (chance to do HIV test, to receive care if they are infected and to protect against HIV infection or re-infection).
- 4.3. Review partner notification strategies (possible reaction by partner, in case of infection, possible social disruptions and strategies to avoid them).

5. Counseling to create a Positive Living Plan:

- 5.1. Inspire the client's basic potential, by reviewing ways that he or she has solved problems in the past.
- 5.2. Nutrition (importance of eating healthy foods to strengthen immune system).
- 5.3. Hygiene (importance of hygiene to avoid germs that could threaten immune system).
- 5.4. Exercise and rest (need to stay fit and rested to maintain overall health).
- 5.5. Review current medications (discuss adherence, etc.).
- 5.6. Alcohol, tobacco, drugs (need to avoid these).

6. Pre-conception and contraception counseling:

- 6.1. Review the reproductive choices, including the willingness of pregnancy, and prophylaxis of mother to child transmission.
- 6.2. Breastfeeding and childbearing.
- 6.3. Contraception and current methods used by subject, if any.
- 6.4. Stability of relationship and the role of the woman in the relationship.

Zambia

A. HIV/AIDS COUNSELLING /EDUCATION

- Assure confidentiality and explain shared confidentiality
- Knowledge on HIV/AIDS:
 - definition
 - Mode of acquisition and transmission,
 - prevention of acquisition/transmission,
 - difference between HIV and AIDS,
 - discussion on CD4 and Viral Load
- Positive Living & ARV care:
 - ABC,
 - diet,
 - exercises,
 - Seeking Medical care etc.
- Clear misconceptions and beliefs on HIV/AIDS
- Identify levels of risk behavior through questioning on sexual and life history
- Discuss the practical implications of having HIV i.e. sexual relationships, work situations, medical follow-up
- Explore available support mechanisms (family friends, clinic and other services)

B. FREQUENCY OF COUNSELLING/EDUCATION SESSIONS

- An intensive session is conducted at the time of person knowing their HIV status
- A re-cap of the session each time there is patient contact, initially every 2 weeks for one to two months, then monthly.
- For those that do not start ARVs they are usually seen every 3 to 6 months for HIV follow-up and care.

C. LENGTH OF TIME OF COUNSELLING SESSION

- Counseling sessions take between a minimum of 15 minutes to a maximum of 45 minutes.

D. RESOURCES

- Human resource- Nurses, Peer Educators, Clinicians.
- Infrastructure-Clinic; rooms with good lighting, ventilation and furniture.
- Information, Education and Communication Materials eg brochures, flyers

APPENDIX VII: OVERVIEW OF EARLY COMMUNITY CONSULTATION AND STUDY PREPARATION

APPENDIX VII: Overview of Early Community Consultation and Study Preparation

During the first 8 months, study sites will gather insights related to the quantitative assessment battery to be used during the quantitative phase of this study. This will not require obtaining IRB approval as this will be done on a consultant/advisory basis with key informants at each of the sites. No data is being collected about these individuals. Input is being solicited from them about the study design and study instruments.

Key informants will include:

- Community Advisory Board (CAB) members
- Community educators
- Relevant Non-Governmental Organization (NGO) leaders
- HIV-infected individuals and their families
- Men who have sex with other men (Thailand and Brazil only)
- Health care professionals who work with HIV-infected individuals
- Institutional Review Board (IRB) members
- Other community stakeholders (according to your local needs).

We envision three meetings at each site regarding shaping of the assessments. The first will be to articulate the domains needed for the quantitative assessment. The second will involve presenting it for review and feedback. The third meeting will be to review the final version, and assist with the readability of the questions.

These consultations will be done to maximize the cultural appropriateness, comprehensibility, and acceptability of the quantitative survey before initiating the quantitative phase of the current proposal. We will also ask these key informants to provide feedback about the qualitative interview guides before they are finalized. In addition, this 8-month period will involve translating the quantitative assessment battery to the local language at each study site, and then obtaining a back translation to ensure accuracy. Once the study assessments have been translated, back translated and approved for correctness, they will be submitted to IRBs and ECs along with the protocol for approval before enrolling participants into the study.

These activities do not fall under the requirements of the human subjects regulations because these individuals, as consultants and members of community advisory boards, do not meet the regulatory definition of 'human subject.' We will not audio record the interviews: we will take comprehensive notes about their suggestions and use these to help shape the interview guides. As these individuals are part of community groups designed to give feedback/advice for studies and programmatic activities on a consultant basis, they are not considered research subjects and will not be subject to an informed consent process. These individuals will also not be asked for any personal information.

Community consultation meetings will be facilitated by a community educator associated with the site or a member of the study team such as the investigator of record or study coordinator. The first meeting will tentatively follow the agenda below:

- Introductions
- Study overview
- Input from the community on major issues influencing sexual risk behavior
- Questions from the protocol team
- Review of preliminary questionnaire
- Other thoughts, comments, concerns, questions
- Next Steps

Input from community members will be transcribed in the local language and then translated into English by a trained individual identified by the site. The protocol team will use this feedback to create an updated draft of the study questionnaire.

Community consultants will meet again to review and discuss the updated questionnaire as well as the qualitative interview guide for the focus groups and individual in-depth interview. Again, their comments will be transcribed in the local language and then translated into English. The protocol team will use this feedback to finalize the questionnaire and prepare it to be used with the ACASI system.

A subset of the community consultants (community educators, HIV-infected individuals and family members, and health care professionals) will assist with the validation of the instrument by carefully reviewing the questions and ACASI system and providing feedback on the content, comprehension, length, and any other feedback. The tool will be finalized following these final comments.