

**A Randomized Clinical Trial of the Efficacy of a Behavioral Intervention  
to Prevent Acquisition of HIV Among  
Men who have Sex with Men**

**HIVNET Protocol No. 015**

Sponsored by:

The National Institute of Allergy and Infectious Diseases  
Division of AIDS  
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## LIST OF ABBREVIATIONS AND ACRONYMS

A-CASI	Audio-Computer-Assisted Self-Interview
AIDS	Acquired immunodeficiency syndrome
AIEDRP	Acute Infection and Early Disease Research Program
ARI	Acute retroviral infection
AVEG	AIDS Vaccine Evaluation Group
BIT	Behavioral Intervention Trials
CAB	Community Advisory Board
CAPS	Center for AIDS Prevention Studies
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CL	HIVNET Central Laboratory
DAIDS	Division of AIDS
DMC	Domestic Master Contractor
DSMB	Data and Safety Monitoring Board
ELISA	Enzyme-linked immunoabsorbent assay
GEE	Generalized estimating equations
GC	Gonococcal infection
HEDS	HIV Early Detection Study
HIV	Human immunodeficiency virus
HIVMOP	HIV Network for Prevention Trials Manual of Operations
HIVNET	HIV Network for Prevention Trials
HSV-2	Herpes simplex virus type 2
ICC	Intervention Coordinating Center
IRB	Institutional Review Board
LE	Leukocyte esterase
LL	Local Laboratory
LCR	Ligase chain reaction
MSM	Men who have sex with men

## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
NIMH	National Institute of Mental Health
OAR	Office of AIDS Research
OSHA	Occupational and Safety Health Administration
PCR	Polymerase chain reaction
PT	Protocol Team
QA	Quality assurance
QALY	Quality-adjusted life year
QC	Quality control
RCT	Randomized Controlled Trial
SC	Statistical Clinical and Coordinating Center
SOP	Standard operating procedure
SSP	Study Specific Procedures Manual
STD	Sexually transmitted disease
UCSF	University of California at San Francisco
UNAIDS	United Nations AIDS Project
VPS	Vaccine Preparedness Study
WB	Western blot

## PROTOCOL SUMMARY

<b>Title</b>	A Randomized Clinical Trial of the Efficacy of a Behavioral Intervention to Prevent Acquisition of HIV Among Men who have Sex with Men
<b>Participants</b>	Four thousand three hundred fifty MSM from domestic HIVNET sites who are HIV seronegative and who report engaging in anal sex within the past 12 months.
<b>Estimated Time Period</b>	Total trial duration of 4.0 years (from 1/99 through 1/03).
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<b>Data Coordination and Analysis</b>	HIVNET Statistical and Clinical Coordinating Center (SC) Fred Hutchinson Cancer Research Center Eileen Hess (206) 667-2841 Barbara Metch (206) 667-4656
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<b>Repository Laboratory</b>	HIVNET Repository Contractor (RC) Biomedical Research, Inc. Roger Rowe (301) 881-7636

**Figure 1: Summary of Activities/Procedures by Study Visit**

<b>Month of study:</b>	<b>-0.5</b>	<b>0</b>	<b>1</b>		<b>2</b>	<b>3</b>			<b>6</b>	<b>9</b>	<b>12</b>	<b>15</b>	<b>18</b>	<b>21</b>	<b>24</b>	<b>27</b>	<b>30</b>	<b>33</b>	<b>36</b>	
Informed Consent	A	A																		
Locator / Locator Update	A	A							A	B	A	B	A	B	A	B	A	B	A	
Enrollment/Randomization		A																		
<b>Laboratory Tests</b>																				
HIV Antibody (LL)	A								A		A		A		A		A			A
GC Leukocyte Esterase (LL)	A								A <sup>2</sup>											
GC Ligase Chain Reaction (CL) <sup>1</sup>	A								A <sup>2</sup>											
GC Culture (LL)	A								A <sup>2</sup>											
HSV-2 (CL) <sup>6</sup>	A																			A
Archive/Future Testing (CL)	A								A		A		A		A		A			A
<b>Interviews/Assessments</b>																				
Pre-screening Assessment	A <sup>7</sup>																			
Eligibility Screening	A																			
Risk Assessment (A-CASI)	A								A		A		A		A		A			A
STD / Use of PEP Assessment <sup>5</sup>	A								A		A		A		A		A			A
Counseling/Therapy History	A																			
Cost Assessment <sup>4</sup>			B																	
Social Impact Assessment									A		A		A		A		A			A
<b>Counseling</b>																				
HIV Pre-test Counseling	A								A		A		A		A		A			A
HIV Post-test Counseling <sup>3</sup>		A							A		A		A		A		A			A
Intervention Module Delivery		B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
Intervention Maintenance/Booster Session									B	B	B	B	B	B	B	B	B	B	B	B
Standard Risk Reduction Counseling		C							C		C		C		C		C			C

A = All participants, B = Behavioral (experimental) Intervention, C= Control Group  
 LL = Local Lab      CL = Central Lab  
 GC = gonococcal infection      HSV-2 = Herpes Simplex Virus type 2  
 1 Only if leukocyte esterase is positive for GC;      2 Decision to continue subsequent months based on interim analysis.      3 Post-test 2 weeks after pre-test  
 4 Cost assessment will be administered at two of the ten separate counseling sessions where an intervention module is delivered.      5 Use of PEP Assessment administered if indicated.  
 6 Decision to test for HSV-2 to be based on results from sub-sample of 600 participants at Month 36.      7 May be administered at recruitment/outreach prior to screening visit.

**Figure 2: Specimen Collection Requirements**

Specimen Type	Volume	Tube Type	Shipping	Lab	Test/Use
<b>Panel A. Specimens at Screening and Scheduled Follow-up Visits Every Six Months</b>					
serum	local SOP	local SOP	local SOP	LL	HIV antibody
serum	2 tubes, 15ml	tiger top SST	batch	CL	QC of LL HIV serology/HSV-2 <sup>2</sup> /archive
urine	15-20 cc first void	available container	local SOP	site	LE urethral inflammation
urine <sup>1</sup>	above sample	50 ml polypropylene centrifuge tube	immediate	CL	LCR urethral gonorrhea
rectal swab	NA	NA	local SOP	LL	culture rectal gonorrhea
<b>Panel B. Specimens for Work-up of Indeterminate HIV Antibody Result / Suspected Acute HIV Infection</b>					
serum	local SOP	local SOP	local SOP	LL	HIV antibody
serum	1 tube, 7.5ml	tiger top SST	immediate	CL	archive
whole anticoagulated blood <sup>3</sup>	2 tubes, 17 ml	yellow top ACD	immediate	CL	DNA PCR/potential viral studies
<b>Panel C. Specimens for Confirmed Incident HIV Infections</b>					
serum	local SOP	local SOP	local SOP	LL	HIV antibody
serum	local SOP	local SOP	local SOP	LL	syphilis RPR <sup>4</sup>
plasma	local SOP	local SOP	local SOP	LL	CBC/diff/platelets
serum	2 tubes, 15 ml	tiger top SST	immediate	CL	archive
plasma	1 tube, 7.5 ml → 2, 2ml cryovials	purple top EDTA	immediate	CL	viral burden
whole anticoagulated blood	8 tubes, 68 ml	yellow top ACD	immediate	CL	viral isolate/host immune response studies/archive

<sup>1</sup> Urine sample sent to CL for LCR **ONLY IF** LE is positive for GC at site.

<sup>2</sup> HSV-2 antibody testing to be done at the end of the study (see section 7.2.1).

<sup>3</sup> Collect **ONLY IF** HIV WB is indeterminate with bands at *p24* and/or *env*.

<sup>4</sup> Assay performed **ONLY IF** informed consent is given in HIVNET 019 or AIEDRP.

LL - local lab

CL - Central Lab

WB - Western blot

LCR - ligase chain reaction

LE - leukocyte esterase

PCR - polymerase chain reaction

# 1. INTRODUCTION

## 1.1 Overview

This Phase IIb randomized controlled trial will assess the efficacy of a behavioral intervention vs. standard risk reduction counseling to prevent acquisition of human immunodeficiency virus (HIV) among men who have sex with men (MSM). It is designed as a proof-of-concept trial - that is, it will provide a preliminary, but direct, assessment of the efficacy of the behavioral intervention in preventing acquisition of HIV infection. This trial builds upon Phase I and II studies that have demonstrated the potential of specific behavioral interventions to reduce self-reported behavioral risk among MSM.

The behavioral intervention consists of ten sessions over a four-month period followed by quarterly maintenance sessions. The control condition consists of semiannual risk reduction counseling based on the Centers for Disease Control and Prevention (CDC)/Project RESPECT model for HIV pre and post-test counseling. The trial will enroll 4,350 MSM recruited at six domestic HIV Network Prevention Trials (HIVNET) study sites. The seroincidence rate of HIV infection will be compared between the two arms of the study.

## 1.2 Behavioral Intervention

The intervention being evaluated in this trial is based on the extensive literature on behavioral approaches to risk reduction in MSM reviewed by the Office of Technology Assessment (Coates et al. 1995) and AIDS Prevention Strategies that Work: A Review of National Institute of Mental Health (NIMH)-Sponsored Research (Office on AIDS, NIMH, 1998). As recommended by these reviews, the intervention addresses the variety of circumstances and emotional issues contributing to unsafe sex among HIV-negative MSM. The intervention is tailored to an individual's unique problems and needs, lifestyle, and situations that contribute to high-risk behavior. As such, the intervention responds to a recent review by the National Institute of Alcohol Abuse and Alcoholism (NIAAA), in conjunction with the OAR, which called for the development and evaluation of behavioral interventions to reduce HIV-related risk behaviors, including the practice of unsafe sex and sharing needles in the context of alcohol and substance use. In addition to being tailored to the individuals, the recommended behavior changes are developed using a participant-centered framework. That is, decisions about specific steps taken to change behavior and the pace of change are generated by active participation by the individual rather than by a prescription from the counselor.

The behavioral intervention consists of ten, one-to-one, one-hour sessions over a four-month period, followed by maintenance sessions that occur at least quarterly for the remainder of the three-year follow-up. The precise schedule of these sessions is tailored to individual participants; however they occur frequently during the initial ten-session phase and at least quarterly during the maintenance phase. The

intervention targets a reduction in the individual participant's specific pattern of risk. This may include, but is not limited to, more effective condom use, safer sexual practices in the context of alcohol and drug use, and safer sexual practices in the context of different types of partners and relationships.

### **1.2.1 Theoretical Framework**

Multiple theoretical frameworks influenced the development of this intervention including: (1) the information-motivation-behavioral skills model (Fisher & Fisher, 1992), (2) problem-posing education (Freire, 1973; Sanchez-Merki & Wallerstein, 1989), (3) self-management and social learning theory (Bandura, 1986), (4) cognitive-behavioral therapy (Beck, 1976; Persons, 1989), and (5) motivational enhancement (Miller, 1985; Carey, 1996). The intervention strategies based upon these frameworks include identifying the needs and risks of individuals being counseled, training in skills for negotiating and implementing risk reduction in the context of various partner relationships. The intervention strategies also include counseling in self-management specific to the relationship between substance use and sex, managing emotions leading to high risk sex, and maintaining risk reduction goals over time. These principles and strategies, common to previously demonstrated successful behavior intervention studies (e.g., Peterson, et al., 1996), provide the content for the proposed behavioral intervention.

### **1.2.2 Intervention Length**

This study is designed as a "proof of concept" trial. The number of sessions, like the selection of dose in a drug trial, is set at a level that has been shown to yield effects in smaller, Phase I and early Phase II studies. If this trial demonstrates that the behavioral intervention significantly reduces HIV seroincidence, it will be important to conduct research on various alternative strategies for delivering the intervention in clinical and public health settings.

The Office of Technology Assessment report on behavioral interventions for MSM in 1995 provided important guidance regarding the number of sessions that characterize effective interventions (Coates, et al., 1995). Greater risk reduction has been observed with behavioral interventions that have more sessions and are conducted over time to allow participants to practice behavior change skills between sessions, and discuss problems and reinforce progress during sessions. A recent critical review of the literature also provides valuable data on what constitutes the number of sessions necessary for change (Oakley, et al., 1995). Five studies were identified in this review to be of "sound design" and to report effective interventions. Of these, two studies focused on young adult and adult populations (Kelly, et al., 1989; Rotheram-Borus et al., 1991); each had 10 to 12 sessions. Another study of direct relevance to the issue of intervention length not ONLY included MSM but focused on an African American sample (Peterson, et al., 1995). This

study compared one three-hour intervention with an intervention conveying the same content over three three-hour sessions. The additional time was devoted to discussion of examples, role play practice and other strategies to integrate the content into participant lifestyles. At the 18-month follow-up, the decline in risk behavior in the group that received the three sessions was almost twice that observed in the group receiving the shorter intervention. Finally, the NIMH Multisite Trial (NIMH, 1998) provides additional evidence supporting a multiple session counseling strategy. Though delivered in a group rather than individual setting, results showed that sexual behaviors associated with risk of HIV and STD infection decreased significantly in the seven-session intervention group as compared to the one-session control group. Considered together, these studies suggest that ten, one-hour sessions is the number of sessions likely to show benefit.

Several additional considerations support the decision of providing multiple intervention sessions. First, data from the HIVNET Vaccine Preparedness Study (VPS) indicate that achieving behavior change among high-risk men will be a challenge. Nearly half of the VPS cohort were enrolled from prior cohort studies in which participants received biannual risk reduction counseling for at least 12-24 months, yet the HIV seroincidence in the rollover sample is somewhat higher, albeit not statistically significantly different, than in the non-rollover sample (1.71 vs. 1.39/100 person-years).

Second, data from sexually transmitted disease (STD) clinics confirm that brief (less than one hour), didactic, one-session HIV risk reduction counseling in which HIV test results are discussed is not sufficient to change behavior. Specifically, two studies have documented the high incidence of gonorrhea and other bacterial STDs among both HIV-positive and HIV-negative STD participants after a single post-test counseling session in which HIV test results were discussed (Zenilman, et al., 1992; Otten, et al., 1993). On the other hand, the recent reports of Project RESPECT I suggest that two or four individual, participant-centered counseling sessions, such as those to be studied in this trial, can lower HIV and STD infection rates among predominantly heterosexual patients being tested and treated for STDs (Kamb, 1998).

This trial extends these positive findings to a higher risk sample of MSM and adds a number of targets for risk reduction, including condom use, sexual behaviors in the context of alcohol and drug use, and sexual behaviors in the context of different types of partners and relationships. Analyses of data collected from VPS MSM indicate that current alcohol and use of specific drugs are significantly associated with risky sexual behavior (Woody, in press) and condom failure (Stone, 1996) in this cohort. Thus, to be effective, this behavioral intervention will need to focus on alcohol and drug use in association with behavioral risk-taking, and this adds to the complexity of the intervention beyond that included in Project RESPECT.

### **1.2.3 Intervention Tailoring and Delivery in Individual Sessions**

The recent reviews of behavioral interventions call for tailoring interventions to address the specific factors that contribute to sexual risk-taking by MSM. Researchers have identified a wide range of such factors which define the varying, individual contexts in which risk behavior occurs (Stall, Coates & Hoff, 1988; Donovan et al., 1994; Hospers & Kok, 1995, Kelly, et al., 1991). Examples include being with a new, desired partner and assuming he is HIV antibody negative, desire to enhance intimacy in a relationship that has the potential to be long-term, being under the influence of drugs or alcohol, seeking the enjoyment of unprotected intercourse, losing control during the "heat of the moment," avoiding discussing HIV for fear of losing a new partner, and pressure or coercion from a partner. Thus, for example, an intervention for MSM who engage in unsafe sex in the context of substance abuse needs to be different from that for persons whose unsafe behavior is associated with fear of losing a new partner if they were to discuss HIV.

Individual rather than group counseling was chosen for this particular intervention for several reasons. First, individual delivery of the intervention will permit optimal tailoring of the intervention to each participant. Second, most clinical settings that refer participants to behavioral interventions, such as STD clinics, counseling and testing sites, and primary care settings, see participants individually. Thus, individual delivery of the intervention may be more transferable to these settings than a group intervention. Third, group interventions may be less acceptable and logistically feasible, in general, than individual interventions. In community-based intervention studies conducted by the Center for AIDS Prevention Studies (CAPS), ONLY 20 percent of MSM who were engaging in high-risk behavior chose to attend group risk reduction sessions (Kegeles et al, 1996). Similarly, in community-level interventions among MSM conducted by CAPS in Portland, ONLY a small minority attended single and multiple group sessions (12 and 4 percent, respectively). Men engaging in high-risk behaviors were much less likely to attend group sessions than men not engaging in these behaviors (Kegeles et al, 1996).

### **1.2.4 Alcohol and Drug Use Track**

The behavioral intervention includes a specialized track for participants whose alcohol and drug use, or frequenting of alcohol or drug-oriented sexual environments, warrants focussed attention on alcohol and drug issues with respect to sexual behaviors. This track takes a 'harm reduction' approach, wherein the emphasis is on modifying or eliminating the harms or sexual risks associated with alcohol or drug use, rather than eliminating use itself. Substance use will be the primary focus in each intervention module for participants in this track; however, as with the general intervention, each module is individually tailored to address contexts in which risk behavior

occurs such that some content areas may be more important than others, e.g., substance use in the context of different types of partners and relationships (e.g. steady vs casual).

### **1.3 Study Endpoints**

The primary endpoint for this trial is HIV seroincidence. Secondary endpoints are seroincidence of Herpes Simplex Virus type 2 (HSV-2), incidence of rectal and urethral gonorrhea, and self-reported frequency of unprotected receptive anal intercourse.

The primary self-reported risk behavior to be used as a secondary endpoint in these analyses is the frequency of unprotected receptive anal sex, behavior that has been identified as conferring increased risk for HIV seroconversion in analysis of the MSM subcohort of the VPS (Buchbinder, 1998). Additional behaviors to be analyzed include numbers of sexual partners, frequency of unprotected insertive anal sex, frequency of condom use, frequency of condom breakage or slippage, and use of alcohol or other drugs in the context of sex. Specifically, we plan to evaluate the relationship between alcohol, substance use and the occurrence of unsafe sex using measures that assess general and event specific behavior, taking into account the situation or context in which the behavior occurs. Other behaviors to be included as secondary endpoints may be identified upon completion of the analysis of VPS seroincidence data.

### **1.4 Rationale for Biological Endpoints**

The National Institute of Health (NIH) AIDS Research Program Evaluation Working Group of the Office of AIDS Research (OAR) Advisory Council, after reviewing existing Phase I and II behavioral research studies on HIV prevention, placed a high priority on efficacy trials of behavioral interventions with HIV infection and other STDs as outcomes. The Behavioral, Social Science, and Prevention Research Review Panel reporting to this working group, similarly pointed out the need to move from small-scale intervention studies to large, randomized clinical trials using biological endpoints in addition to behavior change indices. The report prepared for the Office of Technology Assessment on behavioral interventions for MSM in 1995 (Coates, et al., 1995) also called for HIV prevention intervention trials in high-risk MSM, with biological outcomes and surrogate markers for HIV acquisition. The NIH Consensus Conference reconfirmed the need for prevention studies with HIV seroincidence as an outcome and recommended continued focus on interventions for MSM, including those who are younger and from minority populations. This randomized controlled trial of a behavioral intervention to prevent the acquisition of HIV addresses this important prevention science need and priority.

Both inflammatory and ulcerative STDs have been shown to be risk factors for HIV acquisition (Wasserheit 1992). STDs provide a potential portal of entry for HIV with activated lymphocytes and macrophages (the target cells for HIV) at the site of

mucosal or epithelial ulceration or inflammation. Among MSM, syphilis, rectal gonorrhea, gonococcal and nongonococcal urethritis, and genital herpes have been implicated as independent risk factors for HIV seroconversion (Williams 1996; Buchbinder 1996; Craib 1995; Holmberg 1988).

HSV-2 seroincidence and incident cases of rectal and urethral gonorrhea are important endpoints for this behavioral intervention for several reasons. Both herpes and gonorrhea may be cofactors for HIV acquisition. Subclinical HSV-2 lesions and asymptomatic cases of rectal gonorrhea may increase the risk of transmission of these STDs as well as HIV, for both behavioral reasons (asymptomatic persons may not alter sexual practices) and for biological reasons (subclinical alterations in the mucosal surface may enhance risk of transmission). In addition, HSV-2 and gonococcal infections cause significant morbidity in their own right. For these reasons, it is important to know how the behavioral intervention will effect the likelihood of HSV-2 and gonococcal acquisition in MSM. Nongonococcal urethritis is not included as an outcome in this study since it is a clinical syndrome with multiple causes and the diagnosis is sometimes made on the basis of subjective criteria that are not well-standardized. Syphilis is not included as an endpoint in this trial due to its current low prevalence among MSM (Tabet 1996).

HIVNET provides an excellent vehicle for this research, as a clinical trials network designed to examine the effect of interventions on biological outcomes. As established community-based research programs, HIVNET sites, with substantial experience in recruiting similar samples, can quickly recruit new, eligible MSM from the communities in which the study sites exist. The ability of the HIVNET study sites to carry out this rapid recruitment was demonstrated in the VPS when these study sites recruited, collectively, 3255 MSM in six months, a figure six percent higher than the target of 3060. Thus, HIVNET provides a timely, unique opportunity for this randomized clinical trial.

## **1.5 Results from the Pilot Study**

Prior to the start of the trial, pilot testing was completed at each of the study sites consisting of informal testing and refinement of data collection forms and the intervention and control conditions. The specific information reviewed during the pilot phase included:

- Completion rates for intervention sessions.
- Success of recruiting high-risk men as measured by a review of the number and characteristics of men approached, screened and enrolled by study site and recruitment strategy, including comparison of baseline risk reported by the pilot group and the VPS MSM cohort.

- Adherence to the protocol as measured by a review of study site randomization procedures, audiotapes of intervention and control condition, and data forms.
- Descriptive data on reported reasons for refusing or participating in the trial.

The pilot study accrued 241 participants at the six sites (range 38 - 51 per site). Only 40% of pilot participants were drawn from the VPS cohort; 60% were new to HIVNET studies. Using a 4:1 randomization allocation for purposes of the pilot, 182 participants were randomized to the intervention. The relatively larger intervention group was established to assess more precisely the feasibility of implementing the ten-session intervention, including completion and retention rates and quality assurance of the intervention delivery.

As targeted by recruitment strategies, MSM who enrolled in the pilot study were riskier than the VPS MSM cohort as assessed by self-reported sexual behaviors. A higher proportion of the pilot study cohort reported unprotected receptive and insertive anal sex with HIV-positive and unknown status partners, having an HIV-positive partner, and having ten or more sexual partners in the past six months. Analyses of VPS and Jumpstart data has shown that these behaviors are associated with HIV seroconversion (Koblin, 1996; Buchbinder, 1996; Buchbinder, 1998). Also as targeted, a higher proportion of MSM from minority populations were recruited into the pilot study than had enrolled in VPS.

Of 182 men randomized to the intervention, 80% (145) completed the ten-session program within six months, and 87% (126) of those men completed within the target window of four months. Delays in completing the intervention were attributed primarily to time constraints and scheduling problems and were not related to the intervention itself. Only six (3%) participants in the intervention arm refused to continue to participate or were lost to follow-up. The remainder of the men not completing the intervention continued in the study, receiving counseling at regular follow-up visits. There was no association of increased behavioral risk with failure to complete the intervention; however, demographic characteristics associated with non-completers include African-American and Latino race/ethnicity, low annual income (< \$12,000), and low educational achievement (no high school diploma).

Procedures to assess adherence to the counseling protocol were successfully implemented, including random selection of audiotaped counseling sessions for review by the Intervention Coordinating Center (ICC).

Participants in the pilot phase are not eligible for the main trial and their data will not be used in the analyses of trial data.

## **2. STUDY OBJECTIVES**

This Phase IIb randomized controlled trial (RCT) of a behavioral intervention for MSM will provide a preliminary but direct assessment of the efficacy of a behavioral intervention to prevent acquisition of HIV. By “preliminary” we mean that this trial will provide a proof of concept of the efficacy of the behavioral intervention.

## **2.1 Primary Objective**

To evaluate the efficacy of a behavioral intervention to reduce seroincidence of HIV infections in a population of MSM. Specifically, three-year seroincidence of HIV infections observed in a sample of MSM randomized to the behavioral intervention will be compared with that observed in MSM randomized to the control condition (standard HIV pre-test and post-test risk reduction counseling).

## **2.2 Secondary Objectives**

### **2.2.1 STD Outcomes**

To provide a preliminary but direct assessment of the efficacy of a behavioral intervention to prevent acquisition of HSV-2 and rectal and urethral gonorrhea.

### **2.2.2 Behavioral Outcomes**

To assess self-reported behavior change as a correlate of protection against acquisition of HIV, HSV-2, and GC infections. Specifically, we will assess:

- how much of the difference in seroincidence between intervention and control groups can be explained by changes in self-reported risk behaviors.
- how key psychosocial variables, such as depressed mood, communication skills, and self-efficacy mediate the effects of the intervention on self-reported behavior change.

### **2.2.3 Outcomes Related to Alcohol and Other Drug Use**

To assess the effect of the intervention track targeting alcohol and other drug use on sexual risk-taking associated with alcohol and other drug use. Specifically we will assess whether the intervention reduces the occurrence of sexual risk behaviors engaged in while under the influence of alcohol or other drugs.

### **2.2.4 Cost Effectiveness Outcomes**

To evaluate the cost and cost-effectiveness of the intervention in averting HIV infections and in averting HSV-2 and gonorrhea infections, we will

prospectively collect data on the cost of the intervention (exclusive of research activities).

### **3. STUDY DESIGN**

#### **3.1 Trial Design**

The study is a two-armed, multi-site, prospective randomized controlled Phase IIb "screening" trial of 4,350 MSM, who are HIV antibody negative, and who report engaging in anal sex within the 12 months prior to enrollment. There will be a 1:1 random assignment of participants to receive either the behavioral intervention or the control risk reduction counseling. Participants will be recruited from six domestic HIVNET study sites that currently have cohorts of MSM. The same counseling staff will provide the behavioral intervention and the control risk reduction counseling. The important scientific question to be answered is what is the difference in HIV seroincidence between those receiving a standard public health intervention (the control condition) and a those receiving more extensive behavioral intervention (the treatment condition).

The behavioral intervention consists of ten counseling sessions within a four-month period followed by at least quarterly maintenance sessions. The intervention is conducted by counselors on a one-to-one basis, either at the HIVNET study sites, in the field, or by telephone. In particular, the use of the telephone as a venue for HIV-risk reduction counseling was found to be effective in a group-based, 14-session HIV-risk reduction intervention targeting high-risk MSM (Roffman, 1996). See Figure 1 for a summary of study activities and visits. The intervention will target condom use, change in sexual practices associated with HIV risk, and change in sexual practices in the context of alcohol and drug use, and will be based on past research with MSM that has defined the important components for effecting behavior change. A special track of the intervention designed to address issues of alcohol and other drug use will be delivered to participants who are identified as particularly at risk for unsafe sex in contexts where alcohol and other drugs are used. To the extent feasible, all counseling sessions for the behavioral intervention will be conducted by the same counselor.

The control condition consists of standard semiannual risk reduction counseling based on the CDC/Project RESPECT two-session model for HIV pre- and post-test counseling. As is routine in most public counseling and testing venues, participants in the control condition will not see the same counselor consistently. To the extent feasible, a different counselor will deliver the control condition at each follow-up visit.

Delivery of both the intervention and control conditions will be monitored using the same arrangements for supervision and quality assurance, as described in Section 6.7.1. Participants randomized to the intervention and control arms will be assessed following the same 6-month schedule using identical study procedures. Enrollment

and follow-up risk assessments of self-reported behaviors for all study participants will be conducted using computer-assisted self-interview (CASI) technology. The CASI technology has been adapted for use with audio (A-CASI).

The measurement of behaviors, particularly those that are considered socially undesirable, can be performed effectively through the use of A-CASI technology. The research subject listens to a recorded human voice and responds to the question by keyboard input. Audio capabilities expands the opportunity for assessing populations with low literacy levels.

HIVNET 005, Application of Computer Technology to Assessment of Risk Behaviors among Participants on the Vaccine Preparedness Study, has shown this technology to be a feasible way to collect self-reported behavioral data. Comparing A-CASI to interviewer administered questionnaires indicates that participants are more likely to report sensitive behaviors (e.g., unprotected anal sex) using A-CASI (Metzger, in preparation; Turner, 1998).

The use of A-CASI technology also standardizes interview and questionnaire administration, to which a significant amount of training and supervisory resources otherwise would be devoted. Questions, probes, and branching are pre-recorded and pre-programmed so that all participants with similar behavioral profiles hear the same voice, asking the same questions, in the same sequence. Variations in administration caused by the interviewer are eliminated. In addition, assessment of participant risk activity will be confidential and not available to site staff, which may minimize participant under-reporting of risk activity.

All study participants will be able to come to the study site between scheduled assessments for interim testing and standard HIV pre- and post-test counseling. Participants in the control arm who express an interest in additional counseling will be referred to counseling programs in the community. Also, if they indicate an interest in referral to other services or agencies in the community, these referrals will be made. Data on the number of visits and referrals will be gathered so that these additional activities can be taken into account in the analysis. On-site supervision will assure that study counselors do not provide participants in the control condition with multiple 'case-management' sessions that may approach the experimental condition. This on-site supervision will not compromise control participants' access to care through referrals for programs and services in the community.

### **3.2 Study Duration**

The duration of the full trial will be 48 months:

- twelve-month enrollment/ intervention period (1/99-12/99); and
- the three-year follow-up period (1/00-1/03).

Randomization of participants in the main trial will be completed within a 12-month period. Each participant will be followed for a minimum of three years after

randomization. Thus, the total trial duration will be four years from the time that the first participant is randomized.

## 4. STUDY POPULATION

MSM whose sexual activities place them at high risk of HIV infection will be targeted for participation in this study, specifically, men who report any anal intercourse (receptive or insertive, protected or unprotected) with other men in the previous 12 months. Each study site will enroll between 700-750 participants.

The six study sites will bring different participant populations to the study, reflective of local demographics and the local HIV epidemic. To support the design of this trial, each study site is responsible for selecting participant populations in which estimated annual HIV seroincidence rate is at least 1.55/ 100 person-years.

### 4.1 Participant Eligibility

The eligibility criteria for the trial are described below.

#### 4.1.1 Inclusion Criteria

Persons may be included in the trial if they meet the following criteria:

- Male, age 16 years and older.
- Able and willing to provide written informed consent.
- HIV-seronegative by licensed enzyme-linked immunoabsorbent assay (ELISA) or HIV-seronegative by Western blot (WB) if found to be HIV-seropositive by licensed ELISA.

Note: Men whose WB is indeterminate with *p24* and/or *env* bands are eligible if polymerase chain reaction (PCR) assay performed at the HIVNET Central Laboratory (CL) is negative. Men whose WB is indeterminate with other bands are eligible provided the repeat WB is also indeterminate.

- Reports anal intercourse (receptive or insertive, protected or unprotected) with another man in the 12 months prior to enrollment.
- Available for at least 36 months of the study.

Note: Participants who plan to move from one trial site to another after the first six months in the study are eligible.

- Willing and able to participate in all scheduled study visits and tests.

Note: Unwillingness to donate rectal swab specimen is not exclusionary.

- Willing and able to provide adequate information for locator purposes. *The particular information required may vary across study sites. Minimum, standardized locator information will be gathered across study sites.*

#### **4.1.2 Exclusion Criteria**

Persons will be excluded from the trial if they:

- Have been in a mutually monogamous relationship for two years or more with a known HIV antibody negative male. *Monogamous is defined as a relationship in which the members of the couple engage in sexual activities only with each other, excluding all others.*
- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process, or otherwise contraindicate participation in the study.
- Have any other condition which in the opinion of the study site Principal Investigator will interfere with achieving the study objectives. *In such cases the site Principal Investigator will discuss the condition with the Protocol Co-chairs and Domestic Master Contractor (DMC) Protocol Specialist prior to participant notification.*
- Were enrolled in the HIVNET 015 Pilot Study.
- Are enrolled in HIVNET Protocol 014.
- Are enrolled in any Phase III HIV vaccine trial, including the AIDSVAX Phase III trial sponsored by VaxGen, Inc.

*Note: Participants will be discouraged from enrolling in a Phase III HIV vaccine trial after enrolling in HIVNET 015, but will not be disenrolled from 015 if they choose to participate in a vaccine trial.*

#### **4.1.3 Withdrawal from Study**

Following enrollment, participants may discontinue study participation for the following reasons:

- Voluntary withdrawal.
- Withdrawal requested by the study site's Principal Investigator. *In such cases the site Principal Investigator will review the reasons for withdrawal with the*

*Protocol Co-chairs, DMC Protocol Specialist and Protocol Biostatistician prior to participant notification.*

All participants will be included in study analyses, so it is important to have information on the serostatus of as many participants as possible. If a participant wishes to withdraw from the study, every effort should be made to encourage the participant to allow routine telephone or other minimum-level contact and to encourage him to have HIV testing at 6- month intervals.

#### **4.1.4 HIV Infection**

Study participants who become infected with HIV will be counseled, referred to appropriate medical and psychosocial support services, advised about clinical trials of therapeutic agents for primary infection, and invited to enroll in other research studies including the Acute Infection and Early Disease Research Program (AIEDRP) or HIVNET 019, the infected participants protocol to evaluate the natural history of HIV infection in newly infected persons in HIVNET target populations. Regular visits for HIV testing and participation in either the control group or the behavioral intervention will be discontinued. For HIV-infected participants in the behavioral intervention as well as the control arms, the counseling noted above would include topics relevant to persons who are HIV-positive, including disclosure of serostatus, coping with HIV-related stress, maintaining safe behaviors, and accessing care.

## **4.2 Recruitment**

Each study site is responsible for selecting populations in which HIV seroincidence rates are adequate to support the objectives of this study, based on VPS data and discussions with focus groups and local Community Advisory Boards (CABs). Each study site will review the results of strategies used for VPS recruitment and other local data on patterns of risk and HIV incidence among MSM in formulating strategies for enrollment of non-VPS participants in this trial.

Study sites will use information from the Pre-screening Contact (see Section 6.1) and develop further methods to monitor recruitment of potential participants that previous studies have suggested are at increased risk of infection, i.e., young men, men of color, men who report unprotected receptive anal intercourse, men who use substances, and men who report a recent STD (syphilis, rectal gonorrhoea, gonococcal and nongonococcal urethritis, and genital herpes). The intent is to:

- permit ongoing monitoring of the productivity of various recruitment strategies in assembling the study cohort at the required rate;

- enroll members of the target populations who, in addition to meeting risk behavior eligibility criteria, represent the local at risk population with regard to race/ethnicity, age, and other factors relevant to the local HIV epidemic.

### 4.3 Retention Strategies

Retention of participants is critically important to the trial. Study sites will utilize strategies developed in VPS that have resulted in 88.7 percent retention at 18 months (Seage, submitted). A set of these strategies will be standard across all sites. Such efforts will include obtaining a standard set of locator information across study sites at time of enrollment, updating locator information at each visit, developing and administering comprehensive protocols for follow-up, performing field visits when participants are unable to come to the site for visits, and implementing remote access protocols for participants who move away from study sites. In addition, study sites will use novel strategies designed for their specific populations to enhance retention.

Examples of procedures to enhance participation in the intervention phase and retention during the follow-up phase include:

- complete locator information
- appointment cards
- thank you letters after enrollment
- self-addressed postcard for notification of address changes
- reminder letters and calls before appointments
- follow-up calls
- letters and home visits to participants and contact for missed visits
- searches of local resources to locate participant (e.g. post office check).

## 5. BEHAVIORAL INTERVENTION

The intervention consists of ten core counseling *modules* (see section 5.5) typically to be delivered at ten separate one-on-one counseling *sessions* within four months of randomization. Maintenance or ‘booster’ counseling modules are to be delivered at sessions every three months beginning with the Month Six follow-up visit. Because the intervention is individually tailored to each participant’s needs, it is not necessary that each session will correspond to the delivery of a discrete module; some modules may be emphasized/de-emphasized as appropriate. However, the core content of all ten modules must be delivered.

The intervention guidelines and procedures outlined below are described in detail in an Intervention Manual for the counselors.

### 5.1 Guidelines:

- (1) The behavioral intervention will consist of ten, one-on-one counseling sessions delivered over a four-month period followed by at least quarterly maintenance sessions over two and one-half years of follow-up.
- (2) A trained counselor will deliver the intervention. Every effort will be made to have the same counselor conduct all the sessions for a given participant. In case of staff turnover, illness, or participant requests for a change in counselor, the site clinical coordinator will work to select another counselor and meet with the participant, previous counselor (if feasible) and new counselor to facilitate the transition.
- (3) The intervention will target condom use, change in sexual practices associated with HIV risk, and change in sexual practices in the context of alcohol and drug use, but the emphasis will be tailored to the individual participant's specific pattern of risk.
- (4) To maximize participation, sessions will be offered at the study site, in the field, or by telephone. During the intervention phase, the first three sessions and at least one session per month after the first three will be administered face-to-face. All quarterly maintenance sessions will be delivered face-to-face. The counseling modules are written with supporting materials that will allow the information and other strategies to be delivered over the phone.
- (5) All participants will receive all modules. The relative weight (including number of sessions) given to each module will vary with the participant's need. While there are guidelines for the order of module delivery, these guidelines will be flexible to allow for individual tailoring.
- (6) The emphasis placed on each module will be based on the participant's pattern of risk behavior. If participants are highly unlikely to engage in certain behaviors that relate to a module, such as injection drug use, the module will still be covered, but with less intensity; more attention will be placed on other modules. If key components in a module do not relate to a participant's situation, the counselor will review previous modules, reinforcing the participant's efforts to apply the modules relevant to his life. The goal will be to take advantage of the extra time to reinforce new safer behaviors and emphasize their application in social contexts that might have been associated with risk in the past.
- (7) A special track will be delivered to men who demonstrate higher risk related to consumption of alcohol and other drugs. Materials particular to each module will focus on the participant's use of alcohol and other drugs and accompanying sexual risk taking. Counselors will use a specially devised screening instrument during the third session to determine the need and relevance of the alcohol and other drug focused material.

- (8) If an individual requires or desires referral for substance abuse, the counselor will provide a referral to specialized agencies chosen in advance for their ability to serve this population in a sensitive way. Decisions regarding referrals will be standardized across study sites. Follow-up data would be collected from the participants regarding whether they decided to follow-through on the referral. Referral for substance use will not disqualify individuals from the remainder of this intervention. Thus, alcohol and drug use would continue as a theme in the entire intervention for those individuals for whom alcohol and/or drug use may increase the likelihood of HIV transmission.
- (9) As a “proof of concept” trial, emphasis is placed on insuring that counselors are well-trained to deliver the intervention with fidelity and consistency.
- (10) While participants will receive reimbursement for the 6-month HIV counseling, testing and data collection visits, they will not be paid to participate in the intervention itself in order to assure equal reimbursement for experimental and control participants.
- (11) The target window for delivery of the ten core modules of the intervention is four months after enrollment. However, there is no time restriction on the delivery of the core modules; the date of module delivery will be recorded so that analyses of variable length of intervention delivery can be performed. Quarterly maintenance sessions will be delivered within an eight-week window(+/- four weeks) around the due date. Those not delivered during this window will be skipped.

## **5.2 Procedures and Schedule of Intervention Contacts**

To increase participation in the intervention, the physical site of these sessions will be chosen to be convenient for the participant, including study sites in the field that are conducive to private discussions but not necessarily within formal clinical environments. The initial three sessions and a minimum of one session per month thereafter during the first four months will be conducted in person. All sessions during the maintenance phase will be conducted in person. Other sessions could be conducted over the telephone if the participants prefer this form of contact.

## **5.3 Behavioral Intervention Manual**

The intervention manual has been developed in consultation with behavioral scientists within and outside HIVNET who have experience in the field of behavior change. The manual details the material to be covered at each of the ten core behavioral intervention sessions. While the themes addressed in each of the sessions will be standard across participants, the specific content will be tailored to each individual's risk behavior. Counselors will audio tape all sessions that are conducted either in

person (both on and off-site) or by telephone, and complete session monitoring forms to document the topics covered at each session.

#### **5.4 Individual Needs Assessment for Tailoring**

The first three sessions of the intervention will establish rapport between the participant and counselor and provide information about risk factors to which the intervention should be tailored or focused. During these initial sessions, the overall plan of the intervention will be described to the participants who will then work with the counselor to identify the initial targets for intervention. During the third session, the participant and counselor will determine whether the special intervention track focussing on alcohol and other drug use is appropriate.

#### **5.5 Description of Intervention: Modules 1-10**

##### **Module 1. Participating in EXPLORE.**

This session will introduce participants to the intervention objectives and how they will work with counselors over the period of the intervention. Participants will have the opportunity to meet their counselor and have questions about the study answered. They will have the chance to talk about their last negative test result. They will also have the opportunity to discuss their expectations related to participating in the study.

##### **Module 2. Acceptable Risk**

This module introduces the key concept of acceptable risk. The counselor and participant explore his range of acceptable and unacceptable sexual behavior that contributes to his risk of HIV infection. The participant describes a recent example of a time he engaged in sex that did NOT cross his acceptable risk limits. The counselor helps identify any patterns of behavior that may exist, and these are highlighted for future examination.

##### **Module 3. Stepping Outside Acceptable Risk Limits**

The purpose of Module Three is to continue the participant risk assessment and to set the direction for future sessions. Module Three shifts the focus of discussion to a recent unprotected sex event. The format for this session is largely the same as for Module Two. During the telling of the story of a recent unprotected episode, two goals are served:

- 1) The participant further constructs his self knowledge about what risks he took when (and, perhaps, why), and the patterns that may lie in that risk-taking. With the counselor's help he can compare this episode with the protected episode and identify any characteristics that are unique to the risky episode.
- 2) The counseling risk assessment is completed. The counselor identifies co-factors, personal and environmental, that put the participant at risk for

unprotected sex. Armed with this information, the counselor and participant can plan which modules to focus on in the coming sessions, including whether to implement the special intervention track focussing on sexual risk behaviors associated with alcohol and other drug use.

#### **Module 4. Sexual Communication: Spoken and Unspoken Messages**

The purpose of Module Four is to help the participant examine how he operates verbally and non-verbally in sexual situations. The participant and counselor will examine communication patterns that may be associated with sexual risk-taking, and explore how his current communication skills can be developed to provide protection from HIV as well as achieve satisfying sex in the future.

#### **Module 5. How HIV Status Affects Ideas and Decisions About Acceptable Risk Limits**

Module Five acknowledges that many men (as supported by recent research) make decisions about safer sex based on their knowledge of their partner's HIV status. The counselor and participant examine the patterns where knowledge of a partner's serostatus affects behavior. Disclosing or learning serostatus is not a prevention strategy in itself, as people may think they are negative when they might be positive. Also, for various reasons, it can be difficult for individuals to disclose their HIV status. The purpose of this Module is to help the participant become more comfortable in disclosing serostatus and asking others about it. The Module strives to help the participant identify how he can gather and use information about his serostatus and that of his partners to ensure that no one gets infected with HIV, at the same time emphasizing that disclosure of serostatus, in and of itself, is not an effective prevention.

#### **Module 6. Acceptable Risk, Alcohol, and Drugs**

The purpose of Module Six is to help participants examine how alcohol and drug use play into taking sexual risks. The Module employs two perspectives ;

- 1) the effect of a sex partner's drinking and drug use on the ability to practice safer sex for the person who is not using alcohol and/or drugs, and
- 2) the effect of the participant's alcohol and/or drug use on the ability to practice safer sex.

Both viewpoints are followed by the chance to plan for change around risk associated with alcohol and/or drug use.

The counselor and participant examine whether the use of alcohol and/or drugs promotes risk taking. The participant is then offered help in planning for change, if desired. Levels of change will vary from abstinence from alcohol and/or drug use, to altering the pattern of use (reducing the amount taken or switching to less potent or harmful drugs), to changing sexual patterns when the participant and/or his partner

are under the influence. All change is aimed at reducing risk of HIV and other STD infection, not the promotion of sobriety or drug-free lifestyles.

### **Module 7. External Cues to Risk-taking: Places and Life Events**

Places, people, and times can all be ‘triggers’ for unsafe sex. Examination of the participant’s patterns of behavior can help reveal where triggers play a role, how they can be modified, or how coping strategies can be employed. This Module examines such patterns and provides a framework for adopting new skills for dealing with triggers.

### **Module 8. Internal Cues to Risk-taking: Feelings and Thoughts**

Emotions can act as specific triggers (or causes) for unsafe sex. Yet simple cause and effect relationships are probably unlikely in most cases. More likely is the idea that emotions are part of a larger context within which safer or unsafe sex is likely to occur. Environmental factors and social relationships (influenced by norms, beliefs, personal skills, and other factors) make up these complex contexts.

This Module examines the role of emotions as triggers for unsafe sex. The counselor and participant seek to identify emotions which may act as triggers for unsafe sex, develop motivation to examine these triggers, and modify them through skills-building and adoption of alternative coping strategies. The counselor supports and coaches the participant in changing responses to triggers over time. Special attention will be paid to cross-cultural differences in discussing and dealing with emotions.

### **Module 9. External Cues: Partners and Relationships**

In Module Nine, the counselor and participant explore in depth how the participant’s safer sex boundaries are supported or challenged in different partner contexts. They examine how different ‘rules’ may apply for different types of partners and for varying levels of involvement: from intimacy or emotional involvement to sex/drug exchanges and other commercial sex situations.

### **Module 10. Planning for Maintenance: You Can Stay Uninfected - There is a Future!**

Module Ten marks the close of the intensive, ten-session portion of the participant - counselor relationship. The title suggests that the participant has articulated a sense of future; this may not be the case. Yet the counselor and participant can review what’s been learned and explore the participant’s sense of his ability to stay uninfected. The ‘future’ is cast in terms of the immediate three months before the next scheduled visit. The counselor and participant plan how the participant will employ what he has learned in the coming months.

## **5.6 Maintenance Modules**

These modules will be delivered at least quarterly. Individuals may be seen more frequently as needed. At maintenance sessions, individuals will review their behavior since the previous session to identify factors associated with safety or lack of safety. Reinforcement will be provided for self-awareness and interpersonal skills associated with safety, and individuals will be helped to further identify strategies for maintaining safety in the future. The sessions also will include an assessment of any referrals that were made during the intervention phase and the need for further follow-up or additional referrals. Data on maintenance module attendance will be taken into account in the analysis.

## **6. STUDY PROCEDURES**

The activities and specimen collection procedures performed over the 48-month trial period are presented graphically in Figure 1. Information about data collection forms and procedures are provided in Section 8; details on all study procedures and guidelines for form use are included in the Study Specific Procedures Manual (SSP), HIVNET Manual of Operations (HIVMOP), and the Intervention Counseling Manual.

Participants will be screened prior to enrollment to ensure that eligibility criteria are met. Eligibility determination will occur over a two-week period. Required procedures are described in Sections 6.1 - 6.5 below.

### **6.1 Pre-screening Contact (prior to screening visit)**

Prior to the screening visit, pre-screening procedures may occur in public spaces during community outreach/recruitment activities, via telephone calls initiated by either the study site or potential participants, or at the study site. Potential participants will be informed about the study and asked to provide information specified on a pre-screening questionnaire. Information to be collected includes a preliminary assessment of behavioral eligibility, basic demographic information, and sources of previous awareness, if any, of this study. The data from this questionnaire will be analyzed frequently throughout the accrual period in order to guide decisions regarding efficient recruitment strategies and characteristics of persons who refuse and/or agree to participate in study procedures.

Written informed consent will NOT be obtained prior to administering the questionnaire. The questionnaires will not collect any personal identifying information, but will be identified with a unique code. When a participant presents for a screening visit, the unique code will be reconstructed in order to determine whether there is a corresponding pre-screening questionnaire. Upon receiving informed consent for screening, the pre-screening information will be coded with the study ID that corresponds to the prospective participant's other data forms and study records.

## 6.2 Screening Visit (week -2)

- Assign Participant ID number (*if number not previously assigned by study site in a prior HIVNET study*).
- Obtain informed consent for study eligibility screening procedures.
- Administer demographics questionnaire.
- Complete eligibility screening.

*If potential participant does NOT meet behavioral eligibility criteria, he is ineligible; discontinue screening.*

*If potential participant meets behavioral eligibility criteria, proceed with the following:*

- Obtain locator information.
- Complete Participation Questionnaire (assess reasons for participating in prevention trials).
- Administer Baseline Risk Assessment by A-CASI.
- Administer Baseline STD questionnaire.
- *If participant reports PEP use:* Administer Use of PEP questionnaire.
- Administer Counseling/Therapy History questionnaire.
- Administer HIV pre-test counseling (See Counseling Manual).
- Collect and ship specimens as specified in Figure 2, Panels A1 and A2.
- Schedule Enrollment Visit to occur in two weeks.

*If potential participant meets behavioral eligibility criteria, but is unwilling to continue participation:*

- administer Recruitment Assessment (assess reasons for not participating in prevention trials).
- Complete and submit required data collection forms within one working day.

### 6.2.1 Interview Procedures

The baseline and follow-up risk assessments will be completed using A-CASI technology. Participants will be instructed on the use of the computer, and will complete practice questions. Staff will be available to help with any problems during the A-CASI session, but will not be present in the room. The staff person assisting with A-CASI will be a different person than the staff person who will deliver the counseling. If the A-CASI system is not functioning, an interviewer-administered questionnaire will be conducted by a staff member other than the one delivering the counseling.

### **6.2.2 Informed Consent for HIV Testing and HIV Pre-Test Counseling**

Informed consent must be obtained for voluntary HIV testing. Informed consent is obtained prospectively at the Enrollment Visit for all future HIV testing at scheduled and interim study visits, except where local regulations specify that separate informed consent is required for each HIV test.

HIV pre-test counseling must be provided prior to all HIV testing in the trial. Pre-test counseling will cover:

- Information about the meaning of HIV test results.
- The potential benefits and risks of being tested to help the participant decide whether to proceed with testing.
- An assessment of the participant's coping strategies, support systems, likely reactions to positive and negative results, and plan for managing stress while waiting for results.
- Information about HIV/Acquired immunodeficiency syndrome (AIDS) transmission and prevention.
- The participant's individual profile with regard to HIV risk behaviors.
- The development of a personalized, specific plan for the participant to reduce the risk of HIV infection/transmission.

The counseling must be participant-centered, culturally competent, sensitive to issues of sexual identity, developmentally appropriate and linguistically specific, and sensitive to individual differences in behavioral risks for HIV infection or transmission.

During the Screening Visit the counselor will assess the (potential) participant's ability to respond appropriately to an HIV-positive test result. If the counselor deems that the participant does not have the social or psychological resources to respond appropriately, the counselor, in

consultation with the Principal Investigator, will disallow study participation and will make appropriate referrals (see Sections 4.1.2 and 4.1.3).

### **6.2.3 Laboratory Procedures**

Unless otherwise specified, the following laboratory procedures will be completed according to the instructions contained in the HIVMOP.

- HIV ELISA/WB (HIVMOP).
- Gonococcal (GC) cultures performed from rectal specimens inoculated on appropriate media (e.g., Thayer-Martin culture).
- GC LE for urine, and if positive (> trace) , do GC LCR for urine (HIVMOP).
- HSV-2 testing will be done at CL at the end of the study (see Section 7.2.1) with sera run for HSV type-specific ELISA using the Gull ELISA . Samples that do not yield a clear negative or positive result will then have an HSV Western blot performed.

### **6.3 Enrollment and Randomization Visit (week 0)**

- Confirm participant identity and verify Participant ID number.
- Confirm/update participant locator information.
- Administer Enrollment HIV Post-test Counseling Part 1 and disclose HIV and GC results (see Section 6.3.1 and Counseling Manual).

*If HIV infection is confirmed:*

- Refer the participant to appropriate medical and psychosocial support services.
- Determine eligibility for AIEDRP/HIVNET 019 primary infection studies and, if applicable, offer enrollment.

*If HIV status is indeterminate:*

- Collect and ship specimens as specified in Figure 2, Panel B.

*Note: If indeterminate with WB bands at p24 and/or env, collect specimens for PCR testing.*

*Note: Men whose WB is indeterminate with p24 and/or env bands are eligible if PCR is negative. Men whose WB is indeterminate with other bands are eligible provided the repeat WB is also indeterminate.*

- Schedule visit to administer HIV post-test counseling and disclose HIV test result (see Section 6.3.1 and Counseling Manual) to occur in two weeks.

*If HIV infection is ruled out, proceed with the following:*

- Obtain informed consent for trial enrollment and full study participation.

*If participant declines to participate further:*

- Administer Recruitment Assessment (assess reasons for not participating in prevention trials).
- Obtain random assignment from the Statistical and Clinical Coordinating Center (SC) (see Section 6.3.2).
- Administer Enrollment Post-test Counseling Part 2 for controls (see Counseling Manual and Section 6.3.3) or experimental intervention Module # 1 (see Section 5.5) according to randomization assignment (see Section 6.3.2).
- Schedule next visit.
- Complete and submit required data collection forms within one working day.

### **6.3.1 Enrollment Post-test Counseling Part 1 - All Participants**

Study sites will take active steps to minimize failure to return for post-test counseling. Participants who elect not to receive their test results may not enroll in the study until they receive their test results.

HIV post-test counseling should first establish that participants are prepared to learn their test results and understand their meaning. HIV post-test counseling shall:

- Provide the test result.
- Allow the participant to express feelings and reactions.

- Assess the participant's understanding of the test result.
- Provide for additional post-test visits as required.
- Assist an HIV positive participant develop a plan to inform others who may have been exposed to HIV.
- Provide appropriate referrals (e.g., for drug treatment or for any other medical, psychological/psychiatric, support, or social services).

### **6.3.2 Randomization**

The SC will randomly allocate participants in equal number to control or treatment status. The randomization will be stratified on study site and blocked (with random sequences of block sizes) within study site to ensure that the assignment sequence is not predictable and to ensure that balance between intervention and control assignments is maintained within each study site over the entire period of participant recruitment. Study sites will telephone the SC computerized randomization system to obtain the assignment. The caller will be asked to verify that each eligibility criterion has been met. A written verification of the randomization assignment will be sent from the SC to the study sites for each enrollee via FAX.

The SC will use two computers to reduce the likelihood that computer failure will lead to a failure to randomize; however, should both computers fail, a system using ordered, sealed envelopes is in place at each study site to ensure that a random assignment can be determined at any time.

### **6.3.3 Enrollment post-test counseling Part 2 for Controls**

- Review routes of transmission and risk reduction.
- Assess risk behavior and commitment to behavioral change that will reduce risk of HIV transmission.
- Review and renegotiate the risk reduction plan.

## **6.4 Routine Semiannual Follow-up Visits (month 6, 12, 18, 24, 30 and 36)**

All participants will complete six semiannual follow-up visits over the course of the 36 months of study. Follow-up Pre-test Visits are scheduled at 6, 12, 18, 24, 30, and 36 months (+/- 2 week target window) from the date of enrollment. HIV Post-test Visits will be completed within two weeks after each Follow-up Visit. A Risk Assessment will be administered at each Follow-Up Visit, as will phlebotomy for specimen collection for HIV and HSV-2 antibody tests and storage. Rectal and urethral specimens will be collected for gonorrhea testing at the Month Six visit with

a decision to continue for subsequent semiannual visits based on an interim analysis. Standard risk reduction counseling will be provided for participants in the control group; participants in the intervention group will receive the maintenance sessions described in Section 5.6.

#### 6.4.1 Pre-Test Visits

Procedures required at the Routine Semiannual Follow-up Pre-Test Visits are as follows:

- Confirm participant identity and verify Participant ID number.
- Confirm/update participant locator information.
- Administer Follow-up Risk Assessment by A-CASI.
- Administer Follow-up STD questionnaire.
  - *If participant reports STD during the interval since the previous interview, request permission to seek medical records and obtain appropriate consent/ signatures as applicable.*
  - *If participant reports PEP use: Administer Use of PEP questionnaire.*
- Administer Social Impact questionnaire.
- Administer pre-test counseling according to randomization assignment:
  - Control group: Administer follow-up HIV pre-test counseling (see Counseling Manual and Section 6.4.1.2).
  - Intervention group: Administer follow-up HIV pre-test counseling (see Counseling Manual) and maintenance session (see Section 6.4.1.4).
- Collect and ship specimens as specified in Figure 2, Panel A.

*Note: Collect specimens for rectal and urethral gonorrhea testing at Month 6 visit; decision to continue specimen collection and testing at subsequent visits to be based on an interim analysis of results from the six-month visit.*
- Schedule HIV Post-test Visit to occur within two weeks.

- Complete and submit required data collection forms within one working day.

**6.4.1.1 Interview Procedures [same as Section 6.2.1]**

**6.4.1.2 Control Pre-test and risk reduction counseling [same as Section 6.2.2]**

The pre-test and risk reduction counseling for the control participants will be the same as that delivered at the screening visit (see Counseling Manual). If possible, a different counselor will deliver the control condition at each follow-up visit so that participants will not see the same counselor consistently.

**6.4.1.3 Laboratory Procedures [same as Section 6.2.3]**

*[Two exceptions: 1) Depending on results from interim analysis, GC testing may only take place at Month 6; 2) HSV-2 testing takes place after Month 36 on a sub-sample of 600 participants; remainder of participants will be tested for HSV-2 only if indicated based on an interim analysis (see Section 7.2.1)].*

**6.4.1.4 Behavioral intervention maintenance session [same as Section 5.6]**

Administer follow-up HIV pre-test counseling (see Counseling Manual) and maintenance session (see Section 5.6).

**6.4.2 Follow-up Post-test Visits**

The results of the HIV test described in Section 6.4.1.3 will be disclosed as soon as such results are available (within two weeks after each test). Participants who elect not to receive their test results may not continue in the study until they receive their test results.

- Confirm participant identity and verify Participant ID number.
- Administer HIV post-test counseling according to randomization assignment and disclose test results.

*Note: GC results will be disclosed at Month 6 post-test visit. Testing with results disclosure may or may not be done at subsequent follow-up visits (see section 6.4.1.3).*

Control group: Administer Follow-up HIV post-test counseling - controls (see Counseling Manual).

Intervention group: Administer Follow-up HIV post-test counseling - intervention (see Counseling Manual).

*If HIV infection is confirmed:*

- Refer the participant to appropriate medical and psychosocial support services.
- Collect and ship specimens as specified in Figure 2, Panel C.
- Determine eligibility for AIEDRP/HIVNET 019 primary infection studies and, if applicable, offer enrollment.

*If HIV status is indeterminate:*

- Collect and ship specimens as specified in Figure 2, Panel B.

*Note: If indeterminate with WB bands at p24 and/or env, collect specimens for PCR testing.*

- Schedule visit to administer HIV post-test counseling and disclose HIV test result to occur in two weeks.

*If HIV infection is ruled out:*

- Schedule next Follow-up Visit and, for the behavioral intervention group, the next Maintenance visit.
- Obtain written permission to contact participant for possible participation in future studies (Month 36 post-test visit ONLY).
- Complete and submit required data collection forms within one working day.

## **6.5 Remote Follow-up Procedures / Participant Transfer**

Participants who relocate away from the study site prior to the end of the study will be asked to continue participation remotely. A template informed consent form for remote participation may be found in Appendix 3. Participants will be asked to complete all questionnaires and receive all counseling (according to random assignment) by telephone. Laboratory tests will be limited to HIV antibody testing which will be performed using the Home Access<sup>®</sup> HIV-1 Test System. A dried blood

spot home collection kit will be used by the participant to collect a specimen, which is mailed to the Home Access<sup>®</sup> laboratory for testing. To address the possibility that remote participants may test HIV-positive, concurrent with arranging for specimen collection and provision by phone of pre-test counseling, site staff will work with the remote participant to identify potential local HIV care providers. HIV-infected participants will undergo phlebotomy for collection and shipment of specimens as specified in Figure 2, Panel C. Detailed remote participation procedures may be found in the SSP manual.

Participants who relocate away from the study site to another city where HIVNET 015 is being implemented may choose to transfer to the new study site or participate remotely as outlined above.

## **6.6 Interim Visits**

Participants may initiate Interim Study Visits at any time and for any reason. To identify early infection, participants will be encouraged to arrange for off-schedule HIV testing in response to either a high-risk exposure or symptoms suggestive of Acute Retroviral Infection (ARI). At such visits, participants will be asked a brief series of questions detailing their reasons for desiring testing, the nature of symptoms they are concerned about, and the nature of any potential exposure to HIV.

When HIV testing is requested, collect and ship specimens as specified in Figure 2, Panel B. If ARI is suspected, additional specimens are collected for rapid turnaround PCR testing and archival storage by the CL. This testing will be followed-up with an HIV post-test counseling visit as described in the Counseling Manual.

Each study site is responsible for ensuring that appropriate medical personnel are available to perform ARI evaluations when indicated because of symptoms possibly indicative of ARI.

## **6.7 Training**

Study sites will recruit counselors who have experience working with MSM, counseling in HIV/AIDS risk reduction, and interest in the proposed research. The minimum education requirement for the counselors will be a Bachelor's degree. Training in social work, counseling, or psychology would be helpful but not required. An emphasis will be placed on direct experience with research and with MSM populations. Training will follow standard procedures as developed in the pilot phase of this study, the NIMH Multi-site Intervention Study and in the United Nations AIDS Project (UNAIDS), the USAID AIDS Control Project (AIDSCAP) and the CAPS Counseling and Testing Efficacy Study, including the employment of the revised intervention manual and detailed training and quality assurance protocols.

Counselors will be trained to deliver both the control intervention and the ten session experimental intervention, with minimum quarterly maintenance visits. This design

strategy controls for counselor effects, while the supervision and quality control procedures assure that the counseling for each arm of the study is conducted according to protocol.

The ICC at CAPS/UCSF will train the clinical supervisors and one counselor per site both to implement the counseling protocols and to train additional counselors as they are hired at local study sites in a ‘train the trainer’ approach. In addition, the ICC will coordinate the supervision of counselors and conduct quality control and assurance procedures for both the control and intervention conditions.

Prior to beginning the study, site clinical supervisors and one counselor per site will attend a workshop on the background and rationale for the study, and receive extensive training in the intervention and control procedures. For the ten-session behavioral intervention, this training will include a foundation in the process and maintenance of behavior change that will draw on key intervention elements that have been previously studied as self-management approaches, cognitive-behavioral/social learning approaches, stages of change, and motivational interviewing (Miller, et al., 1993). Supervisors and counselors will also be trained in the semiannual risk reduction counseling that constitutes the control condition.

### **6.7.1 Supervision and Quality Assurance**

Once the study begins, counselors will meet weekly with site clinical supervisors for individual (one hour) and for group sessions with all other counselors (one hour).

All control and intervention counseling sessions will be audio taped, and a ten percent random sample of the tapes will be coded for adherence by the ICC. Feedback will be provided to each counselor about protocol adherence. The supervision sessions also may be used to solve other issues regarding intervention delivery. Finally, the ICC clinical coordinator will hold a conference call each week with the study site clinical supervisors to resolve issues in the training and quality assurance of counselors. Counselors hired after the initiation of the study will be trained on site by their site clinical supervisor.

### **6.7.2 Nature of the Counseling Relationship**

As risk reduction counselors, counselors in this study must understand the limits of their relationships with participants and adhere to standards for appropriate professional counseling. Intimate personal relationships between counselors and participants are prohibited, as are contacts outside of the counseling situation. Counselors are not friends to participants, nor are they psychotherapists. Each problematic case should be discussed weekly with the supervisor and difficulties should be clarified with appropriate strategies developed.

Counseling sessions may take place at the study center, over the telephone, or in a place designated by the counselor or participant that is suitable for intervention sessions (see Section 5.2). They should not take place in public sex environments or in bars. Home sessions will be allowed only under extenuating circumstances approved by the site clinical supervisor.

If at all possible, the same counselor will provide all intervention and follow-up sessions for a given participant. Circumstances may dictate that a substitute counselor be used: if the participant requests it, if the counselor becomes ill or takes an extended vacation, or if the counselor leaves the project.

The control group will not see the same counselor for all sessions. The objective of the trial is to provide a test of the intervention counseling compared to the counseling that is generally available throughout the United States at public health STD clinics and anonymous testing sites. The counseling provided in these settings is supposed to meet the guidelines put forth by CDC, which specify that counseling should precede and follow HIV antibody testing, but do not indicate that the same person provide this counseling, even on the two occasions accompanying a test. While there are certain testing sites that offer follow-up counseling, continuity of counseling is not usually offered, including programs in HIV epicenters such as the San Francisco Bay Area. If further counseling is requested, clients are referred to community-based organizations.

Session monitoring forms will be used to document the dates, location, length, and content of the counseling session both to maintain a professional record of encounters and in case another counselor needs to take over the case.

## **7. EVALUATION OF OUTCOMES**

### **7.1 Primary Outcomes**

All potentially eligible participants will be tested at baseline for HIV antibody by ELISA and positive tests confirmed by WB. Participants who are HIV antibody negative will be enrolled and will receive HIV antibody testing every 6 months throughout the course of the study. Participants who become HIV seropositive during the study will similarly be counseled about their positive results and referred for care and to studies for which they are eligible. Participants who are HIV-positive at baseline will not be enrolled but will be counseled about their positive results, receive medical and psychosocial referrals, and referred to ongoing research studies for which they are eligible (including AIEDRP and HIVNET 019).

### **7.2 Secondary Outcomes: STDs**

### **7.2.1 HSV-2**

HSV-2 serostatus will be assessed by WB from stored specimens. At the end of the trial, a random sample of 600 final visit specimens will be selected for HSV-2 antibody testing. For those participants found to be positive, baseline specimens will be tested to identify incident cases of HSV-2. If the estimate of seroincidence from the sample of 600 is of sufficient magnitude, the entire cohort will be tested for HSV-2 antibody (see section 9.3.2).

To determine time of acquisition of HSV-2 for incident cases, specimens will be tested as needed from CL archived serum specimens for interim six-month visits. HSV-2 results will be made available to those participants who receive testing.

### **7.2.2 Gonorrhea**

Because rectal gonorrhea infection may be asymptomatic, participants will be screened for rectal gonorrhea on entry into the study and at the Month Six visit. Screening will be performed by blind rectal swab plated on appropriate medium and sent to local laboratories for processing. Such specimen collection can be performed by non-clinical staff at the time of phlebotomy. Because the incidence of asymptomatic rectal gonorrhea in this population is unknown, an interim analysis will be performed of rectal gonorrhea after the 6-month follow-up is complete.

Urine specimens for testing for urethral gonorrhea will be collected at baseline and at six months. As with rectal gonorrhea, an interim analysis will be performed of urethral gonorrhea after the 6-month follow-up is complete.

All study sites will make arrangements to provide access to rapid, free screening and treatment for urethral and rectal symptoms consistent with GC infection. Participants will be instructed that they should utilize these services should they develop such symptoms during the course of the trial. Participants also will be asked about episodes of intercurrent gonorrhea at each interview, and will be asked to sign medical release forms to enable study sites to confirm of test results for all STD evaluations.

## **7.3 Secondary Outcomes: Behavioral Outcomes**

### **7.3.1 Self-reported HIV Risk Behaviors**

All enrolled participants will report recent HIV risk behaviors using A-CASI technology on entry to the study and at 6-month intervals. These interview assessments are based on the instruments used in the VPS, with refinements appropriate for this specific trial.

The primary self-reported HIV risk behavior end-point is the frequency of unprotected receptive anal sex. Additional behaviors to be analyzed include unprotected insertive anal sex, number of sexual partners, and frequency of condom breakage or slippage. Questions regarding Post Exposure Prophylaxis (PEP) are included since use of PEP may influence study outcomes. Other behaviors may be included upon completion of the analysis of the VPS seroincidence data.

The behavioral risk assessments include both reports of overall risk behavior during the 6-month interval and more detailed reports of behavior with the most recent partners during the 6-month interval. This more detailed information covers such topics as the social context for sexual encounters and the presence of alcohol or drug use.

### **7.3.2 Psychosocial Mediators**

A number of brief scales or sets of items that are known to be correlated with risk behavior change will be assessed. The scales that assess variables that may mediate the effect of the intervention on reducing HIV transmission and risk behavior include:

- a) the shortened version of the Center for Epidemiologic Studies Depression Scale (7 items) for depressed mood, which is a reliable and valid index of depressed mood and has been related to high risk sexual behavior in previous research; and
- b) scales found to mediate high risk behavior change among men who have sex with men, such as the scale of involvement in the gay community, sexual communication skills, perceived social norms for safer sex, enjoyment of unprotected sex, history of sexual abuse and self-efficacy regarding own safe sex behavior.

### **7.3.3 Alcohol and Other Drug Use**

Detailed reports of behavior during the most recent sexual encounters at both baseline and follow-up include information regarding the use of alcohol or other drugs by the participant and his partner. For these episodes, reported at each follow-up visit, HIV risk behavior is linked with information regarding substance use. In addition, the baseline and follow-up risk assessments include questions assessing both the occurrence of concurrent substance use and sex and the participant's self-assessment of the ease/difficulty in having safe sex when substance use is involved.

## **7.4 Secondary Outcomes: Cost Effectiveness**

The following input data for the cost-effectiveness analyses will be collected:

- Direct costs, i.e., hiring, training, and employing qualified counselors and supervisors; space for intervention delivery; and personnel and other costs to contact, retain, and schedule appointments for study participants. We will collect this data from records of participation in counseling and in project budgets.
- Time costs (also referred to as indirect costs), i.e., the time and value of time for participants to attend the counseling sessions. We will collect this data from interviews with study participants and reference tables on the economic value of time.
- Quality-adjusted life years (QALYs) lost due to each type of infection, from published studies.

The primary outcome measures will be:

- Cost per HIV infection averted in intervention recipients: cost of the intervention adjusted for HIV medical care costs averted / number of HIV infections averted.
- Cost per HSV and gonorrhea infection averted in intervention recipients: cost of the intervention adjusted for STD medical care costs averted / number of STD infections averted.
- Cost per QALY gained: cost of the intervention adjusted for medical care costs averted / number of QALYs gained.

## **8. DATA COLLECTION**

### **8.1 Introduction**

Study data will be collected manually by study site staff using standard data collection forms as well as by A-CASI technology.

### **8.2 Data Collection Forms**

#### **8.2.1 Forms used**

Four types of forms are used in this trial:

1. Locally-developed or adapted informed consent, locator, and, if applicable, pre-screening forms.
2. Study-specific data collection forms that document eligibility, reasons for refusal/participation, STD occurrence, use of PEP, social impact

of participation, time costs of participation, counseling history and test results reported to study sites by local laboratories. The appropriate form must be used to document each study visit, whether scheduled or unscheduled.

3. Data collection via A-CASI of risk behavior and psychosocial mediators of behavior change.
4. Administrative and process data forms that document participant demographics, recruitment, enrollment, change of study status, missed visits, CL specimen shipment, participant transfer, inactivation, and inactive follow-up, and that provide a mechanism for study sites to transmit study-related inquiries to the SC.

Detailed description and documentation of standard HIVNET forms used in this trial are found in the HIVMOP. Descriptions of study-specific forms are described in the SSP manual.

Items 2 and 4 are in DataFax format, and are distributed to the study sites as Master Forms by the SC. As modifications are made, replacement Master Forms will be distributed. Each study site will be responsible for duplicating forms as required for local use. The A-CASI program will also be distributed to study sites by the SC.

### **8.2.2 Form Completion and Submission**

All DataFax forms will be completed and transmitted according to instructions in the HIVMOP. Participant names, addresses, or other personal identifiers, such as Social Security Numbers, must not appear on DataFax forms; participants must be identified ONLY by their unique Participant ID number. Study sites will have the option of indicating the ID of the local staff member who completes the DataFax form in a space provided at the bottom of each form. All forms must be reviewed prior to submission for accuracy, consistency and completeness by designated study site staff.

### **8.3 A-CASI Data Collection**

Software for the A-CASI system was developed by the SC modeled in part on software developed by the Research Triangle Institute to create an A-CASI version of the VPS Month 12 and VPS Month 18 questionnaires. This will permit the study instrument to be run on any IBM-compatible Sound Blaster compatible microcomputer and will include: appropriate probes and branching; a recording of an interviewer's voice; and, where appropriate, cross-checks to identify inconsistencies in an individual's responses.

### **8.4 Locator Forms**

The address and telephone number of each participant will be obtained at the Screening Visit and verified at each subsequent visit. Alternative contact information for friends, family members, etc. will be collected and updated at each subsequent visit. This information may be used by study site staff to notify a participant of upcoming visits as well as to locate a participant who has missed a scheduled visit.

## **8.5 Baseline and Follow-Up Questionnaires**

Information about sexual behavior, alcohol and drug use, and psychosocial mediators of behavior change will be collected at the Screening Visit and routine semiannual Follow-up Visits, via A-CASI Baseline and Follow-Up Risk Assessments. Additional questionnaires assessing STD occurrence, use of PEP, social impact of participation, and counseling history use an interviewer-administered format.

## **8.6 Medical records**

Intercurrent STDs self-reported at follow-up visits will be verified by review of medical records if possible. Participants will be asked to sign medical records releases for the records at the time of an STD report. Where local IRBs approve, the informed consent will include an appropriate advance release of medical records for these situations.

## **8.7 Record Storage and Archive**

Study site Principal Investigators will maintain all source records used to complete study forms. Source records may include laboratory requisitions and reports, documentation of referrals, progress notes, and tapes recording interviews and counseling sessions.

All data collection forms and source records must be kept in locked files in a secure area. Provided they contain no participant identifying information, source records should be kept together with the data collection forms in locked participant files. All locator information must be kept in locked files in a secure area apart from all other study documents. All records must be available at all times for inspection by NIAID, DMC, and SC staff.

# **9. STATISTICAL CONSIDERATIONS**

## **9.1 Overview of Study Design**

A total of 4,350 MSM who are not infected with HIV will be enrolled and randomly assigned in equal numbers to receive an individualized behavioral intervention or the semiannual risk reduction counseling. The participants will be followed for 3 years from randomization under a schedule of semiannual visits and assessed for HIV infection status at each study visit.

The study is designed to provide a "screening-type" assessment of the efficacy of the intervention to prevent acquisition of HIV. As such, it will provide clear indications for whether the intervention:

- is not plausibly efficacious and should be discarded in its current formulation;
- is plausibly efficacious and should be evaluated definitively in a subsequent Phase III trial; or
- is demonstrably efficacious and should be promulgated in public health practice.

A sub-sample of participants will be assessed for HSV-2 at Month 36; all participants will be assessed for rectal and urethral gonorrhea at Month 6. Relative rates of acquisition of HIV (and other STDs) will be calculated.

## **9.2 Sample Size, Accrual and Loss to Follow-up**

A total of 4,350 MSM will be recruited, enrolled and randomized to either the control or intervention condition in a 1:1 allocation. Enrollment will take place over a 12-month period. Based upon the VPS experience this accrual goal is feasible. The six HIVNET sites participating in EXPLORE enrolled 3,257 MSM in VPS over a six month period, with recruitment ranging from 300 to over 775 MSM per site. Sites have since refined their recruitment strategies, incorporating lessons learned from VPS and the EXPLORE pilot. During the EXPLORE pilot, several sites tried successfully new sources for recruitment, including advertising and the internet. The follow-up period will be 3.0 years, which will result in a total project duration of 4 years from the start of enrollment.

The study design assumes that the HIV seroincidence during the planned follow-up period will be approximately equal to that observed in VPS. The most recent estimate of annual seroincidence among the MSM subcohort of VPS is 1.55 per 100 person-years. In some cohort studies of high risk individuals, HIV seroincidence has been observed to decline over time (Koblin, 1996), while in others, seroincidence rates have been stable (Buchbinder, 1996). Although reliable prediction of time-trends in seroincidence for the proposed study cohort is not possible, we note that seroincidence among new recruits to the VPS cohort (1.39/100 p-yrs) was somewhat lower than among participants "rolled-over" from previous preparedness studies (1.71/100 p-yrs). This indirectly suggests that HIV seroincidence has not declined dramatically as a function of duration of follow-up in VPS-like cohort studies. This is further supported by measurement of seroincidence in the current VPS, which has not significantly declined over the 18 months of follow-up (1.65 percent for 0-6 months, 1.80 percent at 6-12 months, and 1.21 at 12-18 months; test for trend  $p = 0.37$ ).

The study design anticipates obtaining a blood specimen for the purpose of HIV testing at the end of the trial (after 3.0 years of follow-up) for no less than 80 percent of all trial participants. Experience from the VPS indicates that this goal is achievable. Overall, 88.7 percent of the VPS MSM cohort had an 18 month visit or seroconverted prior to the visit. At each 6 month visit, approximately 4 percent of men were lost to follow-up (inactivated or were passive drop-outs from the study). Using simple extrapolation of this experience to follow-up at 3 years, we project that 78 percent of the study cohort will attend the final study visit or seroconvert prior to the visit. Follow-up will be carefully monitored. At the end of the trial, a special follow-up effort will be conducted to trace the study participants who do not attend the final study visit and who have not explicitly refused participation in the trial (approximately 700 based upon the VPS experience). As a result of this tracing effort and with the use of remote specimen collection techniques (see below), we expect to obtain a final HIV test result from at least 70 men who do not attend a final visit (i.e. a minimum of 10%). This will result in at least 80 percent of the entire study cohort being available for the primary study endpoint. Under these assumptions, we expect to accrue approximately 5,500 person-years of follow-up in each arm and to observe 85 primary end points in the control arm by the end of the study.

Ascertainment of the HIV infection endpoint at the conclusion of the study for individuals not willing or able to attend a clinic visit will be obtained using the Home Access<sup>®</sup> HIV-1 Test System. A dried blood spot home collection kit will be used by the participant to collect a specimen, which is mailed to the Home Access laboratory for testing. In the rare event that a participant tests HIV positive, arrangements will be made to collect a confirmatory blood sample at a site convenient to the participant. New technologies for remote HIV testing will likely become available before the completion of the trial. These technologies will be carefully assessed and, if appropriate, used to maximize the number of study participants for whom a final ascertainment of HIV infection status is obtained.

## **9.3 Analytic Issues and Trial Operating Characteristics**

### **9.3.1 HIV Seroincidence**

The primary analysis of a Phase IIb or "screening" trial is formally based on a three point decision guideline used to set the statistical study design. The decision guideline for this trial is based on whether the estimated efficacy of the intervention is less than 10 percent, between 10 percent and 35 percent, or greater than 35 percent, where efficacy is expressed as a percent reduction in the seroincidence of HIV. Note that these should not be interpreted as strict decision rules but as guidelines (derived from formal statistical procedures) that will be factored into a broader scientific perspective about the public health utility of the intervention. Specifically, the decision guidelines for this trial are:

1. If the estimated reduction in seroincidence of HIV is less than 10 percent, then reconsider the intervention approach (discard or reformulate the intervention strategy).
2. If the estimated reduction in seroincidence of HIV is between 10 percent and 35 percent, then the intervention is considered to be plausibly efficacious and merits further evaluation. The requisite further evaluation would include a detailed analysis/interpretation of trial data with an accompanying broad discussion about 1) potential public health implementation, 2) possible refinements of the intervention and 3) the merits of initiating a Phase III trial to provide a definitive evaluation of the intervention.
3. If the estimated reduction in seroincidence of HIV is greater than 35 percent, then declare the intervention efficacious.

The operating characteristics of this trial are:

1. The false positive rate of the screening procedure is low. In particular, if the intervention has no effect then there is ONLY a 24.7 percent chance of going forward to a Phase III and essentially no chance of declaring the intervention efficacious. If the intervention truly reduces risk by ONLY 10 percent there is a 47.7 percent chance of going forward to a Phase III trial and ONLY a 2.2 percent chance of declaring the intervention efficacious.
2. The false negative rate is low. If the intervention truly reduces risk by 35 percent then there is ONLY a 3.0 percent chance that the intervention would be discarded, a 46.9 percent chance that it would be evaluated in a subsequent Phase III trial and a 50.0 percent chance that it would be declared efficacious.
3. The power to provide a definitive result for a highly efficacious intervention is high. If the intervention truly reduces risk by 50 percent then there is a 92.7 percent chance that it would be declared efficacious and virtually no chance that it would be discarded.

The following Table summarizes the probabilities of each possible decision for a variety of hypothesized true values of efficacy of the behavioral intervention (denoted in the table as "BE"). Probabilities in the table were estimated by computer simulation of 50,000 trials under the assumption that the numbers of observed infections in the control and intervention groups are distributed as a Poisson random variable.

**Table 1: Estimated Probabilities**

BE True	{BE-est <= 10% }	{10% < BE-est <= 35% }	{35% < BE-est }
0%	0.750	0.247	0.003

5%	0.636	0.356	0.008
10%	0.501	0.477	0.022
15%	0.360	0.591	0.050
20%	0.234	0.662	0.104
25%	0.136	0.667	0.198
30%	0.065	0.602	0.333
35%	0.030	0.469	0.500
40%	0.010	0.313	0.677
45%	0.002	0.173	0.824
50%	0.001	0.073	0.927

### 9.3.2 HSV-2 Seroincidence

Because estimates of HSV-2 seroprevalence and seroincidence for the study cohort are not available, it is not possible to provide a reliable description of the statistical characteristics of the assessment of intervention effect on HSV-2 seroincidence. However, if we assume that HSV-2 seroprevalence at baseline is 25 percent and annual seroincidence is 2 percent (based on preliminary data from the VPS site in Seattle) then we would expect to see about 79 incident cases in the control group (within the subcohort of HSV-2 seronegative individuals at baseline) at the end of the study. Thus, if the Seattle experience obtains for the entire study, then a "screening" type evaluation of the impact of the intervention on HSV-2 seroincidence would be obtained from this trial.

Because of the uncertainty in these projections, we plan to perform the assessment of intervention effects on HSV-2 seroincidence in a step-wise fashion by making use of the ability to perform the assays on stored sera. Specifically, we will identify a random sample of 600 trial participants and retrieve and assay their specimens obtained from the final trial visit. For the subset of individuals whose assays are positive, we will retrieve and assay their baseline specimens to distinguish the seroprevalent from the seroincident cases. Based on this information, we will estimate how many informative cases would be available in the entire cohort (i.e., number of HSV-2 seronegatives at baseline) as well as HSV-2 seroincidence over the study period. Based on these two figures, we will assess how informative HSV-2 assays on the entire cohort would be. If these initial data indicate that it is justified, we will seek additional funds to complete the assays on the entire cohort.

We expect 150 of the random sample of 600 participants to be HSV-2 seropositive at baseline (assuming a baseline seroprevalence of 25 percent). Of the remaining 450 that are HSV-2 seronegative at baseline, we expect about 27 to become infected during the 3 year follow-up period (assuming a 2 percent annual HSV-2 seroincidence). Based on these assumptions our estimate of annual seroincidence from this sample will have 95 percent confidence limits of approximately +/- 0.7 percent. Thus our estimate will have sufficient precision to reliably decide whether the HSV-2 endpoint will be informative enough to complete testing for the entire cohort.

### **9.3.3 Rectal and Urethral Gonorrhea**

There are no reliable estimates of the likely semiannual prevalence rates of rectal and urethral gonorrhea in the study population on which to base calculations of statistical power. We will evaluate the gonorrhea endpoint for all study participants at the Month 6 visit. Based on these data, we will then determine if the trial will have sufficient power to detect intervention effects on rates of GC to warrant continued evaluation of this endpoint.

## **9.4 Analysis Plan**

### **9.4.1 Primary Analyses**

The primary analysis of trial data (i.e., analyses addressing the primary study objective) will consist of a comparison of rates of HIV seroconversion, as assessed over the study follow up, among participants assigned to the intervention group and those assigned to the control group. It will be based on an "intent-to-treat" analysis which includes all participants randomized regardless of the amount of counseling received. Formally, this comparison will be made using discrete-time survival analysis techniques (Kalbfleisch and Prentice, 1980) to accommodate loss-to-follow-up during the study period, and will specifically estimate the odds of HIV seroconversion for the intervention group relative to that for the control group. The same statistical techniques will be used to estimate the relative odds of seroconversion for each of the time intervals between each successive follow-up visit in order to evaluate trends in the relative odds as a function of time from randomization.

### **9.4.2 Secondary Analyses: STD Outcomes**

The basic analyses of intervention effect on HSV-2 seroconversion as assessed at semiannual study visits will proceed using the same approach and statistical methods as those described in Section 9.4.1. The analysis of gonorrhea (rectal and urethral) prevalence as assessed at the semiannual study visits will be performed using statistical methods based on generalized estimating equations (GEE). This approach will relate the (logistic transform of) GC prevalence at each assessment time to randomization group making full use

of data on recurrent infections and taking appropriate account of the dependence structure of the data over time. This analysis will provide a statistically valid assessment of differences between groups in prevalence of GC throughout the entire study period.

### **9.4.3 Secondary Analyses: Behavioral Outcomes**

To assess self-reported changes in risk behaviors as a correlate of protection against acquisition of HIV, HSV-2 and GC, we will estimate the fraction of the relative odds of HIV (HSV-2, GC) incident cases associated with the intervention that can be explained by changes in a set of select self-reported risk behaviors. In these analyses, we will use simple adaptations of the statistical techniques described by Freedman et. al (1992) for binary outcome data and by Lin et. al. (1997) for continuous failure time data to estimate this fraction and its standard error. The set of self-reported risk behaviors used in this analysis will be identified in advance based on considerations of: 1) the specific risk behaviors that are targeted for change by the intervention (i.e. condom use and number of episodes of unprotected anal sex), and 2) the attributable risks for HIV (HSV-2, GC) seroconversion of various behaviors as assessed in the absence of the intervention.

Subsequent to the above analyses, the impact of behaviors or psychosocial variables which may mediate the effects of the intervention on self-reported behavioral change and seroincidence will be assessed. Mediator variables include alcohol and drug use and measures of depression (a 7-item short version of CES-D), integration into the gay community, sexual communication skills, perception of community norms that support safer sexual practices, enjoyment of unsafe sex, history of sexual abuse and self efficacy with regard to sexual behavior. Given potential correlations between these scales, the preferred method of analysis to determine the relationship between intervention and changes in these mediators will involve the use of a repeated measures multivariate analysis of variance (MANOVA). We will also develop models to estimate the fraction of the relative odds of HIV (HSV-2, GC) seroconversions associated with the intervention that can be explained by changes in mediators as well as self-reported risk behaviors. Participation in the intervention may be entered as one of the mediator variables, but there is a need to exercise caution in interpretation as differences can reflect variations in motivation as well as participation itself. Participation in counseling outside the study intervention may also be considered as a variable that mediates the effect of the intervention.

### **9.4.4 Secondary Analyses: Alcohol and Other Drug Use Outcomes**

In order to assess the effect of the intervention on sexual risk behaviors that are associated with alcohol, we will perform an intent-to-treat comparison of control and intervention groups with the endpoint being rates of self-reported

risky sexual behavior associated with drug and alcohol use at follow-up visits. Logistic regression models will be used to look at difference in rates at follow-up visits and GEE methods will be used to look at changes over time.

As an exploratory analysis, we will also compare the rates of self-reported behaviors between participants in the intervention arm who received the intervention track targeting alcohol and drug use and men in the control arm who are selected by matching on selected baseline risk variables. These matching variables include CAGE score, substance use and level of sexual risk behavior as assessed in partner-specific episode questions, the occurrence of concurrent substance use and sex, self-assessment of the ease/difficulty in having safe sex when substance use is involved, and frequency of unprotected anal sex. The interpretation of this analysis is limited since any observed differences may be attributable to factors other than the matching criteria.

#### **9.4.5 Secondary Analyses: Cost Effectiveness Outcomes**

Standard methods of cost-effectiveness analysis will be used. All outcome measures are incremental, comparing the intervention to standard care. If there is a net savings for any of the outcomes (i.e., savings in the numerator of the outcome ratios), the outcome will be expressed as savings per 1,000 participants. A discount rate of 3% will be used for health and monetary outcomes. Extensive one-way and multi-way sensitivity analyses will be conducted.

### **9.5 Relationship to Future Prevention Trials**

It is possible that additional randomized controlled HIV prevention trials, including Phase IIB or Phase III HIV vaccine trials, will be initiated at the study sites before HIVNET 015 is completed. In particular, an intermediate-sized trial to evaluate a candidate HIV vaccine may be initiated as early as Fall 2000. We do not expect that HIVNET 015 operations will have a significant impact on the design and operation of a future intermediate-sized trial of preventive HIV vaccines. First, the intense behavioral intervention activities would be complete well before the time recruitment to the vaccine trial would begin. Thus, we do not expect to encounter the operational complexities that would obtain if study sites were simultaneously performing two such intense activities. Second, the data are not likely to show conclusively that the behavioral intervention is efficacious by Fall 2000. Thus the intervention, if eventually shown to be efficacious, would not be recognized as the community standard of care that should be delivered to all vaccine trial participants in such a first, large-scale, NIH-sponsored HIV vaccine trial.

### **9.6 Data Monitoring**

This trial will be monitored by the NIAID HIV Prevention Trial Data and Safety Monitoring Board (DSMB). Summaries of trial operations and outcomes will be

provided to the DSMB for their review approximately every six months. These summaries will include overall and site-specific descriptions of participant recruitment, enrollment and randomization, comparability of intervention and control groups at baseline, delivery of the behavioral intervention, participation in the intervention, and retention of participants for follow-up visits. Summaries of primary and secondary efficacy endpoints will also be provided by randomization group. These latter summaries will be presented with interval estimates of the relative endpoint rates appropriately adjusted for inspection of these data at multiple time points during the trial. The symmetric O'Brien-Fleming sequential analysis guidelines will be used to make these adjustments. We consider it very unlikely that the symmetric O'Brien-Fleming boundary will be crossed by the primary endpoint at an interim analysis.

Because of the purely behavioral nature of the intervention, we do not anticipate any "biological" adverse experiences directly attributable to the intervention. However, we will monitor other potential adverse experiences through the Social Impact assessment administered to all participants at 6-month intervals.

## **10. HUMAN SUBJECTS**

### **10.1 Institutional Review**

Prior to study implementation, the protocol and informed consent forms must be approved by the IRB of each participating study site. All protocol amendments effecting the safety and welfare of study participants must be approved by the IRB prior to implementation. The study site Principal Investigator is responsible for preparation of all submission documents and periodic reports required by the IRB.

### **10.2 Informed Consent**

Written informed consent will be obtained from each participant prior to the Screening Visit and prior to enrollment. Participants will be provided with a signed copy of both consent forms.

Each study site is responsible for developing consent forms for local use based on the attached consent templates in Appendix A. The forms must be developed in accordance with the principles of informed consent as described in Title 45, Code of Federal Regulations (CFR) Part 46 and Title 21 CFR, Part 50, as well as in accordance with current community standards of practice. Individual study sites are responsible for obtaining local IRB approval of study procedures and forms.

Copies of IRB-approved consent forms must be provided to the DMC prior to the implementation of any study procedures. Documentation of any subsequent changes in the consent forms must also be provided to the DMC.

### **10.3 Confidentiality**

### **10.3.1 Local Protections**

All study data, laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number **ONLY**, to maintain participant confidentiality. All study data will be stored separately from study records that contain names or other personal identifiers (such as locator forms and informed consent forms). All local databases must 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 must be stored in a separate, locked file in an area with limited access. If participant names and corresponding Participant IDs are entered into a computer database, this database must be password protected and must be maintained in a directory separate from any study-specific data. File encryption is encouraged, but not required.

Study-related information will not be released without the written permission of the participant, except as necessary for monitoring by the DMC, CAPS Coordinating Center, Statistical and Clinical Coordinating Center, and/or NIAID.

### **10.3.2 Statistical and Clinical Coordinating Center (SC) Protections**

The SC provides several layers of participant data security including physical, network, and computer access security.

Physical security of all SC computers and data is obtained through controlled and limited access to areas containing the SC network. Access to the building and floor requires a personal key card during off hours (5:10 p.m. to 6:40 a.m. weekdays and all day weekends). A key card is needed at all times to gain entry to the SC offices. All server computers are kept in locked offices. All network wiring closets are locked and **ONLY** accessible to designated personnel.

Network security is accomplished using a firewall computer to protect participant data and other SC files from attack via the Internet connection. This computer restricts and tightly regulates all network traffic between our internal (secure) SC network and the rest of the Internet.

Access security is obtained through the use of network login ID's, passwords and file protections. Every user is required to have his or her own login name and password. A user that connects to any SC computer from a network outside of the HIVNET SC (e.g., through a dial-up connection or the Internet) will be required to use a SecureID card. The SecureID card generates a new, six digit number every 60 seconds. This, along with a

Personal Identification Number known ONLY to the registered owner of the SecureID card, forms the user's password. This system provides for an extremely secure remote access to SC computing resources.

In addition, the DataFax data management system provides additional levels of security that go beyond the normal system security. Users are limited by login name and password to the level of access that they have to any part of the DataFax system or data. Since incoming faxes are stored directly on the DataFax server computer they immediately fall under the DataFax security umbrella. User's must both be registered to their DataFax security level as well as their system security level.

### **10.3.3 Federal Protections**

The DMC has obtained a federal Certificate of Confidentiality that applies to all study sites. The Certificate of Confidentiality states that study staff may not be compelled to disclose study-related information by any Federal State or local civil, criminal, administrative, legislative, or other proceedings. The Certificate thus serves to protect the identity and privacy of study participants.

## **10.4 Benefits**

### **10.4.1 Support for HIV Prevention**

Participation in this study may help participants remain HIV-uninfected through reinforcement of HIV risk reduction. During the study, participants will receive the most current information and counseling about how to avoid HIV, as well as testing for HIV infection. In addition, study site staff may provide materials, such as condoms, lubricants, and clean syringes/needles, as applicable, to study participants.

### **10.4.2 Access to Care**

This protocol provides for periodic HIV-related risk assessments as well as testing for HIV and STD infection. Study staff will be trained to refer participants to such services as STD treatment, drug treatment and/or other psychosocial services, as applicable to the participant.

In the event of HIV infection, study staff will refer participants to appropriate medical and psychosocial services, as well as monitor their access to follow-up care.

In addition, participants who become infected with HIV will be referred to appropriate ongoing studies such as the AIEDRP and HIVNET 019. These studies provide periodic monitoring, advice about current treatment guidelines, referrals or access to appropriate clinical trials and other services

including routine medical and dental care, emotional support, and counseling.

### **10.4.3 Remuneration**

Study participants will be compensated for their time and effort in this study. (See Section 10.8.)

### **10.4.4 Benefits to Humanity**

The trial will provide information on whether the proposed behavioral intervention reduces the incidence of HIV infection compared to standard counseling and testing. This study may provide direct evidence of the efficacy of behavioral interventions on acquisition HIV.

## **10.5 Risks**

### **10.5.1 Health Risks**

Study participants may experience discomfort associated with rectal swabs and blood sample collection. Blood sample collection may be associated with pain during blood drawing, and subsequent bruising or, in very rare instances, local infection.

### **10.5.2 Psychosocial Risks**

Study participants may experience social harm if disclosure of their participation results in their being labeled as being at high risk for HIV infection. In addition, names of trial participants who develop HIV or other STDs may be required by state or local officials under health department regulations providing for reporting of communicable diseases, partner notification, and/or contact tracing (see Section 10.7.) Periodic HIV testing may increase the participant's anxiety level. Finally, names of trial participants who report (in the context of a counseling session or via response to a questionnaire) an intention to harm self or others, current or recent child abuse, or current or recent statutory rape may be required by state or local officials.

## **10.6 Study Withdrawal and Discontinuation**

The study may be discontinued at any time by NIAID or the NIH. The participants will be informed through the process of informed consent that they may withdraw from the study at any time for any reason. Participants may be withdrawn from the study by site Principal Investigators if they are found to have:

- An obvious psychological/psychiatric disorder that would invalidate the informed consent process, or otherwise contraindicate participation in the study.
- Any other condition which in the opinion of the study site Principal Investigator will interfere with achieving the study objectives. *The decision to withdraw a participant must be done in consultation with the Protocol Co-Chairs, DMC Protocol Specialist, and the Protocol Biostatistician.*

## **10.7 Communicable Disease Reporting**

State or local health department regulations may require disclosure of the identities of study participants who test positive for HIV infection. Other regulations may require reporting to a health department names of people referred for, or receiving treatment for syphilis, gonorrhea, or other infectious diseases. In turn, these disclosures may trigger procedures for contact tracing or partner notification under the standards of confidentiality that govern the local health department practice.

Consent forms will be explicit about any applicable local public health reporting requirements for HIV, gonorrhea or HSV-2.

## **10.8 Incentives to Participation**

At each regularly scheduled study visit participants may be reimbursed for travel expenses. For their time and effort in this study, participants may receive compensation for each regularly scheduled study visit that involves an interview assessment and HIV-antibody testing, in the form of cash or check, or merchandise or a gift certificate. Participants who complete the study by attending all scheduled follow-up visits also may receive a bonus payment. The same incentives will be provided irrespective of random assignment. Incentive packages are site-specific and target population specific to accommodate local variations in standards of practice for sponsored research projects.

## **10.9 Community Preparedness**

Each study site will develop strategies to increase community awareness, knowledge and acceptance of this trial, particularly among populations most likely to be targeted for trial enrollment.

Recognizing the importance of participation by members of the communities that will be invited to participate in the intervention trial, efforts will be made to include representatives of these communities in HIVNET deliberative, protocol development, and decision making bodies.

Each study site will convene and provide logistical support for a CAB. The CAB will meet at least quarterly, and will:

- Collect and make available to the investigators information that can be used to preemptively address concerns likely to arise during the intervention trial.
- Provide the investigators informed commentary on study protocols and related informational, educational and promotional materials, including documents related to the informed consent process.
- Support study recruitment efforts and promote referral arrangements associated with this intervention trial.
- Assist with community education and dissemination of information related to study goals, procedures and progress.

Individual CABs may elect to add activities and functions as necessary or desired in their communities.

## **11. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT**

Specimens collection requirements for LL and the CL are detailed in Figure 2 and in Section 11.1 and 11.2. All participant specimens collected and sent to either the LL or CL should be labeled with the pre-printed barcode labels provided by the CL; corresponding labels are attached to the Specimen Collection Form.

### **11.1 Local Laboratory (LL)**

The LL is responsible for:

- HIV serologic testing.
- Resolution of indeterminate results.
- LE testing for urethral inflammation.
- GC culture of rectal swab specimens.

### **11.2 Central Laboratory (CL)**

The CL is responsible for:

- Archival storage of serum specimens from participants.
- HSV-2 serology.
- LCR testing for GC.

- Rapid turnaround PCR testing of blood specimens from participants being evaluated for suspected ARI or indeterminate HIV testing results.
- Forwarding test results of dried blood spot specimens from Home Access<sup>®</sup> HIV-1 Test System to study sites for confirmation of participant report.
- Guidance to study sites regarding quality assurance and certification of local laboratories; biohazard control advisories, specification of requirements for collection, processing; storage, and shipment of biological specimens.
- Provision to study sites of packing materials, cartons and shipping labels for all specimens.

### **11.3 Biohazard Containment**

Since HIV and other blood-borne infectious agents can be transmitted through contact with contaminated needles, blood or blood products, appropriate precautions must be employed by all personnel involved in this study as required by the Occupational Safety and Health Administration (OSHA) and recommended by the CDC. For reference, the Public Health Service's Guidelines for Prevention of Transmission of Human Immunodeficiency Virus and Hepatitis B Virus to Health-Care and Public-Safety Workers is included in Appendix C. The contractual terms of the Public Health Service's Safety and Health Clause (PHS 352.223-70) are also included in this Appendix C.

## **12. ADMINISTRATIVE PROCEDURES**

### **12.1 Study Coordination**

The study site Principal Investigators (or designees) will participate in monthly telephone conference calls in which site operations, progress and coordination will be discussed, with more frequent calls if necessary during initial enrollment and intervention implementation. The Principal Investigator, co-investigators, and other study site personnel may be included as a member of one or more working groups contributing to the design, oversight, analysis, and reporting for various components of the Trial.

### **12.2 Intervention Coordinating Center (ICC)**

The ICC at UCSF CAPS will coordinate the aspects of the study that involve the delivery of the intervention and control conditions. This will include the training and supervision of the counselors throughout the intervention. Specifically, the ICC will:

- Collaborate with the SC, DMC, and trial Protocol Team in developing an Intervention and Control condition Counseling Manual, study procedures, study protocol and the SSP manual.
- Collaborate with the SC, DMC, and Trial Protocol Team (PT), to design standardized forms and or procedures for carrying out the intervention and collecting intervention-specific data from study sites.
- Collaborate with the DMC, SC, and CL, to organize and coordinate development of material and programs for staff training, and remedial instruction as required in study protocol and procedures.
- Maintain coordination between study sites, the DMC, SC, and CL.
- Carry out quality assurance activities according to the protocol, including review of tape recordings of the sessions.
- Evaluate the adequacy of resources provided to study sites and make recommendations as necessary.
- Collaborate with SC for the production of reports to the DSMB.
- Lead conference calls among study site clinical supervisors.
- Collaborate in the development of strategies and methodologies for analysis of study data and in manuscript development and dissemination of study/trial results.
- Collaboration with the DMC and SC to respond to inquiries from study site investigators and Division of AIDS (DAIDS) staff on logistics and procedures for the trial.

## **12.3 Domestic Master Contractor (DMC) and Statistical and Clinical Coordinating Center (SC) Responsibilities**

### **12.3.1 Domestic Master Contractor (DMC)**

The DMC shall be responsible for a) monitoring study sites to assure compliance with study protocol and applicable regulatory requirements, and b) monitoring resource utilization in relationship to performance of study/trial protocol.

In addition, the DMC will collaborate with the ICC, SC, and the trial PT to:

- Help develop study protocol, procedures, and the SSP manual.

- Help design standardized data collection forms and procedures.
- Help organize and coordinate development of materials and programs for staff training, and remedial instruction as required in study protocol and procedures.
- Help develop strategies and methodologies for analysis of study data and participate in manuscript development and dissemination of study/trial results.
- Respond to inquiries from HIVNET study site investigators and staff on logistics and procedures for the trial.

### **12.3.2 Statistical and Clinical Coordinating Center (SC)**

The SC shall:

- Develop, maintain and refine hardware and software systems (including A-CASI) and related procedures for collecting, cleaning, and analyzing study data and meeting any applicable reporting requirements (e.g. DSMB).
- Collaborate with trial PT, ICC, and DMC to develop standardized forms and procedures for collection of data.
- Develop, implement and operate a specimen tracking system for specimens shipped to the CL.
- Develop and implement randomization and treatment allocation scheme for trial.
- Provide periodic reports to the trial PT, DMC, and DAIDS on accrual, retention, intervention participation and other key process measures.
- Provide Quality Control (QC) reports and appropriate site-specific data to each trial field site.
- Identify problems in data collection and propose remedial changes in study procedure to the trial PT.
- Collaborate with trial PT and DMC in developing the Study Procedures, Study Protocol and SSP manual.

- Provide lead Biostatistician and analytic support for interim and final analysis of primary study outcomes and collaborate in final analyses and in manuscript development.

## **12.4 Study Site Monitoring**

A minimum of one site visit per year by NIAID staff and/or the DMC will be made to monitor the progress of study recruitment, the quality of data collected in the research records, the accuracy of the data submitted, and to determine that all process and/or regulatory requirements are met. The ICC will be asked to participate in site monitoring visits as appropriate, in addition to its independent responsibility for quality assurance (QA), training, and oversight of the intervention (See Section 6.5.1).

The Trial study site Principal Investigators will allow the DMC site liaison to inspect study documents (e.g., consent forms, process data collection forms, questionnaires) for confirmation of the study data.

## **12.5 Protocol Compliance**

This study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the PT and DMC Project Officer. Protocol amendments requiring IRB approval must be submitted to the IRB by the study sites' Principal Investigators and approval obtained prior to implementing the amendment.

Written approval must be obtained for any additional data or specimen collection conducted in the cohort assembled in conjunction with this protocol.

Requests to implement additional research protocols should be submitted in writing to the DMC Project Officer, who will forward these requests to the Protocol Co-chair(s). The Protocol co-chair(s)' written response will determine the DMC Project Officer's written response to the study sites's request.

## **12.6 Investigator Records**

The study sites' Principal Investigators will maintain complete, accurate and current study records for a period of at least five years after the completion of the study period or until notified by NIAID that retention of records is no longer required. Study records include all of the following:

- Administrative files, including initiation documents and all reports and correspondence relating to the study.
- Records for each participant including: Informed Consent, Locator, all DataFax forms, and all source documents.

## 12.7 Use of Information and Publications

Publication of study results will be governed by publications and confidentiality clauses in the study sites subcontract with the DMC, by DAIDS policies, and by the HIVNET Governance document.

## 12.8 Signatures and Timetable

Study site: \_\_\_\_\_

Projected starting date: \_\_\_\_\_

Projected number of participants: \_\_\_\_\_

Projected completion date: \_\_\_\_\_

The following documents must be submitted to the sponsor prior to initiation of the study:

\_\_\_\_ Curriculum Vitae for Principal and Co-Investigators

\_\_\_\_ approval

\_\_\_\_ Copy of IRB approved informed consent form

\_\_\_\_ Signed copy of the protocol

I have read the protocol entitled Behavioral Intervention Trial and agree to conduct the study in accordance with its provisions.

For [study sites]:

\_\_\_\_\_  
Principal Investigator Date

For DAIDS, NIAID, NIH:

\_\_\_\_\_  
Protocol C0-Chairs Date

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