

Clarification Memo #4 to:

HPTN 064: The Women's HIV Seroincidence Study (ISIS, DAIDS ID 10705) Version 1.0, 9 July 2008

Clarification Memo Final Version dated 20 July 2010

Summary of Revisions and Rationale

1. The protocol for HPTN 064, The Women's HIV Seroincidence Study (ISIS), uses the term "High Risk Areas" (HRAs) to reference the communities that were selected to participate in the research study. This clarification memo is being provided to explain how the communities were selected, and to further explain the use of the term HRA.
 2. Update of Protocol Roster to include Wairimu Chege.
-

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance by the HPTN CORE.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1 Clarification of HRA, "High Risk Areas"

The protocol for HPTN 064, The Women's HIV Seroincidence Study (ISIS), uses the term "High Risk Areas" (HRAs) to reference the communities that were selected to participate in the research study. This clarification memo is being provided to explain how the communities were selected, and to further explain the use of the term "HRA".

The ISIS communities were selected using a mathematical formula based on HIV prevalence and poverty rates. In order to identify these geographic areas, data on poverty was obtained from the United States census bureau and data on HIV prevalence was obtained from state or local health departments. Geographic areas with both higher rates of HIV prevalence and poverty were considered as possible communities for ISIS. In addition, communities that were ultimately selected for ISIS were also in an area accessible by research institutions participating in ISIS. This process is explained in further detail in section 3.7 of version 1.0, dated 9 July 2008 of the ISIS protocol.

The term "HRA" intended to describe the possible risk of HIV infection that community members living in an area with both a high rate of HIV transmission as well as a high rate of poverty may experience as a result of their living environment. The term HRA was not intended to suggest that members of ISIS communities engage in risk behaviors at a higher rate than members of non-ISIS communities. For example, poverty rates have been used as a proxy to predict factors such as the availability of, and access to, healthcare services, including testing and treatment for sexually

transmitted infections (STIs). This may be a particular risk factor for women living in high poverty communities, since a lack of access to healthcare has been linked to higher rates of untreated STIs and a resulting increased susceptibility to HIV transmission. The use of the term was also not intended to suggest that any other forms of behavioral risk were higher in ISIS communities in comparison to any other United States community that does not share the combined characteristics of high poverty and high HIV prevalence rates.

ISIS is part of the HPTN's larger commitment to domestic HIV prevention efforts and to community involvement in research ensuring that community representatives and stakeholders have input on key decisions and are updated regularly by study staff. It is hoped that the information gained from this study will inform the design of future, larger-scale trials of promising HIV prevention interventions among women in the US

Revision 2 Updates to Protocol Roster:

Addition of Wairimu Chege as NIH Medical Officer

Wairimu Chege, MD, MPH

NIH Medical Officer

Rm 5252

6700B Rockledge Drive

Bethesda, MD 20892

Tel: 301-451-2782

Fax: 301-496-8530

E: chegew@niaid.nih.gov

Clarification Memo #3 to:

HPTN 064: The Women's HIV Seroincidence Study (ISIS, DAIDS ID 10705) Version 1.0, 9 July 2008

Clarification Memo FINAL Version dated 12 November 2009

Summary of Revisions and Rationale

1. Clarification that the Study Specific Procedures Manual includes the procedures for determining total length of follow-up for enrolled women.
 2. Update of Protocol Roster to include Jonathan Lucas and Noranik Zadeyan and the removal of Rhonda White.
 3. Inclusion of the Harlem Prevention Center's new name and removal of their former title.
-

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance by the HPTN CORE.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1

2.3.1 Study Visits and Sample Collection (Cohort Component, Women only)

Two hundred women will be enrolled over a six-month period in each community. Women enrolled in months 1–3 will be followed for 12 months (monthly phone contacts, in-person follow-up visits at 6 and 12 months post-enrollment) and women enrolled in months 4–6 will be followed for 6 months (monthly phone contacts, in-person follow-up visit at 6 months post-enrollment) (see Figure 1). As a result we anticipate that the duration of study enrollment and follow-up will be 15 months. However, if accrual is slower than anticipated (i.e., <50% of cohort enrolled by month 3), we will extend to 12 months the follow-up duration for individuals enrolled in month 4 and, if needed, in month 5. **Details regarding the procedures used to determine whether participants will be followed for 6 or 12 months will be included in the HPTN 064 Study Specific Procedures (SSP) Manual.**

Revision 2 Updates to Protocol Roster:

Addition of Noranik Zadeyan as the HPTN 064 Community Working Group Liaison

Addition of Jonathan Lucas as the HPTN 064 Community Program Manager

Removal of Rhonda White as the HPTN 064 Community Program Manager

Jonathan Paul Lucas, MPH
Community Program Manager
Family Health International
Science Facilitation Department
Post Office Box 13950
Research Triangle Park, North Carolina
27709, USA
Tel: 919-544-7040 ext. 11458
Fax: 919-544-0207
Email: jlucas@fhi.org

Noranik Zadeyan, MPH
HPTN 064 Community Working Group
Liaison
Project Advance, Bronx-Lebanon Hospital
Center
1645 Grand Concourse, #1D
Bronx, NY 10452
Tel: 718-960-1452
Fax: 718-960-1455

Columbia University
Harlem Prevention Center
215 125th St. Suite A-100
New York, NY 10027
Work Cell: 646-226-6873
Fax: 646-448-0952

nz2162@columbia.edu

~~**Rhonda R. White, RHEd**
Community Program Manager
Science Facilitation Department
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
P: 919-544-7040 ext. 515
F: 919-544-0207
Email: rwhite@fhi.org~~

Revision 3

From SCHEMA (Page 12)

Revision of the name of Harlem Hospital CRS to it's newly adopted name, Harlem Prevention CRS. Please note, the change reflects a modification in name only, the clinical research site did not change.

Study Sites: This study will be conducted at the following clinical research sites. Each site may have one to three HRAs:

- ~~Harlem Hospital~~ **Harlem Prevention Center CRS**

Clarification Memo # 2 to:

**HPTN 064: The Women's HIV Seroincidence Study (ISIS, DAIDS ID 10705)
Version 1.0, 9 July 2008**

Clarification Memo FINAL Version dated 8 June 2009

Summary of Revisions and Rationale

1. Appendix I: Schedule of Evaluation has been updated to remove the "X" indicating that condoms must be offered at screening.

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance by the HPTN CORE.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1

	Screening Visit [#]	Enrollment [#]	Telephone Follow-up (Monthly)	Week 26*	Week 52*
PROCEDURES					
CLINICAL/COUNSELING PROCEDURES					
Obtain medical history		X		[X]	[X]
Provide HIV pre/post-test and risk reduction counseling (as applicable) ²		X		X	X
Offer condoms	X	X		X	X

Clarification Memo # 1 to:

**HPTN 064: The Women's HIV Seroincidence Study (ISIS, DAIDS ID 10705)
Version 1.0, 9 July 2008**

FINAL Version: 20 February 2009

Summary of Revisions and Rationale

1. Section 2.3 and 2.3.2 of the protocol has been updated to clarify recruitment of women for focus groups.
2. Section 9.2 of the protocol has been updated to clarify testing requirements for special cases.

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance by the HPTN CORE.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1

Section 2.3 Study Design

Table 2: ISIS Qualitative Components

Participants	Methods	Number (per each of 4 sites)
Enrolled Women At-Risk	Semi-structured behavioral interview	~20-30 per site (for a total of ~80 to 120 interviews, depending on rate of saturation)
	Focus Group discussion (8-10 participants each)	~2-3, Black women ~2-3, Hispanic women ~2-3 FGs per key demographic groups identified by site (for a total of 2-6 FG per site depending on demographics of community, 8-24 FGs total)
Men at ISIS Venues	Focus Group discussion (10-12 participants each)	~2-3, Black men ~2-3, Hispanic men ~2-3 FGs per key demographic groups identified by site (for a total of 2-6 FG per site depending on demographics of community, 8-24 FGs total)

2.3.2 Qualitative Components (Men and Women)

Focus groups with women will take place once selection for the individual interviews has been completed at the site. Women will be sampled in consecutively ~~blocks of ten~~ in order to facilitate timely implementation of each FG.

Revision 2

9.2 Network Laboratory Specimens

Blood samples collected above will be processed at the LL, and plasma will be frozen and stored. The site will receive instructions from the HPTN SDMC to ship selected samples to the HPTN NL for testing (see below). Some of these shipments will occur after the end of the study (i.e. after the last study participant completes the final study procedures).

Special Cases:

Plasma for resolution of discordant or inconclusive HIV diagnostic test results. The NL may request a stored sample for further HIV diagnostic testing, in which case results may be provided back to the site for clinical management of the participant.

HPTN 064

**The Women's HIV SeroIncidence Study (ISIS)
DAIDS ID: 10705**

A Study of the HIV Prevention Trials Network

Sponsored by:

US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institute of Mental Health
US National Institutes of Health

Protocol Chair

Sally Hodder MD

New Jersey Medical School
Newark, New Jersey, USA

Protocol Co-Chair

Jessica Justman MD

Columbia University
New York, New York, USA

Final Version 1.0

9 July 2008

HPTN 064

**The Women's HIV SeroIncidence Study (ISIS)
DAIDS ID: 10705**

**Final Version 1.0
9 July 2008**

A Study of the HIV Prevention Trials Network

Sponsored by:

**US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institute of Mental Health
US National Institutes of Health**

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

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

Name of Site Principal Investigator

Signature of Site Principal Investigator

Date

HPTN 064

The Women's HIV SeroIncidence Study (ISIS)

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES	5
LIST OF ABBREVIATIONS AND ACRONYMS	6
PROTOCOL TEAM ROSTER.....	8
SCHEMA	11
1 INTRODUCTION.....	13
1.1 BACKGROUND.....	13
1.2 RATIONALE.....	14
1.2.1 <i>HIV Prevalence and HIV Incidence in US Women</i>	14
1.2.2 <i>ISIS Behavioral Components</i>	16
1.2.3 <i>ISIS Laboratory Studies</i>	16
1.2.4 <i>Future HIV Prevention Trials</i>	19
2 STUDY OBJECTIVES AND DESIGN	19
2.1 PRIMARY OBJECTIVE.....	19
2.2 SECONDARY OBJECTIVES	19
2.3 STUDY DESIGN.....	20
2.3.1 <i>Study Visits and Sample Collection (Cohort Component, Women only)</i>	20
2.3.2 <i>Qualitative Components (Men and Women)</i>	22
3 STUDY POPULATION	24
3.1 INCLUSION CRITERIA	24
3.2 EXCLUSION CRITERIA	25
3.3 RECRUITMENT PROCESS.....	25
3.3.1 <i>Determination of Sampling Universe and Frames</i>	26
3.3.2 <i>Recruitment at Venues</i>	27
3.4 CO-ENROLLMENT GUIDELINES	27
3.5 PARTICIPANT RETENTION.....	27
3.6 PARTICIPANT WITHDRAWAL.....	28
3.7 COMMUNITY DEFINITION AND SELECTION.....	28
4 STUDY PROCEDURES FOR FEMALE PARTICIPANTS	29
4.1 SCREENING/ENROLLMENT	29
4.2 FOLLOW-UP PHONE CONTACTS: ALL COHORTS: WEEK 4, 8, 12, 16, 20, 24 (ALSO WEEK 30, 34, 38, 42, 46, 50 FOR PARTICIPANTS WITH 12 MONTHS OF FOLLOW-UP).....	31
4.3 WEEK 26 VISIT.....	31
4.4 EXIT VISIT FOR PARTICIPANTS WITH 12 MONTH FOLLOW-UP (WEEK 52).....	32
4.5 INTERIM VISIT (AD HOC)	33
4.6 POST-TEST VISITS FOR PERSONS WHO HAVE A REACTIVE HIV RAPID TEST AT OR AFTER ENROLLMENT.....	33
4.7 MISSED VISIT/LOST-TO-FOLLOW-UP.....	33
4.8 GENERAL PROCEDURES	34
5 STUDY PROCEDURES FOR MALE PARTICIPANTS.....	35
6 SAFETY MONITORING AND ADVERSE EVENT REPORTING	36
6.1 SAFETY MONITORING	36

7	STATISTICAL CONSIDERATIONS	36
7.1	REVIEW OF STUDY DESIGN.....	36
7.2	ACCUAL, FOLLOW-UP, AND SAMPLE SIZE	36
7.3	DATA ANALYSIS	37
7.3.1	<i>Primary Analyses</i>	38
7.3.2	<i>Secondary Analyses</i>	39
7.3.3	<i>Qualitative Analysis</i>	40
7.4	INTERIM MONITORING	41
8	HUMAN PARTICIPANTS CONSIDERATIONS.....	41
8.1	ETHICAL REVIEW	41
8.2	INFORMED CONSENT	41
8.3	RISKS	42
8.4	BENEFITS	42
8.5	ACCESS TO HIV-RELATED CARE.....	43
8.5.1	<i>Counseling</i>	43
8.5.2	<i>Care For Participants Identified As HIV-Infected</i>	43
8.6	USE OF INVESTIGATIONAL ASSAYS FOR IDENTIFICATION OF RECENT INFECTION	43
8.7	PARTICIPANT REIMBURSEMENT	44
8.8	CONFIDENTIALITY.....	44
8.9	COMMUNICABLE DISEASE REPORTING REQUIREMENTS.....	44
8.10	STUDY DISCONTINUATION	44
9	LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT.....	45
9.1	LOCAL LABORATORY SPECIMENS	45
9.2	NETWORK LABORATORY SPECIMENS.....	45
9.3	QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES	46
9.4	SPECIMEN STORAGE AND POSSIBLE FUTURE RESEARCH TESTING.....	46
9.5	ESTIMATES OF HIV INCIDENCE.....	47
9.6	BIOHAZARD CONTAINMENT	47
10	ADMINISTRATIVE PROCEDURES.....	47
10.1	STUDY ACTIVATION.....	47
10.2	STUDY COORDINATION	47
10.3	STUDY MONITORING.....	48
10.4	PROTOCOL COMPLIANCE.....	48
10.5	INVESTIGATOR'S RECORDS.....	48
10.6	USE OF INFORMATION AND PUBLICATIONS	48
11	REFERENCES	49
	APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR HPTN 064	53
	APPENDIX II: OPTIONAL SCREENING VERBAL INFORMED CONSENT (WOMEN)	55
	APPENDIX III: SCREENING AND ENROLLMENT INFORMED CONSENT (WOMEN)	57
	APPENDIX IV: QUALITATIVE INTERVIEW INFORMED CONSENT (WOMEN).....	65
	APPENDIX V: FOCUS GROUP INFORMED CONSENT (WOMEN)	69
	APPENDIX VI: OPTIONAL VERBAL SCREENING INFORMED CONSENT (MEN)	73
	APPENDIX VII: FOCUS GROUP INFORMED CONSENT (MEN)	74
	APPENDIX VIII: AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES	80

LIST OF TABLES AND FIGURES

TABLES

TABLE 1. ASSAYS FOR IDENTIFICATION OF RECENT HIV INFECTION.....	17
TABLE 2. ISIS QUALITATIVE COMPONENTS.....	20
TABLE 3. WIDTH OF 95% CI FOR HIV-INCIDENCE BASED ON TOTAL PERSON-YEARS OF DATA, POOLED ACROSS ALL COMMUNITIES.....	37

FIGURES

FIGURE 1. ILLUSTRATION OF ENROLLMENT AND FOLLOW-UP IN HPTN 064 (FOR EACH SITE).....	21
--	----

HPTN 064

The Women's HIV SeroIncidence Study (ISIS)

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ARV	antiretroviral (treatment)
CDC	Centers for Disease Control and Prevention
CFR	(United States) Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CORE	(HPTN) Coordinating and Operations Center
CRF	case report form
CRS	clinical research site
CV	Coefficient of Variation
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC	ethics committee
EIA	enzyme immunoassay
ELISA	enzyme linked immunosorbent assay
FDA	(United States) Food and Drug Administration
FG	focus group
FHI	Family Health International
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HIV-1	HIV type 1
HRA	high risk area
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
IQA	Immunology Quality Assurance
IRB	institutional review board
ISIS	Women's HIV SeroIncidence Study
LDMS	Laboratory Data Management System
LL	local laboratory
MSM	men who have sex with men
NAAT	Nucleic Acid Amplification Test
NHBS	National Health and Behavior Survey
NHBS-HET	National Health and Behavior Survey among heterosexuals
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIDA	(United States) National Institute on Drug Abuse
NIH	(United States) National Institutes of Health
NIMH	(United States) National Institute of Mental Health
NL	(HPTN) Network Laboratory

ODA	other day appointment
OD	Office of the Director, National Institutes of Health
OHRP	Office for Human Research Protection
PCR	polymerase chain reaction
PHI	Protected Health Information
QA	quality assurance
RNA	ribonucleic acid
RCC	DAIDS Regulatory Compliance Center
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	(HPTN) Statistical and Data Management Center
SOP	standard operating procedure
SSP	Study Specific Procedures manual
STARHS	Serologic Testing Algorithm for Recent HIV Seroconversions
STD	sexually transmitted disease
STI	sexually transmitted infection
US	United States of America
VBS	venue based sampling
WB	Western blot
VCT	voluntary counseling and testing
VDT	venue-specific-day-time periods

HPTN 064

The Women's HIV SeroIncidence Study (ISIS)

PROTOCOL TEAM ROSTER

Sally Hodder, MD

Protocol Chair
UMDNJ- New Jersey Medical School
185 South Orange Ave. MSB I-510
Newark, NJ 07101
United States
P: 973-972-3846
F: 973-972-2122
E: hoddersa@umdnj.edu

Wafaa El-Sadr, MD

Chair, HPTN Domestic Prevention Working Group
Columbia University
Mailman School of Public Health
722 West 168th Street
Room 715
New York, NY 10032
P: 212-342-0532/212-939-2936
F: 212-342-1824/212-939-2968
E: wme1@columbia.edu

Ada Adimora MD, MPH

University of North Carolina, Chapel Hill
Division of Infectious Diseases
130 Mason Farm Road, CB #7030
UNC School of Medicine
Chapel Hill, NC 27599-7030
adimora@med.unc.edu
T: 919-966-2536
F: 919-966-6714
E: adimora@med.unc.edu

Jessica Justman, MD

Protocol Co-Chair
Mailman School of Public Health
Columbia University
722 West 168th Street, Rm 714
New York, NY 10032
P: 212-342-0537
F: 212-342-1824
Email: jj2158@columbia.edu

Danielle Haley, MPH

HPTN CORE Protocol Specialist
Family Health International, Science Facilitation
PO Box 13950
Research Triangle Park, NC 27709
P: 919-544-7040 x221
F: 919-544-0207
E: dhaley@fhi.org

Elizabeth A. DiNenno, PhD

Protocol Consultant
Behavioral and Clinical Surveillance Branch
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention
1600 Clifton Road, MS E-46
Atlanta, GA 30333
P: 404-639-8482
F: 404-639-8640
E: eid8@cdc.gov

Lynda Emel, PhD
HPTN SDMC Project Manager
SCHARP-FHCRC
1100 Fairview Avenue North
LE-400
PO Box 19024
Seattle, WA 98109
P: 206-667-5803
F: 206-667-4812
E: lemel@scharp.org

Cathie Fogel, RN
University of North Carolina, Chapel Hill
4012 Carrington Hall CB# 7460
School of Nursing, UNC-CH
Chapel Hill, NC 27599-7460
T: 919-966-9938
F: 919-966-3647
E: cfogel@email.unc.edu

Jim Hughes, PhD
HPTN SDMC Statistician
University of Washington
Mailstop 359931
Seattle, WA 98195
P: 206-744-3633/206-616-272
F: 206-744-3693/206-616-2724
E: jphughes@u.washington.edu

Ann O'Leary, PhD
Protocol Consultant
Prevention Research Branch
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention
1600 Clifton Road, MS E-37
Atlanta, GA 30333
P: 404-639-1931
F: 404-639-1950
E: aao0@CDC.GOV

Susan Eshleman, MD, PhD
HPTN NL Representative
Johns Hopkins Univ. School of Medicine
Ross Bldg Room 646
720 Rutland Ave.
Baltimore, MD 21205
P: 410-614-4734
F: 410-502-9244
E: seshlem@jhmi.edu

Carol Golin, MD
University of North Carolina, Chapel Hill
725 Airport Road, CB 7590
Chapel Hill, NC 27599
T: 919-966-7939
F: 919-966-3811
E: carol_golin@med.unc.edu

Bernie Lo, MD
HPTN Ethics Working Group Representative
University of California San Francisco
521 Parnassus Avenue
Room C126
San Francisco, CA 94143-0903
P: 415-476-5370
F: 415-476-5020
E: bernie@medicine.ucsf.edu

Paul Richardson, MSc
HPTN NL QC Representative
Johns Hopkins Univ. Dept. of Pathology
Pathology Building 306
600 N. Wolfe St.
Baltimore, MD 21287
P: 410-502-0435
F: 410-614-0430
E: pricha18@jhmi.edu

Waheedah Shabbaz-El
CHAMP Representative
32 Broadway, Suite 1801
New York, NY 10004
P: 401-427-2302
F: 215-985-4492
E: wshabazz@champnetwork.org

Lydia E. Soto-Torres, MD, MPH
NIH Medical Officer
Rm. 5138
6700B Rockledge Dr.
Bethesda, MD 20892-7628
(Overnight Delivery Zip: 20817-7628)
P: 301-594-9705
F: 301-402-3684
E: lsoto-torres@niaid.nih.gov

Rhonda R. White, RHed
Community Program Manager
Science Facilitation Department
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
P: 919-544-7040 ext. 515
F: 919-544-0207
Email: rwhite@fhi.org

Nirupama Sista, PhD
HPTN CORE
Associate Director, Science Facilitation
Family Health International
PO Box 13950
Research Triangle Park, NC 27709
P: 919-544-7040, x590
F: 919-544-0207
E: nsista@fhi.org

Sten Vermund MD, PhD
HPTN Principal Investigator
Vanderbilt University, Institute for Global
Health
2215 Garland Avenue
Light Hall, Room 319
Nashville, TN 37232
P: 615-322-9373/ 615-322-9374
F: 615-322-9400
E: sten.vermund@vanderbilt.edu

Gina Wingood, PhD
Behavioral Sciences and Health Education
Rollins School of Public Health
1518 Clifton Road NE
Atlanta, GA 30322
T: 404-727-0241
F: 404-255-6779
E: gwingoo@sph.emory.edu

HPTN 064

The Women's HIV SeroIncidence Study (ISIS)

SCHEMA

- Purpose:** To estimate the overall HIV type 1 (HIV-1) incidence rate in women at risk for HIV acquisition in the US and to evaluate the feasibility of enrolling and following a cohort of these women.
- Design:** Multi-site, prospective observational cohort with a retrospective component.
- Qualitative components are also incorporated including semi-structured interviews of participants and focus group (FG) discussions with women enrolled in the cohort and FGs with men recruited from high risk area (HRA) venues.
- Populations:** Women in the US residing in an HRA and possessing specific characteristics that place them at risk for HIV acquisition.
- Men in the US who reside in HRAs (for qualitative component only).
- Study Size:** 2,000 women from 10 geographically distinct HRA communities (200 women per HRA) will constitute the study cohort.
- A subset of women already enrolled in the study cohort from 4 of the 10 communities will also participate in either a semi-structured interview or FG. Approximately 120 women (30 per community, 4 communities) will participate in individual interviews and approximately 120 women will participate in FGs (2-6 FGs in each of 4 communities).
- Approximately 120 men from 4 of the 10 communities will participate in FGs (2-6 FGs in each of 4 communities).
- Study Duration:** 2 years total duration with follow-up of all participants for 6-12 months.
- Primary Objective:** The primary objective of this study is to estimate the overall HIV-1 incidence rate among 2,000 women in the US from defined geographic areas with high HIV prevalence and poverty.

- Secondary Objectives:** The secondary objectives of this study are to:
- Evaluate laboratory assays for HIV-1 incidence determination
 - Estimate recruitment and retention rates
 - Describe sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk of HIV acquisition
 - Assess women’s preferred recruitment and retention strategies for future studies
 - Describe social, structural and contextual factors in a subgroup of female participants to inform future intervention studies
 - Estimate HIV-1 prevalence rate among women who have not reported previously testing HIV positive
 - Explore facilitators and barriers to HIV testing among men residing in HRAs to inform future intervention studies

Study Sites: This study will be conducted at the following clinical research sites. Each site may have one to three HRAs:

- Emory University, Atlanta, Georgia (Ponce de Leon Center CRS and Hope Clinic CRS)
- Johns Hopkins Adult AIDS CRS, Baltimore, Maryland
- University of North Carolina-Chapel Hill, North Carolina (UNC AIDS CRS and Wake County Health and Human Services CRS)
- Columbia University, New York, New York (Bronx-Lebanon Hospital Center CRS and Harlem Hospital CRS)
- New Jersey Medical School Adult Clinical Trials Center, Newark, New Jersey
- George Washington University School of Public Health and Health Services, Washington D.C.

1 INTRODUCTION

1.1 Background

Since 1981 more than 1.5 million people in the US have been infected with Human Immunodeficiency Virus (HIV), including more than 500,000 who have already died.(11) Women accounted for 8% of new Acquired Immunodeficiency Syndrome (AIDS) diagnoses in 1985 but now account for 26%¹ of new HIV/AIDS cases.(10) There is a striking racial disparity in the distribution of HIV/AIDS in the US, with 80% HIV/AIDS cases in women occurring in Black and Hispanic women.(8) Moreover, HIV/AIDS is the number one cause of death for Black women in the US ages 25-34 years, and the third leading cause of death in Black women ages 35-44.(9) Although HIV/AIDS is a preventable disease, it is clear that HIV has a substantial impact on the health of Black and Hispanic women in the US.

Most women of color acquire HIV infection from heterosexual intercourse; the Centers for Disease Control and Prevention (CDC) has reported that 80% of HIV acquisition in US women is due to heterosexual contact.(9) To realize major, durable reductions in new HIV cases among women, evidence-based approaches targeting heterosexual risk are needed. While perinatal antiretroviral (ARV) treatment prevents mother to child transmission and male circumcision appears to offer protection for uninfected men from HIV acquisition, neither biomedical nor behavioral prevention methods for women have been established with known effectiveness in prevention of HIV acquisition. Lyles et al (24) reported 18 best-evidence behavioral interventions, nine of which were studied in populations of women. Most of the cited best-evidence trials in women used either behavioral endpoints or sexually transmitted infection (STI) incidence endpoints, while none of the trials conducted with women used HIV incidence as the primary endpoint.

A major limitation in domestic HIV prevention research in general has been the lack of prevention intervention studies that use HIV incidence as an endpoint. Scant HIV incidence data exist for US women, limiting the ability to design robust domestic HIV prevention trials. Remarkable prevalence data, however, have been recently collected by the CDC's National Health and Behavior Survey among heterosexuals (NHBS-HET). HRAs in 25 US cities where NHBS-HET was conducted were chosen based on poverty index data at the census tract level, as well as estimated HIV prevalence rates. Approximately 750 individuals were enrolled per site; inclusion criteria were age ≥ 18 years and reported heterosexual sex at least once in the prior 12 months. Demographic and behavioral data were collected and HIV rapid tests were performed. Preliminary results indicate an average overall HIV prevalence among the 25 cities of 2.63%, with a range of 0.47-8.99%.(14)

In New York City, preliminary results from NHBS-HET indicate an HIV prevalence among women of 9.2% versus 7.6% in men.(4) Serologic Testing Algorithm for Recent HIV Seroconversions (STARHS) assays indicated that 20% of seropositive individuals likely acquired their infection in the 6-month period before study entry.(6) NHBS-HET in New York City focused on specific communities characterized by known high HIV prevalence: Harlem, South Bronx and Central Brooklyn. These data are consistent with the concentrated nature of the HIV epidemic in the US; distinct "hot-spots" of infection or HRAs with high rates of ongoing HIV transmission. HIV

¹ As of 2006 based on the 33 states with confidential, name-based HIV reporting.

incidence rates in these areas may be of sufficient magnitude to support the feasibility of conducting HIV prevention trials with HIV incidence as the primary endpoint.

In addition to the absence of precise HIV incidence information among at-risk women based on rigorously conducted and appropriately powered studies, the lack of accurate laboratory methods for identification of recent HIV infections in cross-sectional studies has also hampered the development of prevention studies in US women, prompting a call for further research to develop methods for cross-sectional incidence determination.(21) The proposed vanguard study, ISIS, will address both of these critical issues. ISIS will provide an estimate of HIV incidence among women at risk of HIV acquisition in ten “hot-spot” communities and evaluate the feasibility of enrolling and following such a cohort of women. ISIS will use eligibility criteria that will focus on sexually active women from HRAs with high poverty and high HIV prevalence rates, similar to the strategy used by the NHBS-HET study described above, thereby targeting those populations of US women most at-risk for HIV acquisition.

Secondly, ISIS will use state-of-the-art laboratory methods to evaluate and optimize laboratory techniques for identification of recent HIV infections, information that is needed for any large-scale cross-sectional HIV intervention study in women or in men. ISIS will estimate HIV incidence by using both laboratory assays to identify recent infection and a traditional cohort approach (HIV acquisition during a six- to twelve-month period). Women who meet the inclusion criteria and consent to participate will be enrolled. Enrolled women will include those who are HIV seronegative at screening, as well as a minority (estimated 5%) who are HIV seropositive at screening without a reported history of past HIV diagnosis. The estimate of HIV incidence will include women enrolled in the study who fall into two categories: (1) women with recent HIV infection identified by antibody-based assays and (2) women who acquire HIV infection between the enrollment and follow-up visits.

In addition, ISIS will be augmented by the addition of qualitative research components for both men and women. The qualitative component in women will evaluate social, structural and other contextual factors likely to affect women’s sexual and other risk-related decision-making and also assess women’s preferred recruitment and retention strategies for future studies. For men, the purpose of the qualitative component is to explore barriers and facilitators to HIV counseling and testing, in order to inform a future HIV testing community intervention.

Findings from ISIS will inform the design and implementation of a subsequent randomized HIV prevention trial in women in the US (see Section 1.2.4) and will contribute to the ability to perform cross-sectional measures of incidence in domestic as well as international studies.

1.2 Rationale

1.2.1 HIV Prevalence and HIV Incidence in US Women

Overall HIV prevalence rates among US women are low, with an estimate of 0.14% among women ages 18-39 years.(29) HIV prevalence rates in the US vary considerably, however, by race/ethnicity and by geographic region. As mentioned above, 80% of HIV/AIDS cases in women occur in Black and Hispanic women,(1) even though Black and Hispanic women constitute only 12% and 13% of

the US female population, respectively.(40) Black women have an AIDS rate three times higher than Hispanic women and 23 times higher than white US women.(1) In addition to racial disparity, the geographic disparity in prevalence rates is striking. Recent literature has demonstrated that HIV/AIDS rates are much higher in the southeastern and northeastern United States than in either the western or Midwestern US.(15) Additionally, striking differences in HIV prevalence have been observed within a relatively small geographic area. For example, the overall HIV prevalence for all women in the state of New Jersey is 264/100,000. However, Black women in Newark, New Jersey have an HIV prevalence roughly ten-fold higher.(3) To address geographic variation, some public health departments are using geomapping techniques to identify individuals at high risk of HIV acquisition. This type of information is critical for targeting HIV prevention trials, as well as HIV prevention interventions.

There are few published studies which characterize HIV incidence rates among women, especially women of color. The advent of detuned assays (e.g., Vironostika-LS and BED) to estimate rates of recent infections, however, has facilitated these incidence estimates. For example, HIV seroincidence rates among women in New York City tested in public settings in 2001 were estimated at 0.16 overall, with higher rates among Black women (0.31), women age 40-44 (0.55) and among women in correctional facilities (1.10).(31) Similar rates were recently reported among Black women in Texas (0.64) and Louisiana (0.41).(23) Using back-calculation modeling, Rosenberg and Biggar reported that while HIV incidence was declining in white men aged 20 to 25 years, it was increasing in women overall in the same age group.(35)

Data from the New York City Department of Health and Mental Hygiene further indicates that the rate of recent HIV infections in women is higher than previously appreciated. STARHS analysis of blood samples from seropositive individuals who were HIV tested through the New York City Department of Health Public Health Laboratory (e.g., all municipal hospitals and municipal sexually transmitted disease (STD) clinics) in 2005-2006 found that 28% of African American and 41% of Hispanic HIV seropositive women under age 30 had evidence of recent infections (i.e., within the prior 6 months). In the same study, 31% of seropositive Black men who have sex with men (MSM) under age 30 years were infected within the prior 6 months, a strikingly similar proportion.(39) Furthermore, preliminary New York City data from NHBS-HET, described above, also used STARHS, with results indicating approximately 20% of all infections (in men and women) were recent.(6)

ISIS proposes to focus recruitment efforts on women residing in defined high-risk communities. The importance of reaching the appropriate target population of at-risk women was highlighted by the findings from the STEP trial, a placebo-controlled double-blind HIV vaccine trial conducted at sites in the North, Central, and South America and Australia that was recently halted. The STEP trial enrolled 1,150 women (~50% of whom resided in the US or Puerto Rico).(25) However, only one woman became HIV infected during the follow-up period before the study was stopped. Since other epidemiologic studies clearly indicate that African American and Hispanic women in the US are acquiring HIV infection (see above), it is logical to conclude that the women at highest risk were either not accessed and offered enrollment in the study or were not interested in participating in the STEP trial. The novel approach to be taken by ISIS holds promise of reaching at-risk women by targeting enrollment of women from high-risk geographic areas defined by poverty index and HIV prevalence, and then utilizing specific criteria for identifying women within those communities who are at the highest risk of HIV acquisition. These criteria relate not only to the characteristics of the women themselves but also take into account the characteristics of their partners.

Building on previous data, such as NHBS-HET, ISIS will identify HIV “hot spot” HRAs and enroll women believed to be at high risk of HIV acquisition residing in those communities, an approach that has not been utilized in any study to date in the US. ISIS will employ a strategy similar to that used by NHBS-HET to recruit women at risk for HIV acquisition. However, in contrast to NHBS-HET which was cross sectional in design and assessed HIV incidence in few locations, ISIS will use cohort follow-up as well as state-of-the-art laboratory methods to estimate HIV incidence at all study sites.

Additionally, ISIS inclusion criteria will address both partner and individual woman characteristics, such as incarceration and recent diagnosis of sexually transmitted infection (STI), in an effort to enroll a cohort that may be at greater HIV acquisition risk than that enrolled in NHBS-HET.

1.2.2 ISIS Behavioral Components

Behavioral interventions to reduce HIV risk have shown effectiveness among heterosexual women.(24) However, there is growing recognition that structural and other contextual factors prevent many women from being able to respond to such interventions.(32) These include substance use and domestic violence,(5) housing,(42) sex partner concurrency exacerbated by male incarceration,(17) and poverty.(16) There may be ways to assist women in negotiating some of these structural and contextual barriers beyond offering referrals for services. ISIS will conduct qualitative studies with women in a subset of study sites to address such factors. Semi-structured interviews will be conducted in a subset of participants for purposes of identifying social, structural and other contextual factors likely to affect women’s sexual and other risk-related decision-making. Focus-group brain-storming will discuss barriers to HIV prevention as well as the feasibility and acceptability of potential evidence-based interventions for purposes of informing future HIV prevention trials in at-risk women. Preferred characteristics of intervention activities (e.g., small-group versus one-on-one) will also be elicited. Focus groups will also discuss strategies to optimize recruitment and retention of at-risk women in future trials.

The qualitative studies with men have been designed to inform future HIV prevention efforts that will tentatively involve men in the communities. One potential plan is to encourage HIV testing among men using social marketing, with the recognition that those found to be positive are likely to reduce their sexual risk behavior (27) and, if eligible for HAART, will have lower viral load and thus lower infectivity.(12) It is hypothesized that the behavioral interventions for women combined with HIV counseling and testing of community men will create synergy and reduce HIV incidence in intervention communities more than either approach alone. During ISIS, FGs consisting of men residing in HRAs will convene to identify barriers and facilitators to HIV testing, in an effort to inform a future trial that seeks to incorporate a community-wide HIV counseling and testing initiative.

1.2.3 ISIS Laboratory Studies

There are three well-recognized approaches for estimating HIV incidence: 1) cohort studies, 2) mathematical modeling, and 3) biomarker methods. Cohort studies enroll a well-defined cohort of at-risk, uninfected individuals who are then followed over time and serially tested for presence of HIV antibody. The advantage of cohort studies is that they provide a direct measure of HIV incidence. Disadvantages of cohort studies include the cost and time required to obtain a result. In addition, individuals who are willing to participate in a study that requires long-term follow-up may

not be representative of the broader community. Mathematical modeling is the least direct method of determining incidence and relies on analysis of serial cross-sectional HIV prevalence data.

Biomarker-based methods of HIV incidence determination use laboratory assays to detect signs of recent infection. The major advantage of biomarker-based methods is that they can estimate HIV incidence by testing blood samples from a single point in time, thereby avoiding the cost and time of a prospectively followed cohort. Careful consideration must be given to possible ascertainment bias when incidence is estimated from a cross-sectional survey as individuals may agree to be tested because of recent exposure. This could inflate the estimated incidence rate.(13) A major obstacle to this approach, however, is the lack of a reliable method to identify recent HIV infections in the laboratory. Several assays have been developed for this purpose, but international data suggest that no single assay can reliably distinguish between individuals with recent vs. chronic HIV infection. Table 1 lists some of the assays that have been used to identify recent HIV infections. Some are commercially available, or are “home-brew” modifications of commercial HIV diagnostic assays. None is Food and Drug Administration cleared (FDA-cleared) for HIV incidence testing.

Table 1. Assays for Identification of Recent HIV Infection

Assay type	Method	Source
BED	Antibody capture assay; measures the portion of antibody that is HIV-specific	Calypte BioMedical
Affinity - Avidity	Measures the maturation of the anti-HIV antibody response.	Modification of Ortho anti HIV-&2 VITROS Eci, BioRad ELISA, AxSYM HIV1/2gO test, or Abbott HIV Ag/Ab
Ab titer	Measures the titer of anti-HIV antibody	Homebrew (STARHS - no longer available)
Isotype determination	Measures the amount of anti-p24 IgG3	Homebrew
V3 IDE	Measures the amount of antibody directed against the HIV V3 region	Homebrew
Detuned rapid test	Compares the ability of antibody to detect HIV antigen in a standard vs. less-sensitive assay format	Modification of Determine HIV-1/2, OraQuick HIV-1/2, or SeroStrip HIV-1/2

While several earlier studies showed promise for using these assays in HIV incidence determination, it is now clear that a variety of factors may lead to misclassification of individuals as having recent HIV infection. Individuals may be misclassified if they have advanced HIV disease or AIDS, are receiving ARV treatment, or are long-term non-progressors. In theory, the reliability of HIV incidence assays may also be influenced by host factors that affect the HIV immune response, or by viral factors, such as HIV subtype. In some cases, particularly when the clinical history of tested participants is unknown, incidence determinations may be improved by considering other laboratory information, such as HIV viral load, CD4 cell count, or the presence of detectable ARV drugs in a test sample.

It is becoming clear that cross-sectional HIV incidence studies will not be able to rely on a single laboratory measurement. Instead, data from several assays will be needed for accurate identification

of individuals with recent HIV infection. Development of laboratory algorithms for HIV incidence determination is a top priority at the HPTN Network Laboratory (NL). Sample sets from well-characterized study cohorts have been identified that include individuals with known recent HIV infection (e.g. from longitudinal studies), as well as individuals with chronic HIV infection of known duration. These samples are being analyzed using the BED assay (see below), an HIV avidity assay, and a variety of other laboratory methods to obtain the data needed to evaluate different laboratory approaches for incidence determination. Investigators from the HPTN Statistical and Data Management Center (SDMC) are working with the HPTN NL to analyze data from these assays to determine which assays are most informative, and how to combine data from different assays to optimize HIV incidence determination.

ISIS will use the BED assay and other laboratory methods to characterize samples from study participants. Other information, such as CD4 cell count, will be obtained on all study participants who have a reactive HIV rapid test result. These data will be analyzed using the best available laboratory algorithms for determination of HIV incidence. While ISIS will obtain laboratory data using a variety of assays, the central assay that will be used to estimate HIV incidence is the BED assay.(7) This assay (named because it was developed using clades B, E, and D) uses an enzyme linked immunosorbent assay (ELISA) method to measure the proportion of total IgG that is HIV-specific. Incidence estimates require determination of a window period (the time it takes for the portion of antibody that is HIV-specific to increase above a defined cut-off). The window period is determined in advance by analyzing sample panels from HIV infected individuals with known duration of infection. Most studies suggest that a window period of 5 to 6 months is appropriate for the BED assay, but this may vary from cohort to cohort.

The assays described above, including the BED assay, were developed and optimized for subtype B HIV-1. Though there are limited published studies on BED use in North American patients, performance of the BED assay in estimating HIV incidence was evaluated in the AIDSVAX B/B (28) vaccine trial, a trial conducted in North America and Europe. The BED assay was performed every 6 months on specimens obtained from the 3-year longitudinal cohort. There was excellent agreement between the observed and BED-estimated incidence for all intervals with cumulative annualized incidence observed in the cohort of 3.10 per 100 person-years (95% CI 2.57-3.63) compared with the corresponding BED-estimated incidence of 2.91 (2.30-3.53).(28) In a second study, Priddy et al (34) reported excellent agreement between Vironostika-LS and BED in samples procured in Atlanta, Georgia. However, in the international setting, substantial errors in incidence estimates have been seen when BED has been used to analyze non-B HIV-1. BED has overestimated incidence rates by 2-3 fold (20) and by as much as 6-fold (36) in some international settings with high prevalence rates. These overestimates have led to recent recommendations (2) against the use of BED for “routine surveillance applications, neither for absolute incidence estimates, nor for monitoring trends.” Because ISIS will be performed in the US, where the majority of women are likely to have subtype B HIV infection, subtype-related performance problems should be minimal. In ISIS, results obtained with the BED assay will be analyzed in the context of clinical information and data obtained from other laboratory assessments (e.g. CD4 cell count, avidity testing), thereby improving accuracy of BED-based incidence estimates. In addition, use of a cohort design allows ISIS to validate BED results obtained from study participants at enrollment by repeating BED testing at subsequent follow-up visits. This approach of combining use of BED with other assays, clinical information, and longitudinal assessments should maximize the accuracy of incidence estimates in ISIS. Furthermore, the data obtained will be invaluable for validating and optimizing laboratory algorithms for HIV incidence determination. This information

will be essential for the design of any subsequent prevention trial in US women, and for the design of future cross-sectional HIV trials utilizing an HIV incidence endpoint.

1.2.4 Future HIV Prevention Trials

Findings from ISIS will determine whether it is feasible to enroll and follow a cohort of women to power a trial with HIV incidence as an endpoint, and will characterize risk behaviors among participants in order to assess the applicability of interventions in which proof-of-concept data already exists. For example, the evidence-based Project SAFE intervention,(37) a small-group, motivational and skill building intervention, has been shown to be effective in reducing risky sexual behaviors and STIs among women, particularly substance-using women and women of color. Should ISIS prove that it is feasible to enroll and follow a cohort of women with a sufficient HIV incidence to power a trial on HIV incidence, and should behavioral information collected in ISIS indicate Project SAFE to be an appropriate intervention for at-risk women, then a subsequent trial may randomize women to receive Project SAFE or a control intervention with a primary endpoint of HIV incidence.

It is likely that such a future large randomized intervention trial will utilize a factorial design, adding community HIV counseling and testing campaigns for men from the target communities. Evidence for the effectiveness of such campaigns in increasing uptake of HIV testing services has been evaluated in a Cochrane review.(41) In addition, it is well-established that receiving an HIV diagnosis is associated with profound reductions in risk behavior.(19) Focus groups of men from some of the HRAs will be conducted during the ISIS trial and will inform the design of the subsequent community testing and counseling intervention.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objective of this study is to estimate the overall HIV-1 incidence rate among 2,000 women in the US from defined geographic areas with high HIV prevalence and poverty.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate laboratory assays for HIV-1 incidence determination
- Estimate recruitment and retention rates
- Describe sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk of HIV acquisition
- Assess women's preferred recruitment and retention strategies for future studies
- Describe social, structural and contextual factors in a subgroup of female participants to inform future intervention studies
- Estimate HIV-1 prevalence rate among women who have not reported previously testing HIV positive
- Explore facilitators and barriers to HIV testing among men residing in HRAs to inform future intervention studies

2.3 Study Design

The study is a multi-site, prospective observational cohort with a retrospective component that will enroll 2,000 women across 10 communities (200 women per community). ISIS will estimate HIV incidence by combining laboratory assessments from cross-sectional surveys with cohort follow-up over a six- to twelve-month period.

The study includes distinct qualitative components for women and men that will take place in four of the ten ISIS communities (Table 2). For women, approximately 240 participants that are enrolled in the ISIS cohort will take part in either a semi-structured interview or a FG (participants are not eligible to participate in both); approximately 120 women (20-30 per community, four communities) will take part in the individual interviews and approximately 120 women will take part in FGs (2-6 FGs in each of four communities). Focus groups will also be conducted with approximately 120 men recruited from HRA venues (2-6 FGs in each of four communities).

Table 2: ISIS Qualitative Components

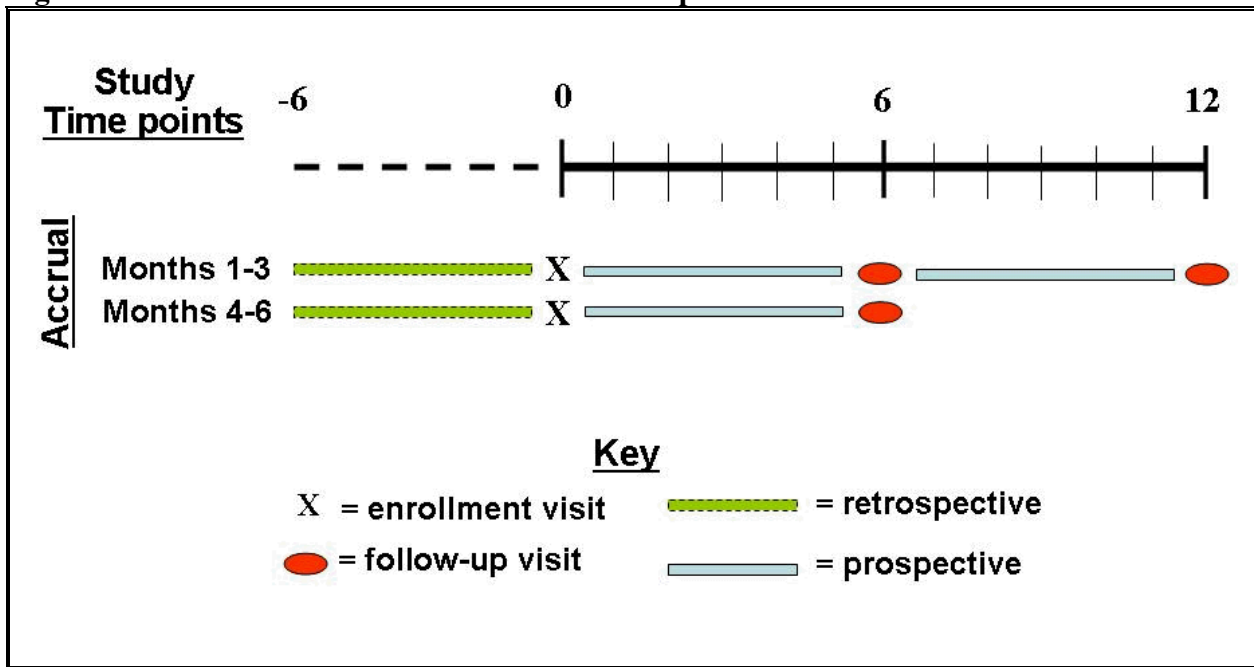
Participants	Methods	Number (per each of 4 sites)
Enrolled Women At-Risk	Semi-structured behavioral interview	~20-30 per site (for a total of ~80 to 120 interviews, depending on rate of saturation)
	Focus Group discussion (8-10 participants each)	~2-3, Black women ~2-3, Hispanic women (for a total of 2-6 FG per site depending on demographics of community, 8-24 FGs total)
Men at ISIS Venues	Focus Group discussion (10-12 participants each)	~2-3, Black men ~2-3, Hispanic men (for a total of 2-6 FG per site depending on demographics of community, 8-24 FGs total)

2.3.1 Study Visits and Sample Collection (Cohort Component, Women only)

Two hundred women will be enrolled over a six-month period in each community. Women enrolled in months 1–3 will be followed for 12 months (monthly phone contacts, in-person follow-up visits at 6 and 12 months post-enrollment) and women enrolled in months 4–6 will be followed for 6 months (monthly phone contacts, in-person follow-up visit at 6 months post-enrollment) (see Figure 1). As a result we anticipate that the duration of study enrollment and follow-up will be 15 months. However, if accrual is slower than anticipated (i.e., <50% of cohort enrolled by month 3), we will extend to 12 months the follow-up duration for individuals enrolled in month 4 and, if needed, in month 5. Please see Section 3.3 for additional information on recruitment. This design will provide HIV incidence and study retention information up through 12 months of follow-up, approximating

the time period of a future intervention study. The total duration for study activities, including start-up and close-out, will be 24 months.

Figure 1. Illustration of Enrollment and Follow-up in HPTN 064



Women will be recruited directly from venues in study HRAs. Each study site will tailor recruitment and retention strategies to local circumstances and strategies using the recruitment guidelines outlined in Section 3.3 and the Study Specific Procedures Manual (SSP) in order to maximize enrollment (to reach the women at highest risk) and retention rates. Sites will be expected to work closely with community-based organizations or other appropriate groups with ties to the women in study communities. Women who are interested in the study will undergo prescreening activities. The prescreening process involves administering a behavioral screener to assess study eligibility, to include, knowledge of HIV status and willingness to get an HIV test, residence, age, as well as sexual behavior, alcohol dependence and drug use, incarceration and STI history, as well as partner characteristics. If prescreening indicates that the woman may be eligible for the study, she will be invited to undergo informed consent for combined screening and enrollment activities. Alternatively, sites may choose to consent participants verbally for screening and obtain written consent only for enrollment (see Section 8). All study visits may take place at a location identified by study staff which assures adequate privacy and confidentiality, such as, the venue, the study clinical site, mobile vans or another suitable public area.

At the screening visit, each woman will complete a set of questions to assess eligibility and provide locator information. Enrollment visit procedures will begin once the eligibility screener has been administered. Participants will complete a questionnaire including topics such as sociodemographics, sexual risk behaviors drug and alcohol use, mental health, domestic violence, interest in future HIV prevention trials and partner characteristics. A brief targeted medical history will be performed to collect information on prior HIV testing, prior or current use of ARV medications, and access to health care. Locator information will also be obtained. Participants will then undergo HIV rapid testing in the context of pre-and post-test counseling. For all participants, blood samples will be collected for clinical and investigational testing related to the estimation of

HIV incidence. Participants who have a reactive HIV rapid test result will be tested for CD4 cell count and confirmatory Western blot assays (WB) will be performed according to the criteria outlined in Section 4.6. Participants with an indeterminate or positive WB will return in 1-2 weeks for further confirmatory testing with a repeat WB. Women who meet the inclusion criteria specified in Section 3.1, provide informed consent and who undergo the blood draw will be considered enrolled. Women at select sites will also be asked to consent to participate in the qualitative component of the study as part of the enrollment process. However, women who refuse to participate in the qualitative component will not be excluded from the cohort.

At each study follow-up study visit, participants will complete a behavioral questionnaire assessing the topics outlined above. Blood samples will be collected from all participants for testing related to the estimation of HIV incidence. For all participants who did not have confirmed HIV infection at enrollment, HIV rapid testing will take place in the context of pre- and post-test counseling. Participants who have a reactive HIV rapid test result will be tested for CD4 cell count and WB. Participants with an indeterminate or positive WB will return in 1-2 weeks for further confirmatory testing with a repeat WB.

In order to enhance retention, permission will be obtained in advance to contact participants through a number of methods, to include monthly phone contacts, mail reminders and /or “door-knocking” between study visits. A dedicated toll-free line will be set-up at each site so that participants may contact study staff regardless of location or phone access.

It is expected that approximately 1,900 women will be HIV seronegative at study entry, and approximately 100 women will be HIV seropositive without past history (at study entry) of HIV diagnosis. Laboratory results from the enrollment, 6- and 12-month samples of each seropositive woman will be evaluated using current best algorithms for determination of recent HIV incidence. Participants who have BED and other laboratory results consistent with recent HIV infection will be considered “incident by BED”. Participants with HIV seroconversion during follow-up (i.e. who have a negative or indeterminate WB, with a positive WB 6 or 12 months later) will also be classified as having recent HIV infection (“incident by follow-up”). The HIV status of other participants will be assessed, based on the results of WB testing, CD4 cell count, BED, and other assays. Samples collected at each study visit will be stored for future testing (See Section 9).

All women with confirmed HIV infection will be rapidly referred for HIV care, treatment and support. Study CRSs will be encouraged to have memoranda of agreement with multiple organizations rendering care and services, so that women will be able to choose from multiple care and treatment organizations and will not be limited to receiving care from the home institution of the CRS. Should a participant desire care outside of their community, every effort will be made to assure connection to quality care.

2.3.2 Qualitative Components (Men and Women)

ISIS will include distinctive qualitative components for men and women that will be conducted in two urban and two non-urban ISIS communities. Each community will conduct approximately 30 semi-structured interviews and two to six FGs with women enrolled in ISIS. Women who provide consent to participate in the qualitative component of the study at enrollment will be invited to participate in either a semi-structured interview or FG using the qualitative sampling plan described below. Participants may not take part in both the interview and the FG (they may only agree to

participate in the component to which they are selected). For the male FGs, men will be recruited directly from venues identified through ISIS.

Semi-structured, recorded interviews with women will be conducted with approximately 30 women in each of four communities (2 urban and 2 non-urban) to identify social, structural, and contextual factors likely to affect women's HIV-related decision-making. Every second woman enrolled in the cohort will be invited to participate in an individual interview. Topics covered in the interview will include economic hardship, which may be associated with sex exchange and other risky sexual or drug use behaviors including alcohol use, caring for and educating children, reasons for tolerating concurrency and ways to discourage it, and a number of community-level factors including community roles, women's use of services, community and domestic violence, housing availability and other similar issues. Interviews will ideally be conducted within 45 days of study enrollment and may take place at a location identified by study staff that assures adequate privacy and confidentiality, such as, the study clinical site, a mobile, community-based organizations or another appropriate public area. All interviews will be recorded and transcribed by qualified personnel and identifying information removed. Interviewers should be matched to interviewees by ethnicity and gender when possible.

Focus groups with women will take place once selection for the individual interviews has been completed at the site. Women will be sampled in consecutive blocks of ten in order to facilitate timely implementation of each FG. Focus groups will explore ways to enhance recruitment for the intervention trial. Incentives, barriers and facilitators to enrollment and retention (e.g., child care; transportation), and convenient times and locations for intervention participation will be discussed. In order to inform eventual participation in a group-level intervention, we will compare women who refuse participation in a FG to those who agree, to ascertain whether systematic bias is present. Focus groups will ideally be conducted within 45 days of the date of enrollment of the final participant in the sampling block and may take place at locations identified by study staff that assures adequate privacy and confidentiality and have the facilities to house up to ten participants, such as the CRS or a local community organization. All FGs will be recorded and transcribed by qualified personnel and identifying information removed. Focus group moderators should be matched to participants by ethnicity and gender when possible.

Male focus group participants will be enrolled through venue-based strategies during the enrollment period for women. Male FG participants will be recruited from a subset of venues that are identified for ISIS participants; these venues must be attended by enough men to allow staff to recruit men for FGs. Ten to twelve men will be recruited per FG using the sampling strategy outlined in the SSP. Men who are interested in the FGs will undergo prescreening activities. If prescreening indicates that the man may be eligible for the study, he will be invited to undergo informed consent for screening and enrollment. For men who agree to participate, informed consent will be obtained and locator information collected. Alternatively, sites may choose to consent participants verbally for screening and obtain written consent only for enrollment (see Section 8). Once informed consent has been obtained, a brief questionnaire including demographics, place of residence, age, as well as sexual behavior and drug use in the last 6 months, incarceration and STI history, as well as partner characteristics and locator information will be collected. Men who meet the study eligibility criteria outlined in Section 3.1, provide informed consent, and participate in the focus group will be considered enrolled. Focus groups will explore barriers and facilitators to male-mediated factors of HIV prevention, such as male perceptions of community-level HIV testing campaigns. Data collected from the FGs will be used to inform future HIV prevention trials which

may prevent HIV infection among women by engaging heterosexual men in community-level HIV testing and connection to care campaigns. When possible, FGs will occur either at or near the recruitment venue. If this is not possible, FGs will ideally be conducted within 45 days of enrollment of the final participant in the sampling block and may take place at locations identified by study staff that assures adequate privacy and confidentiality and have the facilities to house up to ten participants, such as the CRS or a local community organization. All FGs will be recorded and transcribed by qualified personnel and identifying information removed. Focus group moderators should be ethnically matched to participants when possible.

3 STUDY POPULATION

3.1 Inclusion Criteria

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

- Self identify as a woman.
- 18 to 44 years of age, inclusive on the date of screening.
- Willing to receive HIV test results.
- Resides in an HRA.
- Unprotected (e.g. without a condom) vaginal and/or anal sex with a man during the prior 6 months.
- **AND self-reports** at least one of the following criteria:
 - Illicit injected and/or noninjected drug use (e.g. heroin, cocaine, crack cocaine, methamphetamine, and/or prescription drugs used outside the oversight of a medical professional) within 6 months. Participants whose only illicit drug use is marijuana do not meet the illicit drug use eligibility criteria.
 - Alcohol dependence (within 6 months).*
 - Binge drinking defined as four or more drinks at one time (e.g. during the morning, afternoon or evening) within 6 months.
 - Incarceration within 5 years (jail and/or prison).
 - STI (gonorrhea, Chlamydia, trichomonas, or syphilis) within 6 months.
 - Exchange of sex for commodities (e.g. drugs, money, shelter) within 6 months.
 - Male sexual partner within 6 months with any history of self-reported use of illicit injected or noninjected drugs (e.g. heroin, cocaine, crack cocaine, methamphetamine, and/or prescription drugs used outside the oversight of a medical professional) within 6 months (male partners whose only illicit drug use is marijuana do not meet the illicit drug use eligibility criteria), incarceration (within 5 years), STIs (within 6 months), HIV seropositive diagnosis, or history of binge drinking defined as 5 or more drinks at one time (within 6 months) and/or alcohol dependence* (within 6 months).

*Please see the SSP for the protocol definition of alcohol dependence.

NOTE: Women will be selected for participation in qualitative component per Section 2.3.2

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

- Self identify as a man.
- 18 years of age or older on the date of screening.
- Resides in an HRA.
- Unprotected vaginal and/or anal sex with a woman during the prior 6 months.
- **AND self-reports at least one** of the following criteria:
 - Illicit injected and/or noninjected drug use (e.g. heroin, cocaine, crack cocaine, methamphetamine, and/or prescription drugs used outside the oversight of a medical professional) within 6 months (Participants whose only illicit drug use is marijuana do not meet the drug use eligibility criteria for this specific bullet.).
 - Alcohol dependence (within 6 months).*
 - Binge drinking defined as five or more drinks at one time (e.g. during the morning, afternoon or evening) within 6 months.
 - Incarceration (within 5 years, including jail and/or prison).
 - STI (gonorrhea, Chlamydia, trichomonas, or syphilis) within 6 months.
 - Exchange of sex for commodities (e.g. drugs, money, shelter) within 6 months.
 - HIV positive serostatus.

* Please see the SSP for the protocol definition of alcohol dependence.

3.2 Exclusion Criteria

Women who report **any** of the following criteria are **not eligible** for this study:

- History of prior positive HIV test.
- Planning on moving out of state within the study follow-up period or traveling out of state for more than 2 consecutive months during the study follow-up period.
- Current enrollment in an HIV prevention trial.
- Current or past participation in an HIV vaccine trial.
- Any condition that, in the opinion of the study staff, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Men who report **any** of the following criteria are **not eligible** for this study:

- Any condition that, in the opinion of the study staff, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

3.3 Recruitment Process

Each CRS will be responsible for enrollment of 200 women per community. Each CRS may be responsible for one to three communities (see Section 3.7). Recruitment methods used to enroll this cohort of women will be similar to recruitment methods anticipated for large scale trials. Residents of HRAs will be recruited using venue-based techniques.

Venue based, time-space sampling (VBS), will be conducted in order to ensure the resulting sample is replicable and inclusive of women at high risk for HIV acquisition. VBS is a cross-sectional

survey of persons who attend venues within locally defined geographic areas. Survey methods are based on an application of time-space sampling that has been proven successful in obtaining large and diverse samples of MSM.(26;30;38) VBS was piloted for NHBS among heterosexuals at risk in 2006-2007.(22)

There are three activities in VBS. The first two activities are “preparatory steps” intended to determine the suitability of venues as study recruitment sites. First, study personnel construct an initial “universe” of venues and identify potential sampling and recruitment barriers. In the second activity, staff will use the identified universe to construct monthly sampling frames of venues and venue-specific-day-time periods (VDTs) that are expected to produce sufficient eligible women. The third activity consists of actual study recruitment, in which women are recruited at venues and day-time periods that are randomly sampled from constructed frames.

3.3.1 Determination of Sampling Universe and Frames

Venue identification activities take place 2-3 months prior to the recruitment period. The initial sampling “universe” – the list of all venues that exist in the HRA – is comprised of venues frequented by women who live in an HRA. Study sites will identify areas, locations, or buildings where women most likely to meet ISIS eligibility criteria can be approached and recruited to participate in the study. A venue could be retail businesses (e.g., Laundromats, beauty salons, grocery and liquor stores), bars, dance clubs, cafes and restaurants, health clubs, social organizations, sex clubs and sex strolls, high-traffic street locations, parks, beaches, and special events such as festivals or raves. Initial venue identification will be liberal; that is, few venues will be excluded at this point.

Once this list (the “universe”) of potential venues is created, project staff will determine the suitability of each venue (or category of venues) for the purposes of ISIS. A venue may not be suitable for sampling if any of the following are true:

- Men but few women frequent it.
- Not enough women meeting the eligibility criteria are likely to attend the venue.
- It would be impossible logistically to recruit, interview and conduct HIV testing.
- Venue owner(s) refuse to allow the project staff access to venue attendees.

Project staff will assess venue suitability by observing venues, informally talking to residents of the community and community leaders, and conducting brief interviews with women and other key stakeholders attending venues to assess how many would meet the eligibility criteria. Venues that are deemed suitable will be placed on the sampling “frame”. Also during this phase, day-time periods when eligible women are likely to attend each venue will be identified. Day-time periods are 4-hour time blocks when women meeting ISIS eligibility criteria are most likely to attend the venues. Please note that during this phase, no study specific information will be collected from women. Interactions with women will be used explicitly to determine the appropriateness of the venue as an ISIS recruitment site.

Once the list of suitable venues, and their associated VDTs, is created (called the “sampling frame”), project staff will randomly select VDTs from the frame each month.

3.3.2 Recruitment at Venues

Recruitment activities will be held at the venues and their associated day time periods throughout the month. A systematic process is used at each recruitment event to approach potential participants for the study prescreening activities is included in the SSP. For those who meet eligibility criteria and consent to participate in the study, study activities may take place at location identified by staff that assures adequate privacy and confidentiality, and may be concurrent at the venue, at a space or field site near to the venue, or in a mobile unit or van equipped to conduct the necessary tests. Participants who are screened but do not meet the eligibility criteria for ISIS will not be enrolled. Other day appointments (ODAs) will be allowed in cases where women are eligible and interested in participating in the study, but are unavailable at the time of the screening.

ISIS will use recruitment standards that include, but are not limited to: (1) hire and train a Recruitment/Retention Coordinator who has worked in this capacity on other projects with the Principal Investigator; (2) compensate participants for their time and transportation in the study; (3) describe the follow-up compensation to maintain participants' interest and; (4) ensure confidentiality of participants' data and identifying information (i.e. all data will be maintained in a locked cabinet that is limited to access by key staff only.)

3.4 Co-Enrollment Guidelines

Women participating in another HIV prevention trial will not be eligible for enrollment in ISIS. In addition, co-enrollment in another HIV prevention study during ISIS follow-up will not be permitted. Women who have previously participated in HIV vaccine trials will not be eligible to participate in this trial, since prior vaccination may influence serologic test results.

Men participating in the FGs will have no restrictions on study co-enrollment or past prevention study participation.

3.5 Participant Retention

Participant follow-up visits may take place in a location that assures adequate privacy and confidentiality, such as a clinical site, a community-based organization or mobile van. Once a participant has enrolled in the study, the study site will make every reasonable effort to retain them for the entire study period. Every effort will be made to maintain loss to follow-up at minimum. A maximum of 10% per year loss-to-follow-up of enrolled participants during participation in ISIS is anticipated based on the rates of loss-to-follow-up from previous trials. Study enrollment and retention will be closely monitored by the site investigators, SDMC and HPTN CORE.

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

- Thorough description of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Explanation of the importance of study visits to the overall success of the study.
- Completion of extensive locator form at Screening Visit (with multiple means to contact participants and to include place of residence and important landmarks, if use of postal address is not feasible) to be updated at every study contact.

- Ensuring availability of childcare and/or transportation services.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up of missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Use of a dedicated, toll-free study line for participants to contact study staff.
- Obtain advance permission using the Enrollment Consent to contact participants that are incarcerated during the study by mail, phone, and if possible, in person.
- Regular review of data on scheduled contacts/visits as well as missed contacts/visits to ensure prompt reconnection to participants.
- Community education to increase awareness about HIV/AIDS and importance of prevention.
- Garnering support of community advisory boards, advocacy groups and others in support of the study.

For each participant, research staff will obtain confidential contact information. Each study site will develop its own Locator Form, and determine the best way to collect this information for its own study population. This information will be updated during each study visit (both in-person and via phone). In the event that a participant misses a scheduled appointment, clinic staff will try to establish communication with the participants through all agreed upon means relevant to specific participant (e.g., telephone, including toll-free lines, e-mail, mail contact, and home or workplace visits). The importance of maintaining phone contact and scheduled visits will be emphasized to study participants.

3.6 Participant Withdrawal

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

The clinical site will make every effort to enroll, follow, and obtain samples from all enrolled participants according to the schedule of evaluations, while recognizing that each participant may not be able to return for all visits or undergo all protocol-dictated procedures.

Every reasonable effort will be made to complete a final evaluation (see Section 4) of participants who terminate from the study prior to the end of the 6- or 12-month follow-up period, and study staff will record the reason(s) for all withdrawals from the study in participants’ study records.

3.7 Community Definition and Selection

Two hundred women will be enrolled from each of ten communities, and each CRS will conduct ISIS in one to three communities. Clinical research sites have been selected based on proven experience with the study population and surrounding community and capacity to conduct ISIS (both in terms of infrastructure and local HIV prevalence). Within the clinical sites, two urban and two non-urban sites have been selected to conduct the qualitative component based on prior

experience in the area of qualitative research. Communities have been defined and selected based on methods used by the CDC National HIV Behavioral Surveillance Survey (NHBS) and proximity to selected CRSs. The methodology is based on a combination of HIV prevalence and where a substantial proportion of the inhabitants (>25%) are living below poverty. For the purposes of ISIS, communities will be defined in urban settings as areas delineated by either zip code or census tract with HIV prevalence rates of roughly 1,000/100,000 or more and poverty rates greater than 25% in which formative assessments suggest that enrollment goals may be achieved. In non-urban settings, the HRAs will be based on an assessment of HIV prevalence at the county, census tract or zip code level. There are limited data on HIV prevalence in women in non-urban areas. Moreover, as the HIV epidemic is at an earlier phase, a low prevalence may not reflect low incidence. Nonetheless, it is anticipated that non-urban target communities would likely fulfill the HIV prevalence rate criterion of approximately 1,000/100,000 and poverty rates greater than 25%. It is important to keep in mind that this study will target women at high risk of HIV acquisition within these areas resulting in a prevalence that is higher than the prevalence in the total population. Details on the process and criteria for ISIS community selection will be included in the SSP.

4 STUDY PROCEDURES FOR FEMALE PARTICIPANTS

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

4.1 Screening/Enrollment

Prescreening activities with women will take place at venues identified by sites conducting ISIS. The purpose of the prescreening activities is to provide general information about the study to potential participants and to assess interest in screening for the study. No identifiable study data will be recorded until after written informed consent has been obtained. Participants who appear eligible and are interested in the study will be invited to consent for screening and enrollment in the study. For participants who do not meet the study eligibility criteria, the screening process may be discontinued when ineligibility is determined. Study participants will be defined as enrolled once the blood draw has been completed.

Screening Procedures

Administrative, Behavioral, and Regulatory Procedures

- Obtain verbal informed consent for screening or written consent for screening* and enrollment and, if applicable, for the qualitative study.**
- Administer eligibility screener.
- Collect locator information, if written informed consent obtained.***
- Schedule (or continue on to) enrollment, if eligible.

* See Section 8.2 and the SSP for detail on screening and enrollment informed consent procedures.

** Participants are not required to participate in the qualitative component.

*** Note: No identifiable data will be collected prior to obtaining written informed consent. If the participant has provided verbal informed consent for screening and appears eligible, obtain written informed consent for enrollment prior to collecting identifiable information.

Enrollment Procedures

Administrative, Behavioral, And Regulatory Procedures

- Obtain informed consent for enrollment (if not obtained at screening visit).
- Confirm eligibility.
- Collect/Update locator information.
- Administer behavioral questionnaire (must take place prior to risk reduction counseling).
- Review monthly contact procedures.
- Schedule the next contact or visit (after the participant has received results of the HIV rapid test).
- In sites conducting the qualitative component, for women who have been selected for the qualitative component, schedule (or conduct) interview or FG.

Clinical/Counseling Procedures

- Obtain brief and targeted medical history.
- Provide HIV pre-test and risk reduction counseling.
- Collect blood.
- Provide HIV rapid test results and post-test counseling, once available.
- For participants who have reactive HIV rapid test results, explain that they should meet with study staff in 1-2 weeks to receive results from the WB and CD4 cell count testing, and to have a repeat (confirmatory) WB sent if the first WB is indeterminate or positive (see Section 4.6).
- Refer for management of symptomatic STIs and additional services, as necessary.
- Offer condoms.

Laboratory Procedures

- FDA-cleared HIV rapid test.
- HIV WB test (only for participants with a reactive HIV rapid test result).
- CD4 cell count (only for participants with a reactive HIV rapid test result).
- Storage of plasma samples.

4.2 Follow-up Phone Contacts: All cohorts: Week 4, 8, 12, 16, 20, 24 (also Week 30, 34, 38, 42, 46, 50 for participants with 12 months of follow-up)

Administrative, Behavioral, And Regulatory Procedures

- Update locator information.
- Reinforce importance of study participation.
- Offer contact information for local resources as necessary.
- Remind of next scheduled visit.

There will be no clinical or laboratory procedures at these time points.

4.3 Week 26 Visit

This will be the 6-month follow-up visit for all participants and also considered the Exit visit only for those women who enrolled during the later phase of enrollment (e.g., during months 4 - 6). The following activities will take place:

Administrative, Behavioral, And Regulatory Procedures

- Update locator information.
- Administer behavioral questionnaire (must take place prior to risk reduction counseling).
- Review monthly phone contact procedures.
- Schedule next the next contact or visit, if applicable (after the participant has received results of HIV rapid test).
- Conduct other Exit Visit administrative procedures, as needed (e.g. case report forms (CRFs) associated with termination) for participants terminating from the study.

Clinical/Counseling Procedures

- Obtain brief and targeted medical history, if clinically indicated.
- Provide HIV pre-test and risk reduction counseling.
- Collect blood.
- Provide HIV rapid test results and post-test counseling, once available.
- For participants who have reactive HIV rapid test results, explain that they should meet with staff in 1-2 weeks to receive results from the WB and CD4 cell count testing, and to have a repeat (confirmatory) WB sent if the first WB is indeterminate or positive (see Section 4.6).
- Refer for management of symptomatic STIs and additional services, as necessary.
- Offer condoms.

Laboratory Procedures

Note: Some laboratory procedures are performed for a subset of participants; additional details are provided in Section 9.

- FDA-cleared HIV rapid test.
- HIV WB test (for participants with reactive HIV rapid test result).
- CD4 cell count (for participants with reactive HIV rapid test result).
- Storage of plasma samples.

4.4 Exit Visit for participants with 12 month follow-up (Week 52)

This will be the Exit visit for those women who enrolled during the earlier phase of enrollment (e.g., at months 1, 2 and 3). Women will not be terminated from the study until all HIV follow-up testing is completed. The following activities will take place:

Administrative, Behavioral, And Regulatory Procedures

- Update locator information.
- Administer behavioral questionnaire (must take place prior to risk reduction counseling).
- Schedule next visit for those whose HIV rapid test result at Week 52 is reactive.
- Conduct other Exit Visit administrative procedures, as needed (e.g. CRFs associated with termination) for participants terminating from the study.

Clinical/Counseling Procedures

- Obtain brief and targeted medical history, if clinically indicated.
- Provide HIV pre-test and risk reduction counseling.
- Collect blood.
- Provide HIV rapid test results and post-test counseling, once available.
- For participants who have reactive HIV rapid test results, explain that they should meet with staff in 1-2 weeks to receive results from the WB and CD4 cell count testing, and to have a repeat (confirmatory) WB sent if the first WB is indeterminate or reactive (see Section 4.6).
- Refer for management of symptomatic STIs and additional services, as necessary.
- Offer condoms.

Laboratory Procedures

Note: Some laboratory procedures are performed for a subset of participants; details are provided in Section 9.

- FDA-cleared HIV rapid test.
- HIV WB test (for participants with reactive HIV rapid test result).
- CD4 cell count (for participants with reactive HIV rapid test result).
- Storage of plasma samples.

4.5 Interim Visit (ad hoc)

Participants with suspected HIV seroconversion will be scheduled for an interim study visit. If the study participant suspects that she may have become HIV infected, the clinic staff will follow the laboratory plan outlined for the 6-month visit. The participant will continue to be followed according to her established study visit schedule and complete the next scheduled visit for all study procedures.

The SSP will state in detail how these visits will be handled, and the type of forms that should be completed depending on the nature of the visit. All visits will be documented in the participant's study record.

4.6 Post-Test Visits For Persons Who Have a Reactive HIV Rapid Test At or After Enrollment

These visits are required for any participant with a reactive HIV rapid test result. For those participants, a WB and CD4 cell count will have been performed. The purpose of this visit is to communicate the results of WB and CD4 cell count testing and to send a confirmatory WB, if necessary (see below).

Post-test visit:

Individuals who have an indeterminate or reactive WB result will be counseled about the interpretation of the test result, will have a new sample collected and sent for repeat (confirmatory) WB testing, and will be asked to meet with study staff in 1-2 weeks for purposes of following up the confirmatory studies. They will be counseled about clinical and social services for persons who are HIV-infected and methods to reduce the likelihood of transmitting HIV to others, and will be referred to appropriate services and other studies for HIV infected persons as needed. If a woman has an indeterminate or reactive initial WB, but does not have a positive WB on repeat (confirmatory) testing, the site will contact the NL to determine whether additional HIV testing is needed to determine the participant's HIV infection status.

4.7 Missed visit/lost-to-follow-up

Site research staff will make every effort to have participants complete follow-up study visits. Should the participant be willing, site staff will conduct the appropriate visit off-site (not in the clinic) at locations which assure adequate privacy and confidentiality. If a participant refuses any protocol-specified procedures, this should be appropriately documented in the clinic/chart notes.

For visits that are designated as in-person, per the Study Schedule of Visits and Procedures, in-person contact with participants is the preferred method of collecting study data. However, there may be rare circumstances in which telephone contact may be the only method available for collecting data. Determining that a telephone visit is necessary will be done only after all other options for scheduling the visit have been explored (e.g., earlier or later office hours, interim visits, off-site visits). All scheduling efforts will be documented in the participant's chart notes and/or contact logs.

4.8 General Procedures

Study visits may take place at a location identified by study staff which assures adequate privacy and confidentiality, such as, the venue, the study clinical site, mobile vans, or another public area.

Semi-structured interviews and FGs will be conducted by trained staff. When possible interviewers and FG moderators will be ethnically matched to participants. All interviews and FGs will be recorded and transcribed by qualified personnel. Personal identifiers will be removed from final transcripts. Focus group participants will not be asked to identify themselves within the group, but will instead be encouraged to provide a “made-up” name. Further details regarding the conduct of interviews and FGs can be found in the SSP.

Selection of items for inclusion in the behavioral survey is guided by prior research experience using measures that have shown satisfactory reliability in assessing HIV-risk factors and prevention practices among ethnic minority women and may include, but is not limited to, the following domains:

- Sociodemographic data required of US National Institutes of Health (NIH) studies and needed to describe the characteristics of the participants and their sex partners, including age, living situation, income, race and ethnicity, education, and length of sexual relationships. More constant variables such as race, age and education will be collected at baseline only.
- Sexual behavior, including frequency of vaginal and anal intercourse, condom use characterized as the proportion of condom protected vaginal and anal acts of intercourse over time (e.g., the past 90 days and 6 months) and condom use at last intercourse, number of sex partners, concurrency of sexual partners, partners’ risk status (e.g. concurrency, substance use, incarceration history) and transactional sex (e.g. exchange of sex for drugs, money, or shelter). Sexual behaviors will be assessed with a primary partner (defined as the man with whom the respondent has the committed long-term relationship) and other partners.
- Adaptations of commonly used instruments to assess various risk factors, including exposure to domestic violence, depression, alcohol dependence, and substance use.
- Social harms.
- Participant interest in HIV prevention studies, such as group interventions (e.g., Project SAFE), individual interventions (e.g., microenterprise, vaccines) and community level interventions.

Interviewers will be trained in recall-enhancing techniques, such as using calendars and visual clues to enhance accurate reporting of sexual and other sensitive behaviors.

HIV pre-test and risk reduction counseling will be provided according to each site’s state standards, at minimum.

5 STUDY PROCEDURES FOR MALE PARTICIPANTS

Screening

Prescreening activities with men will take place at venues identified by sites conducting ISIS. The purpose of the prescreening activities is to provide general information about the study to potential participants and to assess interest in screening for the study. No identifiable study data will be recorded until after written informed consent has been obtained. Participants who appear eligible and are interested in the study will be invited to consent for screening and enrollment in the study. For participants who do not meet the study eligibility criteria, the prescreening and/or screening process may be discontinued when ineligibility is determined. Men who participate in the focus group will be considered enrolled. Study procedures for male participants will follow the applicable general procedures outlined in Section 4.8.

Administrative, Behavioral, And Regulatory Procedures

- Obtain verbal informed consent for screening or written consent for screening and enrollment.*
- Collect locator information, if written consent obtained.**
- Administer eligibility screener.
- Collect demographic information.
- Schedule (or conduct) FG, if eligible.

*See Section 8.2 and the SSP for details on screening and enrollment informed consent procedures.

**Note: No identifiable data will be collected prior to obtaining written informed consent. If the participant has provided verbal informed consent for screening and appears eligible, obtain written informed consent for enrollment prior to collecting identifiable information.

Enrollment Visit

Administrative, Behavioral, And Regulatory Procedures

- Obtain informed consent for enrollment (if not obtained at screening).*
- Collect/update locator information.
- Confirm eligibility
- Administer behavioral questionnaire.
- Conduct FG.
- Offer condoms

*See Section 8.2 and the SSP for details on screening and enrollment informed consent procedures.

There are no laboratory or clinical/counseling procedures for male qualitative component participants.

6 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

As ISIS is an observational cohort study, standard adverse event (AE) reporting will not be undertaken. The study team will monitor for and track serious adverse events (SAEs) related or possibly related to study procedures and/or to participation in the study. Such events that are unanticipated will be reported to the Division of AIDS (DAIDS) HPTN Program Officer at the same time as they are reported to IRB/ECs according to pre-established written procedures, as required by 45 CFR 46. This information will not be recorded on CRFs or entered into the study database. Data on social harms will be collected at each in person follow-up visit as part of the overall assessment of participant safety.

7 STATISTICAL CONSIDERATIONS

7.1 Review Of Study Design

The primary objective of this study is to estimate the overall HIV-1 incidence rate among 2,000 women in the US from defined geographic areas with high HIV prevalence and poverty. We will not attempt to precisely characterize HIV incidence rates within each community; rather, we will show that the proposed strategy for identifying women and communities will provide a precise estimate of HIV seroincidence across all ten communities.

This study will enroll 2,000 women at risk of HIV acquisition across 10 communities, including approximately 1,900 seronegative women and approximately 100 HIV seropositive women who have no reported history of past HIV diagnosis. Women who have a reactive HIV rapid test result will have samples sent to the HPTN NL for testing that includes the BED assay. Results from these tests will be combined with clinical data to identify participants with recent HIV infection. Clinical data will likely include, but will not be limited to, the following: current/previous antiretroviral therapy, CD4 counts, etc. The multi-assay algorithm to define recent HIV infection based on cross-sectional testing will be defined and validated before it is used to generate HIV incidence estimates in ISIS. Participants will be followed for up to 12 months, with repeated collection of samples for HIV testing at 6 and 12 months. The 6- and 12-month HIV testing results will be used as follows:

Among those who are seronegative at study entry:

- To identify cases of incident HIV infection (traditional seroconversion analysis).
- To validate the “sensitivity” of the algorithm used for cross-sectional incidence testing.

Among those who are seropositive at study entry:

- To validate the “specificity” of the algorithm used for cross-sectional incidence testing.

7.2 Accrual, Follow-Up, and Sample Size

For this study, the ISIS team will identify 10 communities from which women at risk of HIV acquisition will be recruited using criteria outlined in Section 3.1. Within each community, 200 women will be enrolled. Women enrolled in the first 3 months at each site will be followed for 12 months, while women enrolled in the next 3 months at each site (months 4 – 6) will be followed for 6 months. However, if accrual is slower than anticipated (i.e., if < 50% of the cohort is enrolled by month 3), we will extend the follow-up duration to 12 months for individuals enrolled in month 4

and, if needed, in month 5. We assume that approximately 5% of the enrolled cohort will be HIV seropositive at study entry. The HIV seronegative women will be followed for seroconversion; the HIV seropositive women will be followed to help determine whether they had recent versus non-recent HIV infection at enrollment, using a multi-assay laboratory algorithm for determination of HIV incidence. This will provide a total effective follow-up period for incidence calculations of ~220 person-years per community (about 40% from the enrollment visit based on a retrospective window period of 160 days, and 60% from the prospective longitudinal follow-up). A maximum of 10% loss-to-follow-up per year is assumed, yielding a total of ~210 person-years per community for analysis. Note that the estimated window period of 160 days is based on the BED assay, which is likely to be a major component of the multi-assay HIV incidence algorithm.

Based on a recent infection window period of approximately 160 days, with a seropositivity rate of 5% and a seroincidence rate of 2%, the number of recently infected participants at enrollment is expected to be approximately 16. Assuming a similar seroincidence rate over the prospective follow-up period, and accounting for loss to follow-up, an additional 26 infections should be observed after enrollment (18 infections in months 1- 6; 8 infections in months 7-12). Overall, this should yield approximately 42 incident infections. Assuming that a multi-assay algorithm for identifying recent infections is developed and validated at the HPTN NL in the near future, it will be possible to combine the cross-sectional HIV incidence estimate from enrollment with the longitudinal incidence estimate from follow-up into a single incidence estimate. Table 3 (below) gives the width of a 95% CI for the HIV incidence rate (pooling across communities) as a function of the total number of person-years in the feasibility study, assuming an underlying incidence of 2% per year and coefficient of variation (CV) in incidence across communities of 0.0 (we will, however, use the data from this study to estimate the CV – see Section 7.3.2). Once the multi-assay algorithm for identifying recent infections is validated, then the combined cross-sectional and longitudinal data will provide 2,000 – 2,200 person-years for incidence estimation and a 95% confidence interval (CI) of ± 0.0066 or less. An incidence estimate based only on the longitudinal (follow-up) data will include 1,200 – 1,300 person-years.

Table 3. Width of 95% CI for HIV-incidence based on total person-years of data, pooled across all communities

Person-years	800	1200	1600	2000	2400
CV = 0	± 0.010	0.0085	0.0074	0.0066	0.0060
CV = 0.1	± 0.010	0.0087	0.0075	0.0067	0.0061
CV = 0.2	± 0.011	0.0091	0.0080	0.0071	0.0065

7.3 Data Analysis

The primary analysis shown below describes how HIV incidence will be estimated, both separately from the cross-sectional and longitudinal components of the study, and using both sources of data combined into an overall incidence estimate.

Secondary analyses describe how we will summarize the cohort of women, compare the cross-sectional and longitudinal incidence estimates, and estimate the community-to-community variation in HIV incidence. We also describe statistical methods to be used in validating the laboratory algorithm for identifying recent infections.

7.3.1 Primary Analyses

Data from all communities will be pooled to estimate HIV incidence. Below, we describe approaches for estimating incidence from either the cross-sectional portion of the study, or the longitudinal portion of the study. If a validated algorithm for identifying recent infections is developed (which we believe is likely) then these two estimates will be combined into a single incidence estimate. If a validated algorithm for identifying recent infections cannot be developed, then only the incidence estimate based on longitudinal follow-up will be reported.

An estimate of HIV incidence based on identification of recent infections at study entry (retrospective estimate) is given by the formula (31)

$$I_r = \frac{F_1 N_i}{N_{sn} + F_1 N_i}$$

where N_i is the number of recently infected individuals, N_{sn} is the number of HIV negative individuals in the sample and F_1 is a scaling factor to account for the window size (W) i.e. $F_1 = 365/W$. For example, for the BED assay, Parekh et al. (33) uses the value $W = 160$ days. The variance of this incidence estimate is

$$Var(I_r) \approx \frac{F_1 I_r}{N_{sn} + F_1 N_i}$$

Bootstrap procedures may also be used to evaluate the uncertainty in the estimated incidence. As noted above, an incidence estimate based on the cross-sectional component of the study will only be generated if a validated approach for identifying recent infections is developed. Complete details on the laboratory algorithm and methods to be used for estimating HIV incidence estimate will be developed jointly by the NL and SDMC, and will be described in detail in the Statistical Analysis Plan prior to the final analyses of the data from this study.

Incidence will be estimated from the follow-up data by the standard formula

$$I_f = \frac{N_f}{Y_f}$$

where N_f is the number of incident infections observed over follow-up and Y_f is the total person years of follow-up (expected to be 1,200 – 1,300 person-years). The variance of this estimate is

$$Var(I_f) = \frac{I_f}{Y_f}$$

The two incidence estimates can be pooled using a weighted average

$$I_p = v \cdot I_r + (1-v) \cdot I_f$$

where the weighting factor is $v = \text{Var}^{-1}(I_r) / (\text{Var}^{-1}(I_r) + \text{Var}^{-1}(I_f))$. The variance of this estimator is $1 / (\text{Var}^{-1}(I_r) + \text{Var}^{-1}(I_f))$ and can be used to compute CIs for I_p .

7.3.2 Secondary Analyses

Standard descriptive methods (means, medians, variances and interquartile ranges for continuous variables and proportions for dichotomous variables) will be used to characterize sexual risk behaviors, alcohol and drug use, domestic violence and depression rates at each in-person study visit. Prevalence of HIV infection at enrollment will be estimated by the proportion of women testing HIV positive at enrollment. If p is the estimated prevalence then the standard error $\sqrt{p \cdot (1-p) / N}$ quantifies the uncertainty of this estimate where $N \approx 2,000$. If the estimated prevalence is 5%, then a 95% CI for the true prevalence will have width $\pm 1.96 \cdot 0.005 = \pm 0.01$.

Each woman in the study will be assigned a time of seroconversion as follows: i) prior to the window period defined by the laboratory algorithm (i.e. chronic infection); ii) within the window period defined by the laboratory algorithm (i.e. recent infection); iii) within the first 6 months of follow-up (documented seroconversion); iv) within months 7 – 12 of follow-up (documented seroconversion); v) negative and censored at month 6 or 12, as appropriate. Individuals in groups iii – v will be included in a discrete time proportional hazards model to identify which risk factors identified at enrollment, such as concurrency, injecting drug use, depression, etc. are associated with (and predictive of) seroconversion. With only 26 projected seroconversion events during follow-up, however, we acknowledge that such analyses will have relatively low power.

These data, as well as data from other HPTN and non-HPTN studies, will be used by the NL to optimize and validate an algorithm for identifying recent infections among HIV seropositive individuals. It is likely that the BED assay (31), other laboratory assays, and clinical data will be used in such an algorithm. We define the “sensitivity” of the algorithm as the probability that the algorithm defines an individual as recently infected (within some predefined window period, W) given that he or she is in fact recently infected. The “specificity” is the probability that an individual who is not recently infected is classified as not recent. Women who seroconvert during the longitudinal follow-up portion of this study will be used to validate the sensitivity of the algorithm (i.e. a high proportion of samples from women who seroconvert during the study should be classified as recently infected). Women who are seropositive at entry and contribute 6- and/or 12-month samples in the longitudinal follow-up will be used to validate the specificity of the algorithm (i.e. the samples collected at 6 and 12 months should be classified as not recent). Sensitivity and specificity will be estimated by simple proportions and exact methods will be used to generate CIs.

Finally, these data will be used to test the hypothesis

$$H_0: I_r = I_f$$

$$H_a: I_r \neq I_f$$

Effectively, this is testing whether or not the incidence observed in cross-sectional testing at study entry is similar to the incidence observed over follow-up. Assuming 42 total incident infections and 40% of the person-years from the cross-sectional incidence estimate versus 60% of the person-years from the longitudinal incidence estimate, we will have 80% power to detect a relative incidence (I_r / I_f) of 2.4.

Another important secondary analysis of these data will be to estimate the CV of incidence among the communities. The estimated CV is given by

$$CV = \frac{\sqrt{S^2 - I_p * \sum_j \left(\frac{M}{Y_j} \right)}}{I_p}$$

where S^2 is the observed variance in incidence across the $M=10$ communities and Y_j is the number of person-years from community j .(17) This information will be important in determining sample size for future intervention trials. Hughes(18) describes how baseline data such as these can be used to help inform the design of such trials.

7.3.3 Qualitative Analysis

Data collected during interviews and FGs will be analyzed using qualitative content analysis methods. Focus groups will be characterized based on demographics, risk behaviors and geographic distribution. Data analysis by the HPTN CORE will begin during data collection by transcribing and translating each recorded interview. As soon as possible after the interviews are conducted, transcript text will be read and re-read carefully by the Protocol Co-Chairs, CORE Manager and site PIs in order to (1) become familiar with the qualitative component; (2) identify text that may be unclear; (3) point out areas in which interviewing and transcription techniques could be improved; and (4) identify recurrent themes.

Timely analysis of the data will occur at multiple points throughout data collection in order to assess saturation and to provide ISIS research staff with preliminary data to inform the development of future interventions. For example, summary information will be provided on community characteristics and the economic hardships that women in ISIS communities may face. Summaries may also include participant (both male and female) views on HIV prevention strategies and participant perceptions of potential interventions. More in-depth analysis of the data will also be carried out, as described below. Final data cleaning and analysis should be conducted within two months after the end of data collection.

Data-derived codes developed through inductive coding and retrieving will be used. Codes for retrieving text for key concepts related to the overall objectives will also be applied to the data. The Protocol Co-Chairs, CORE Manager and site PIs will determine a coding frame to be used based on the first few interviews available for analysis. Appropriate software programs will be used to organize all qualitative data and prepare it for analysis. Input from community representatives will be obtained at specific intervals throughout the data analysis process to enhance the validity of the coding and analysis process. Procedures will be put into place to check for inter- and intra-site discrepancies as well as inter- and intra-coder reliability.

Discrepancies will be noted, discussed and resolved by the Protocol co-chairs, CORE Manager, and site investigators. The resolution of such discrepancies will be amended to the existing coding framework. Once all the transcripts have been coded, textual coding reports will be produced. Data display matrices will be developed to examine each code in detail for sub-themes and patterns across the interviews, followed by data reduction tables. Based on data analysis, specific themes will be identified that tie into the secondary study objectives, and recommendations will be made on strategies to enhance understanding of ISIS communities and the recruitment, retention and prevention strategies to reduce HIV acquisition in women in future trials.

7.4 Interim Monitoring

There will be no interim efficacy analysis or stopping criteria for this study.

8 HUMAN PARTICIPANTS CONSIDERATIONS

8.1 Ethical Review

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

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents, and any subsequent modifications, will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at each study site. For sites intending to utilize verbal consent for screening, a waiver of written consent must be obtained from their Institutional Review Boards/Ethical Committees (IRBs/ECs) for this procedure.

Subsequent to initial review and approval, the responsible local IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human participants or others.

8.2 Informed Consent

Informed consent will be obtained from each study participant. No study procedures will take place prior to informed consent. Each study site is responsible for adapting study template forms for local use based on the templates in Appendices II-VIII, that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, and an optional consent for storage and future use of blood for research purposes, as well as the qualitative components of the study and other than protocol-related testing in accordance with all applicable local and US regulations. The templates in Appendices IV-VII apply only to sites participating in the qualitative component of ISIS. Sites may choose to combine consent forms (e.g. combined written informed consent for screening and enrollment), may obtain either verbal or written informed consent prior to screening, and must adapt the templates in the Appendices accordingly. However, written informed consent must be obtained prior to study enrollment. Each study site will consult with a local

community advisory board to understand concerns about the study, potential misunderstandings about the study by eligible participants, challenges in the informed consent process, and ways to strengthen the informed consent process. An additional informed consent will be developed to include Health Insurance Portability and Accountability Act (HIPAA) regulations (Appendix VIII). Sites may adapt the protocol template or preexisting site HIPAA forms. The study site is responsible for translating the template forms into Spanish if applicable, checking that the consent process and language is culturally appropriate, and verifying the accuracy of the translation by performing an independent back-translation. In addition, the consent form will be targeted to a Grade 6 reading level.

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

8.3 Risks

Venipuncture is sometimes associated with discomfort during phlebotomy, dizziness, and rarely, an infection at the site of phlebotomy. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV testing and counseling. They also may become worried or anxious while waiting for their test results. Trained counselors who meet or exceed local standards will be available to help participants deal with these feelings. Participants who learn that they have HIV infection, may experience anxiety or depression related to their test results. Sites participating in this study will each develop a listing of available resources in the community to address the potential needs of participants. This list would include resources available for intensive counseling and support, support groups, HIV care and treatment, psychological and psychiatric support, shelters among others.

All study staff will be required to have received training in Good Clinical Practices and Human Subject Protection according to DAIDS policies and procedures. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial for women at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. A Certificate of Confidentiality has been obtained by the HPTN and each participating site may register under that umbrella certificate once IRB approvals for the study have been obtained.

8.4 Benefits

Participants will receive HIV counseling and testing in this study. They will also receive counseling to decrease risk of HIV acquisition. They will also be referred for further counseling and treatment, if applicable. Participants will be offered condoms throughout the study.

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study.

8.5 Access To HIV-Related Care

8.5.1 Counseling

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

HIV pre-test, risk reduction, and post-test counseling will be provided to all potential study participants who consent to undergo screening for this study, and to all enrolled participants at each follow-up HIV testing timepoint. Participants who are confirmed to be HIV positive during the study will not undergo additional HIV testing, but will be provided risk reduction counseling at each visit. Counseling will be provided in accordance with local standards of practice at each study site. In accordance with the policies of NIH, participants must receive their HIV test results in order to take part in this study. The study site will document its counseling policies and procedures prior to study implementation for purposes of staff training and study monitoring.

8.5.2 Care For Participants Identified As HIV-Infected

This study will identify persons who are infected with HIV, either as part of the study enrollment or follow-up, and will provide participants with their HIV test results in the context of post-test counseling. Sites also will refer persons found to be HIV-infected to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. Individuals who become HIV-infected during the trial will be referred to local providers for HIV-specific care. Participants will be provided with several options for their care and treatment (see Section 4.1).

8.6 Use of Investigational Assays for Identification of Recent Infection

A key component of this study is the identification of women with undiagnosed HIV infection. FDA-cleared HIV antibody tests (e.g. FDA-cleared HIV rapid tests with follow up of preliminary positives with WB assays) will be used to identify newly diagnosed infections and these results will be shared with participants.

Laboratory assays that have not yet been FDA-cleared will also be performed by the HPTN NL to address the special contribution of recent infection to the HIV epidemic in US women. These assays will include BED and may include testing by other methods. Since these assays are not yet FDA-cleared for clinical use at this time, they will be performed retrospectively in ISIS to determine if recent infections were identified. These samples will be batched and will not be run in real time. In addition, as these assays are not FDA-cleared, results cannot be shared with participants. As a result, all women who participate in the study will be advised to seek regular HIV voluntary counseling and testing (VCT) in the community after the closure of the study. Referrals will be provided for post-study HIV testing.

As the field of HIV testing is dynamic, if current HIV testing recommendations are revised by regulatory bodies, then modification of the protocol would be considered to incorporate additional testing to identify recent and/or acute infections prospectively.

8.7 Participant Reimbursement

Participants will be compensated for their time and effort in this study (including monthly contacts), and may be reimbursed for travel to study visits. Site-specific reimbursement amounts will be specified in the study informed consent form, and approved by the IRB/ECs.

8.8 Confidentiality

All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets and/or in lockable areas with access limited to study staff. Electronic documents will be stored using appropriate computer security protections. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. Interviews and FGs will be transcribed by qualified personnel. All participant identifiers will be removed from transcripts. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the National Institute of Allergy and Infectious Diseases (NIAID) and/or its contractors; representatives of the HPTN CORE, SDMC, and/or NL; and/or other government and regulatory authorities.

All Protected Health Information (PHI) will be protected according to the provisions of HIPAA and will only be used or disclosed as allowed by the Privacy Rule pursuant to relevant waivers, authorizations or as required by Federal or state law.

A Certificate of Confidentiality has been obtained by the HPTN and each participating site may register under that umbrella certificate once IRB approvals for the study have been obtained.

8.9 Communicable Disease Reporting Requirements

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

8.10 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, the Office for Human Research Protection (OHRP), site IRB/ECs, or other local regulatory authorities.

9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

Please note, this section applies to women only. No laboratory samples will be collected for male FG participants.

The following types of specimens will be collected for testing, processing and / or storage at the local laboratory (LL). The same blood samples will be collected from all study participants, but some testing (e.g. CD4 cell count, WB, HIV viral load, HIV incidence testing) will only be performed in a subset of study participants based on HIV infection status and results of other tests.

All female participants

- Blood for HIV rapid testing using an FDA-cleared kit.
- Blood for other testing, in the event that the HIV rapid test is reactive.
- Plasma for future NL testing and storage.

All participants with a reactive HIV rapid test (using samples collected above)

- Plasma for WB testing using an FDA-cleared kit.
- Blood for CD4 cell count* (CD4 cell counts must be performed at a laboratory that is Clinical Laboratory Improvement Amendments (CLIA)-certified; laboratories that are certified through the DAIDS/Immunology Quality Assurance (IQA) program are preferred).

* NOTE: HIV rapid testing, WB, and CD4 cell count are not required at the 6-month or 12-month visits if HIV infection was confirmed at a prior visit.

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

9.2 Network Laboratory Specimens

Blood samples collected above will be processed at the LL, and plasma will be frozen and stored. The site will receive instructions from the HPTN SDMC to ship selected samples to the HPTN NL for testing (see below). Some of these shipments will occur after the end of the study (i.e. after the last study participant completes the final study procedures).

HIV Incidence Testing

The HPTN NL will perform testing to screen participants for recent HIV infection, to characterize HIV from recently infected participants, and to optimize algorithms for identification of recent HIV infection. This will include BED testing and other assays (to be determined by the HPTN NL). Some specialized assays may be performed at a commercial laboratory or at the CDC. Testing for

HIV incidence may be batched to reduce cost and maximize consistency of test procedures. Assays used by the NL for HIV incidence determination may not be FDA-cleared for diagnosis of HIV infection. All testing will be performed retrospectively. Results from these tests will not be provided to study sites, clinicians, or study participants, and will not be used for clinical management. HIV incidence will be determined at the end of the study, when all laboratory and other study data are available for analysis. Note that some HIV incidence testing will be performed only for a subset of study participants, but samples will be collected for testing from all study participants.

9.3 Quality Control And Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are CLIA-certified and that they perform the appropriate External Quality Assurance (QA) testing. NL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, and use of appropriate reagents. NL staff will follow-up directly with site staff to resolve any quality control or QA problems identified through proficiency testing and/or on-site assessments.

HIV QA Testing

HIV QA testing will be performed according to the HPTN NL Manual of Operations. The HPTN NL will repeat WB testing on all samples with indeterminate or positive WB results, and on 10% of samples with non-reactive HIV rapid test results. The HPTN SDMC will provide the NL with locally-obtained WB blot results, and a list of selected samples with non-reactive HIV rapid test results for QA testing. The HPTN SDMC will compare the results obtained by the LL and the NL. NL staff will follow-up directly with site staff to resolve any QA problems identified through this process.

9.4 Specimen Storage And Possible Future Research Testing

Storage of specimens for protocol-related testing (required for all study participants)

Study site staff will store plasma collected in this study until all protocol-related testing is complete. Note that some testing will be performed retrospectively, after the last participant completes the final study visit. Protocol-related testing at the NL using plasma collected at the study sites will include:

- QA testing.
- Determination of HIV incidence, including comparison of BED results to those obtained with other assays.
- Characterization of HIV viruses (e.g. HIV genotyping, HIV subtyping, HIV sequencing and phylogenetics, HIV tropism, etc.) and immunologic studies. Note that some specialized assays may be performed at a commercial laboratory.

Storage of specimens for future research

Participants will be asked whether they consent to having samples stored for future use (long-term storage for testing other than protocol-related testing). This consent is optional. If participants do not consent to have samples stored for future use, samples collected during the study will be destroyed when all protocol-related testing (see above) has been completed.

9.5 Estimates of HIV Incidence

The NL will develop a laboratory analysis plan to classify infections as recent or chronic and will work with the SDMC to develop a statistical analysis plan to estimate HIV incidence.

9.6 Biohazard Containment

Transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products. Therefore, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US CDC.

10 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

Following ethical review and approval, each participating site will complete the DAIDS protocol registration process as described in the DAIDS Protocol Registration Manual. The HPTN CORE, SDMC and NL staff will work closely with each site to ensure completion of this and all other study-specific site activation requirements as detailed in the HPTN Manual of Operations and the SSP Manual. Upon successful protocol registration and completion of all other study-specific site activation requirements, the CORE will issue a study activation notice to the site. Implementation of the study may not proceed prior to receipt of this written notification.

10.2 Study Coordination

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

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

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

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

10.3 Study Monitoring

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

- Verify compliance with human participants and other research regulations and guidelines.
- Assess adherence to the study protocol, SSP manual, and local counseling practices.
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

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

10.4 Protocol Compliance

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

10.5 Investigator's Records

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

10.6 Use of Information and Publications

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

11 REFERENCES

1. Heterosexual transmission of HIV--29 states, 1999-2002. MMWR Morb Mortal Wkly Rep 2004 Feb 20;53(6):125-9.
Notes: CORPORATE NAME: Centers for Disease Control and Prevention (CDC)
2. UNAIDS Reference Group on estimates, modelling and projections--statement on the use of the BED assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring. Wkly Epidemiol Rec 2006 Jan 27;81(4):40.
3. Persons living with HIV/AIDS as of June 30, 2005, Newark Residents. [Web Page]; www.state.nj.us/health/aids/rep/impactcities/newark. [Accessed 30 Jul 2006].
4. Reported HIV/AIDS Diagnoses and Deaths in 2004 and Persons Living with HIV/AIDS as of 12/31/04, New York City. [Web Page]; www.nyc.gov. [Accessed 30 Jul 2006].
5. Burke JG, Thieman LK, Gielen AC, O'Campo P, McDonnell KA. Intimate partner violence, substance use, and HIV among low-income women: taking a closer look. Violence Against Women 2005 Sep;11(9):1140-61.
6. C.Murrill, PhD M. National HIV Behavioral Surveillance among High-Risk Heterosexuals: Preliminary Results. HIV Research Seminar, HIV Epidemiology and Field Services Program; NYC Department of Health and Mental Hygiene and Center for Drug Use and HIV Research, National Development and Research Institutes.
7. Calypte Biomedical Corporation. HIV-1 BED Incidence Enzyme Immunoassay for Population Estimates of HIV-1 Incidence 2004 LN20597.01 . Rockville, MD: Calypte Biomedical Corporation; BED Package Insert.
8. Proportion of AIDS Cases among Female Adults and Adolescents by Transmission Category. US and Dependent Areas. CDC. HIV/AIDS Surveillance in Women. Atlanta, GA: CDC; 2007.
9. CDC. HIV/AIDS Among Women. Atlanta, GA: CDC; 2007 Jun. (CDC Fact Sheet.
10. CDC. HIV/AIDS Surveillance Report, 2006. Atlanta, GA: US Department of Health and Human Services; 2008.
11. Centers for Disease Control and Prevention (CDC). HIV/AIDS Surveillance Report. Atlanta, GA: CDC; 2004. (Volume 15).
12. Cohen MS, Gay C, Kashuba AD, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. Ann Intern Med 2007 Apr 17;146(8):591-601.

13. Edward William White. Assessing confounding by motivated testing when using the serologic testing algorithm for recent HIV seroconversion (STARHS) to estimate seroincidence among clinical testing populations University of Washington; 2006. PhD Thesis Dissertation .
14. Elizabeth DiNenno. CDC Internal Communication with NHBS sites. [E-mail] 2008 Apr 10.
15. Fleming PL, Lansky A, Lee LM, Nakashima AK. The epidemiology of HIV/AIDS in women in the southern United States. *Sex Transm Dis* 2006 Jul;33(7 Suppl):S32-8.
16. Forna FM, Fitzpatrick L, Adimora AA, McLellan-Lemal E, Leone P, Brooks JT, Marks G, Greenberg A. A case-control study of factors associated with HIV infection among black women. *J Natl Med Assoc* 2006 Nov;98(11):1798-804.
17. Harawa N, Adimora A. Incarceration, African Americans and HIV: advancing a research agenda. *J Natl Med Assoc* 2008 Jan;100(1):57-62.
18. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999 Apr;28(2):319-26.
19. Hughes JP. Using baseline data to design a group randomized trial. *Stat Med* 2005 Jul 15;24(13):1983-94.
20. Karita E, Price M, Hunter E, Chomba E, Allen S, Fei L, Kamali A, Sanders EJ, Anzala O, Katende M, et al. Investigating the utility of the HIV-1 BED capture enzyme immunoassay using cross-sectional and longitudinal seroconverter specimens from Africa. *AIDS* 2007 Feb 19;21(4):403-8.
Notes: CORPORATE NAME: the IAVI Collaborative Seroprevalence and Incidence Study Team
21. Lagakos SW, Gable AR. Challenges to HIV prevention--seeking effective measures in the absence of a vaccine. *N Engl J Med* 2008 Apr 10;358(15):1543-5.
22. Lansky A, Sullivan PS, Gallagher KM, Fleming PL. HIV behavioral surveillance in the US: a conceptual framework. *Public Health Rep* 2007;122 Suppl 1:16-23.
23. Linley L, Song R, Sharma CP, et al. Estimates of HIV incidence using STARHS among Persons attending counseling, testing and referral settings in two high morbidity Southern states, 1996-2002. Poster Presentation at 12th Conference of CROI; Boston.
24. Lyles CM, Kay LS, Crepaz N, Herbst JH, Passin WF, Kim AS, Rama SM, Thadiparthi S, DeLuca JB, Mullins MM. Best-evidence interventions: findings from a systematic review of HIV behavioral interventions for US populations at high risk, 2000-2004. *Am J Public Health* 2007 Jan;97(1):133-43.
Notes: CORPORATE NAME: HIV/AIDS Prevention Research Synthesis Team

25. Lyles CM, Kay LS, Crepaz N, Herbst JH, Passin WF, Kim AS, Rama SM, Thadiparthi S, DeLuca JB, Mullins MM. Efficacy Results from the STEP Study (Merck V520 Protocol 023/HVTN 502): A Phase II Test-of-Concept Trial of the MRKAd5 HIV-1 Gag/Pol/Nef Trivalent Vaccine 15th Conference on Retroviruses and Opportunistic Infections; Boston, MA US.
26. MacKellar D, Valleroy L, Karon J, Lemp G, Janssen R. The Young Men's Survey: methods for estimating HIV seroprevalence and risk factors among young men who have sex with men. *Public Health Rep* 1996;111 Suppl 1:138-44.
27. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005 Aug 1;39(4):446-53.
28. McDougal JS, Parekh BS, Peterson ML, Branson BM, Dobbs T, Ackers M, Gurwith M. Comparison of HIV type 1 incidence observed during longitudinal follow-up with incidence estimated by cross-sectional analysis using the BED capture enzyme immunoassay. *AIDS Res Hum Retroviruses* 2006 Oct;22(10):945-52.
29. McQuillan GM, Kruszon-Moran D, Kottiri BJ, Kamimoto LA, Lam L, Cowart MF, Hubbard M, Spira TJ. Prevalence of HIV in the US household population: the National Health and Nutrition Examination Surveys, 1988 to 2002. *J Acquir Immune Defic Syndr* 2006 Apr 15;41(5):651-6.
30. Muhib FB, Lin LS, Stueve A, Miller RL, Ford WL, Johnson WD, Smith PJ. A venue-based method for sampling hard-to-reach populations. *Public Health Rep* 2001;116 Suppl 1:216-22.
Notes: CORPORATE NAME: Community Intervention Trial for Youth Study Team
31. Nash D, Bennani Y, Ramaswamy C, Torian L. Estimates of HIV incidence among persons testing for HIV using the sensitive/less sensitive enzyme immunoassay, New York City, 2001. *J Acquir Immune Defic Syndr* 2005 May 1;39(1):102-11.
32. O'Leary A, Martins P. Structural factors affecting women's HIV risk: a life-course example. *AIDS* 2000 Jun;14 Suppl 1:S68-72.
33. Parekh BS, Kennedy MS, Dobbs T, Pau CP, Byers R, Green T, Hu DJ, Vanichseni S, Young NL, Choopanya K, et al. Quantitative detection of increasing HIV type 1 antibodies after seroconversion: a simple assay for detecting recent HIV infection and estimating incidence. *AIDS Res Hum Retroviruses* 2002 Mar 1;18(4):295-307.
34. Priddy FH, Pilcher CD, Moore RH, Tambe P, Park MN, Fiscus SA, Feinberg MB, del Rio C. Detection of acute HIV infections in an urban HIV counseling and testing population in the United States. *J Acquir Immune Defic Syndr* 2007 Feb 1;44(2):196-202.
35. Rosenberg PS, Biggar RJ. Trends in HIV incidence among young adults in the United States. *JAMA* 1998 Jun 17;279(23):1894-9.

36. Sakarovitch C, Rouet F, Murphy G, Minga AK, Alioum A, Dabis F, Costagliola D, Salamon R, Parry JV, Barin F. Do tests devised to detect recent HIV-1 infection provide reliable estimates of incidence in Africa? *J Acquir Immune Defic Syndr* 2007 May 1;45(1):115-22.
37. Shain RN, Piper JM, Newton ER, Perdue ST, Ramos R, Champion JD, Guerra FA. A randomized, controlled trial of a behavioral intervention to prevent sexually transmitted disease among minority women. *N Engl J Med* 1999 Jan 14;340(2):93-100.
38. Stueve A, O'Donnell LN, Duran R, San Doval A, Blome J. Time-space sampling in minority communities: results with young Latino men who have sex with men. *Am J Public Health* 2001 Jun;91(6):922-6.
39. Torian L. Recent HIV Infection in Various Populations, 2002-2006. Preliminary Data. New York City Department of Health [Personal Communication]. Unpublished .
40. US Census Bureau. [Web Page]; www.census.gov. [Accessed Aug 2007].
41. Vidanapathirana J, Abramson MJ, Forbes A, Fairley C. Mass media interventions for promoting HIV testing. *Cochrane Database Syst Rev* 2005;(3):CD004775.
42. Weir BW, Bard RS, O'Brien K, Casciato CJ, Stark MJ. Uncovering patterns of HIV risk through multiple housing measures. *AIDS Behav* 2007 Nov;11(6 Suppl):31-44.

**APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR
HPTN 064**

SCHEDULE OF EVALUATIONS FOR WOMEN

	Screening Visit [#]	Enrollment [#]	Telephone Follow-up (Monthly)	Week 26*	Week 52*
PROCEDURES					
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES					
Obtain informed consent for screening	X				
Obtain informed consent for enrollment and optional storage of blood (and if applicable, qualitative component) ¹		X			
Collect demographic information	X				
Obtain/update locator information	X	X	X	X	X
Administer eligibility screener	X				
Administer behavioral questionnaire		X		X	X
CLINICAL/COUNSELING PROCEDURES					
Obtain medical history		X		[X]	[X]
Provide HIV pre/post-test and risk reduction counseling (as applicable) ²		X		X	X
Offer condoms	X	X		X	X
Collect Samples for HIV Assessment					
Blood samples: HIV rapid test ² , CD4 cell count ³ , WB ⁴ , HIV incidence testing (performed at the NL) ⁵ , plasma storage ⁶		X		X	X
LAB PROCEDURES					
HIV rapid test ²		X		X	X
CD4 cell count ³		X		X	X
Western blot ⁴		X		X	X
Stored plasma ⁶		X		X	X
BLOOD VOLUME (mL)	0	30	0	30	30

[#]Screening and enrollment may take place on the same visit, if possible.

*Participants will be followed for a minimum of 26 weeks. Total follow-up will vary according to time of enrollment. See Section 4 and the SSP for more detail.

[] =if clinically indicated

¹ Only a subset of participants will be eligible for the qualitative component. See Section 2.3 and the SSP for more detail on visit procedures.

² An HIV rapid test is performed for all study participants at enrollment. HIV rapid testing is not performed at the 6-month or 12-month visit if HIV infection was confirmed at the enrollment or 6-month visit respectively. Risk reduction counseling should be provided for all participants, regardless of HIV infection status. Schedule next visit after participant has received HIV rapid test results.

³ A CD4 cell count is performed at any visit where a reactive HIV rapid test result is obtained. A CD4 cell count is not performed at 6 or 12 months if HIV infection was confirmed at previous visit.

⁴ A WB is performed at any visit where a reactive HIV rapid test result is obtained. A WB is not performed at Weeks 26 or 52 if HIV infection was confirmed at previous visit. Participants who have an indeterminate or positive WB should have a repeat (confirmatory) WB performed within 1-2 weeks see Section 4.6).

⁵ HIV incidence testing will be performed at the NL on selected samples.

⁶ The HPTN SDMC will provide the sites with instructions for shipment of selected plasma samples to the NL for testing.

SCHEDULE OF EVALUATIONS FOR MEN

	Screening Visit*	Enrollment*
PROCEDURES (MEN)		
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES		
Obtain informed consent for screening and enrollment	X	
Obtain informed consent for enrollment		X
Administer eligibility screener	X	
Collect demographic information	X	
Obtain/update locator information	X	X
Administer behavioral questionnaire		X
Schedule focus group	X	
Conduct focus group		X
Offer condoms	X	X

*Screening and enrollment may take place during the same visit, if possible.

**APPENDIX II: OPTIONAL SCREENING VERBAL INFORMED
CONSENT (WOMEN)**

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

OPTIONAL SCREENING VERBAL INFORMED CONSENT FORM (WOMEN)

INVESTIGATOR OF RECORD: [insert name]

PHONE: [insert number]

Interviewer Script:

Hi, my name is [interviewer's name] and I work at [name of institution]. We are conducting a research study in this community and 9 other communities around the United States. The research project is called ISIS. As you may know, HIV is the virus that causes AIDS. About 30% of new HIV infections in the United States occur in women. A disproportionate number of these new cases occur in women of color. The purpose of this study is to learn about new ways to help reduce the number of infections in women who live in the United States. Do you mind if I ask you a short list of questions related to your sex life, drug/alcohol use, incarceration and STI history and sex partners to see if you might be eligible to participate? Please note: You are a volunteer and can decide not to take part or can quit at any time.

Patient Information Sheet (to be offered to all women who are willing to screen).

CLINICAL RESEARCH SITE [insert name and address]

INVESTIGATOR OF RECORD: [insert name]

PHONE: [insert number]

Purpose: The purpose of this study is to help researchers do three things:

- First of all, this study will help estimate the number of women who get new HIV infections.
- Secondly, this study will help researchers understand why some women are more at risk of becoming infected with HIV than others.

- Finally, this study will help researchers learn more about future HIV prevention trials and if women would be willing to participate in future studies related to HIV prevention.

Commitment: Women who are eligible and willing to provide informed consent will take part in the study for up to 12 months. About half the participants will have 2 in person visits (today and 6 months from now). The other half of participants will be asked to come today, 6 months and 12 months from now (3 in person visits). Each visit will take approximately an hour to an hour and a half. Everyone will get a phone call once a month. This study involves a blood draw and questionnaires. Also, a small number of people will be asked to take part in an interview or focus group.

Benefits: You may receive no direct benefit from this study. However, you will receive information about whether you are infected with HIV. We will also give you information about where you can go for care if you have HIV. You will also receive counseling about how to protect yourself from HIV infection. You will be offered free condoms. Information learned in this study may help others in the future.

For more information contact: *[insert name and number]*

The study will take place at: *[insert site address]*

**APPENDIX III: SCREENING AND ENROLLMENT INFORMED CONSENT
(WOMEN)**

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

SCREENING AND ENROLLMENT INFORMED CONSENT (WOMEN)

INVESTIGATOR OF RECORD: [*insert name*]

PHONE: [*insert number*]

Why is this study being done?

You are invited to take part in a clinical research study conducted by researchers at the [*insert institution*]. This study is called HPTN 064: The Women's HIV SeroIncidence Study (ISIS). The United States National Institutes of Health is funding this study. Women from ten communities throughout the US will participate in this study (2,000 women total). 200 women per community will be enrolled in this research study. You are being asked to take part in this research study because you stated that you recently tested negative for HIV or said that you are not sure of your HIV status. You also stated that you live in [*insert name of area*]. Because [*insert name of area*] has a high rate of people living with HIV we are interested in receiving information from women such as yourself who might be able to help us understand more about what can be done to lower the risk of future HIV infections among your neighbors.

As you may know, approximately 30% of new HIV (the virus that causes AIDS) infections in the United States occur in women. A disproportionate number of these new cases occur in women of color. **The purpose of this study** is to help researchers do three things:

- First of all, this study will help estimate the number of women who get new HIV infections. This is known as *HIV incidence*. Unfortunately, we do not have enough information on HIV incidence in women, so it is hard to design clinical studies that try to prevent new HIV infections in women.
- Secondly, this study will help researchers understand why some women are more at risk of becoming infected with HIV than others. While certain sexual and drug use behaviors are known to be risks for HIV (such as unprotected sex with an HIV infected partner), some women who are infected with HIV report very few risk behaviors. Learning more about these characteristics may help researchers

- prevent new HIV infections in women.
- Finally, this study will help researchers learn more about future HIV prevention trials and if women would be willing to participate in future studies related to HIV prevention.

In addition, women and men from four of the study communities may be invited to participate in a study interview or focus group. Thirty women from each of the four communities that are participating in the ISIS research study will be interviewed. Ten women from four of the communities that are participating in the ISIS research study will be asked to participate in each focus group. We will conduct between two and six focus groups in each of these communities. A focus group is a discussion among a small group of people about a specific set of topics. Focus groups are led by a focus group leader. You will not be asked to give your name to the group, but will instead be encouraged to use a “made-up” name. The interviews and focus groups have been designed to give us an opportunity to learn more about some of the community and life factors that are faced by the women who live in your neighborhood. We will also talk to men in these communities about HIV testing, and why or why not men get tested for HIV. *[To be modified to reflect site practices: (Name of community) is/is not participating in the ISIS interviews and focus groups. If you are selected to participate, you will be given more information about this part of the study and asked to give us your permission on a separate form. You do not have to participate in the interviews or focus groups in order to be part of the larger study.]*

Before you can make an informed decision about whether to take part in the study, you should understand the possible risks and benefits of being in this study. That process is called *informed consent*. This informed consent document will give you an idea of what will take place during the study and provides you with detailed information about this research study. This consent form might contain some words that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. If you state that you understand the study and have decided that you want to participate you will be asked to read, sign, and date this form. You will also be offered a copy of this form to keep.

What happens if you do not want to take part?

Before you learn more about the study it is important that you know the following:

- You do not have to be in this study if you do not want to.
- You may decide not to complete the study, or to withdraw from the study at anytime, without losing your regular medical care.
- If you decide not to complete the study you can still join another research study later, if one is available and you qualify.
- Some people may not be able to join the research study because of information that is provided during the screening process.
- You will be told of any important new information in the study that may affect your safety or your choice to continue study participation. If you choose to continue in this study, you will be asked to sign a new (revised) Informed Consent form to document that you have been informed of this new information and do in fact want

- to continue in the study.
- If you decide to discontinue participation in the study or are withdrawn from the study, you may be contacted and asked to return for one last final evaluation.

What Will Happen During This Study?

If you are eligible to join this study and you decide to enroll and provide informed consent, your participation will last between approximately 6 to 12 months after you the date that you enroll. When you enroll, the site will tell you how long you will be in the study. ***[To be modified to reflect site practices:*** Study visits may take place in a variety of locations that the study staff have determined will provide you with privacy and confidentiality during the study visits, such as the clinic, mobile vans, community organizations or other appropriate public places. The study team will talk with you about this so that you can have study visits at a place that works for you./

Screening Visit- You will be asked a short list of questions related to your sex life, drug/alcohol use, incarceration and STI history and sex partners. We will also ask you if you live in one of the study communities. We will use this information to decide if you may be eligible to participate. If you are not eligible, staff may not tell you the reason why. ***[Sites can delete this language if they will only be using verbal consent for screening procedures. Sites should leave this language in the consent form if there is the possibility that written consent for screening may be obtained for some subjects]***

Enrollment Visit - If you are eligible to enroll in the study and you choose to participate, you may be enrolled today. You will be asked to provide contact information so we will be able to maintain contact with you during this study. You will then be asked to complete a longer interview that will include questions about your health (including your emotional health), your sex life (including condom use), drug and alcohol use, domestic violence and incarceration. We will also ask you similar questions about your sexual partner(s). You will be counseled about HIV and offered free condoms. The study staff will draw approximately 30 mls of blood (about 2 tablespoons) from you. This blood will be used for an HIV test. If your HIV test today is positive, we will do other tests to make sure that you really are infected and to look at the health of your blood, such as a CD4 count, which is a measure of your immune (infection-fighting) system. Leftover blood will be used for investigational tests. You will need to come back to the clinic to receive the results of these tests when they are ready. When you come back, the staff will discuss your test results with you.

Please note that sometimes an HIV test result is not clearly positive but is also not clearly negative. This is called an “indeterminate result”. *If you have an “indeterminate result”, or your HIV test is positive*, we will test your blood again until we know for sure whether you are or are not infected with HIV. If they are needed, these follow-up HIV test results will be available about 14 days later. You will be scheduled to come back to receive your results at that time. If those results show you have HIV, the study staff will talk with you about what those results mean for you. You will be referred for care and will be provided with information about additional counseling. We may draw additional blood to confirm your test results.

- When possible, study staff will include the screening and enrollment visit all at once.

If you don't have time to do both today, we will make an appointment as soon as possible to see you on another day.

- ***[To be modified to reflect site practices:*** Together, the screening and enrollment visit will last approximately 1 or 2 hours./
- There are no costs to you for the HIV test you will take to participate in this visit.
- You will receive ***[sites insert site-specific amount of money]*** to reimburse you for time.

Monthly Contacts - You will also receive monthly phone calls to update your contact information if you have plans to move or change your phone number. You will also be provided with a phone number that you can use to contact the research team. ***[To be modified to reflect site practices:*** If we can not reach you by phone, we may try to contact you by mail. The study team has set up a toll-free number that you can use to call staff. We may visit you at your home, work or other locations where you may be found if we can not contact you by phone. You will complete a study form with study staff that describes ways that you prefer to be contacted./

- Each monthly call will last about 5 to 15 minutes.
- There are no costs to you to participate in these calls.
- You will receive ***[sites insert site-specific amount of money]*** to reimburse you for your time for each of the scheduled calls that you complete. ***[To be modified to reflect site practices:*** All reimbursements for calls will be made at the time that you participate in your next scheduled follow-up visit./

Follow-up Visit(s) – About six months from the time you enroll you will be scheduled to have another in-person visit with us to repeat the interviews. You will be counseled on HIV and offered free condoms. You will have 30 mls (about 2 tablespoons) of blood drawn. Similar to the enrollment visit, this blood will be used for HIV testing (if you do not have an HIV positive test at the previous visit). If you test positive for HIV at the follow-up or earlier visits, the blood will be used for tests to evaluate your HIV-related health. Researchers will also use the blood for investigational purposes. Based on enrollment dates some of the women in this study may be asked to have a second visit in another six months, and to continue to receive monthly contacts between the dates of their first and second visits. Members of the research team will be able to let you know if this applies to you.

- ***[To be modified to reflect site practices:*** Each follow-up visit will last approximately 1 or 2 hours./
- There are no costs to you for the HIV test you will take to participate in the visit(s).
- You will receive ***[sites insert site-specific amount of money]*** to reimburse you for time.

How Will Your Privacy Be Protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

In order to keep your information private, your blood samples will be labeled with a code that can only be traced back to your research clinic. When researchers are given your stored samples to study they will not be given your name. The results of future tests will not be included in your health records.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH)) and their representatives, local regulatory authorities, *insert name of site* IRB, and the study staff and study monitors.

To help study staff keep your personal information confidential, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. In addition, the study staff must comply with all local requirements to report communicable diseases and any other reportable condition(s). *[To be modified to reflect site practices: This means that if you test positive for (insert name of reportable conditions) will we have to report this information to (insert name of relevant agencies). The report will/will not include your name.]*

What Are the Potential Benefits?

You may receive no direct benefit from this study. However, you will receive information about whether you are infected with HIV. We will also give you information about where you can go for care if you have HIV. You will also receive counseling about how to protect yourself from HIV infection. You will be offered free condoms. Information learned in this study may help others in the future.

What Are the Possible Risks or Discomforts?

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

The counseling about HIV and other diseases may cause you to worry. If the tests show that you have HIV, knowing your HIV status may cause you anxiety. Answering questions about your sex life or other behaviors may make you embarrassed. We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn of your participation here and think you are infected with HIV, or are at high risk for infection with HIV. Because of this, you could have trouble finding or

keeping a job. You could also have problems being accepted in your family and community.

The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described above.

How Will Your Blood Samples Be Used?

As described above, we will collect blood from you as part of the study. Some of the samples will be used for clinical purposes, such as HIV testing. We will share the results of these tests with you. Some of your blood samples will be used for investigational purposes. Currently there are no tests that doctors can use to tell if someone who receives a positive HIV test was infected for less than 6 months or was infected a long time before they found out they were HIV positive. Knowing this information may have an important impact on HIV-related care for people who were recently infected. These investigational tests will be used to learn more about how to detect if HIV infection was acquired recently. The results of these investigational tests will only become available after the study has ended. These tests are for investigational purposes only, and you will not receive the results of these tests.

After all the tests are done for this research study, there may be some left over blood samples. If you agree, left over blood samples will be kept and used for future research related to HIV incidence and recent infection. We will ask you to give us permission to store these leftover samples at the end of this form. You do not have to provide permission to use your samples for future research in order to be part of this study. *[To be modified to reflect site practices: If you decide at any time that you do not want your leftover samples to be stored and used for future research, contact study staff and your samples will be destroyed.]*

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

What are Your Responsibilities as a Participant?

As a participant in this study, it is your responsibility to meet with the study staff according to the study schedule. You should not participate in this study if you are unwilling to continue to meet with study interviewers, or if you know for sure you are moving outside of *[insert name of area]* or will be gone for more than two consecutive months during the follow-up period. *[To be modified to reflect site practices: In addition, if you are part of ISIS, you may only enroll in one ISIS study community. Staff from sites may compare study information to ensure that no participants are co-enrolled. If you are moving or would like to transfer to another study site, please talk to study staff.]*

What are Some Reasons Why You May Be Withdrawn From the Study Without Your Consent?

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

- The research study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not willing to find out your HIV test results.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.

What Happens If You Are Injured by This Research?

All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. However, you may have to pay for this care. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

Persons to Contact for Problems or Questions

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

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

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

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

HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Sponsor: NIAID, NIDA, NIMH, NIH

SCREENING AND ENROLLMENT INFORMED CONSENT

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

SIGNATURE PAGE

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

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

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

Yes, I agree to have my left-over samples stored for future HIV research.

No, I do not agree to have my samples stored for future HIV research

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

**APPENDIX IV: QUALITATIVE INTERVIEW INFORMED CONSENT
(WOMEN)**

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

QUALITATIVE INTERVIEW INFORMED CONSENT (WOMEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

*****FOR SITES PARTICIPATING IN QUALITATIVE COMPONENT ONLY*****

Introduction

You have been invited to participate in a semi-structured interview because you are a participant in the HPTN 064 (ISIS) research study. This interview has been designed to give us an opportunity to learn more about some of the community and life factors that are faced by the women who live in your neighborhood. Approximately 30 women from four of the communities that are participating in the ISIS research study will be interviewed. The information from these interviews will be combined with the rest of the information that is gathered during this research. We will use all of that information to learn more about HIV and women in the US. We hope this information will help to reduce HIV rates in women who live in the US in the future.

What Will Happen During This Study?

The interview questions will be read to you by a member of the research team. The questions will cover a broad range of issues, including topics such as income, mental health, substance use, and domestic and sexual violence. To minimize that discomfort and to protect your privacy the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. If any of the questions make you very upset the interviewer will stop the interview. You will also be provided with contact and referral information if any of the questions raise issues that you would like to address at this or some later time.

[To be modified to reflect site practices: The interview will take place in a location that the study staff have determined will provide you with privacy and confidentiality during

the study visits, such as the clinic, or other appropriate public places. The study team will talk with you about this so you know where to go for the interview./

To help assure that we get the best understanding possible from your answers, **this interview will be recorded**. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript. After all of the interviews have been completed your answers will be combined with the answers provided by the other women who are interviewed. These combined answers will be analyzed to look for common patterns.

- ***[To be modified to reflect site practices: The interview will take approximately 45 minutes to 1 hour to complete.]***
- There will be **no cost to you** to participate in the interview.
- **You will receive *[insert local compensation amount]*** for your time and effort.

What Are the Potential Benefits?

There may be no direct benefits to you for participating in this interview. We hope that the benefit from these interviews will come in the form of information that might help reduce the risk of HIV among women in your community.

What Are the Possible Risks or Discomforts?

It is possible that answering the interview questions may make you embarrassed or upset. To minimize that discomfort and to protect your privacy the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

If you participate in the interview, your session will be recorded. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript. After this research study has been completed all of the interview recordings will be destroyed.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH)) and their representatives, local regulatory authorities, ***[insert name of site]*** IRB, study staff and study monitors.

To help study staff keep your personal information confidential, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

Also, the Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain in the rest of the research project (ISIS). Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time.

What are Some Reasons Why You May Be Withdrawn From the Study without Your Consent?

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

- The research study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.

What Happens If You Are Injured by This Research?

All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. However, you may have to pay for this care. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

Persons to Contact for Problems or Questions

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

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

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

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

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

QUALITATIVE INTERVIEW INFORMED CONSENT (WOMEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX V: FOCUS GROUP INFORMED CONSENT (WOMEN)

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

FOCUS GROUP INFORMED CONSENT (WOMEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

*****FOR SITES PARTICIPATING IN QUALITATIVE COMPONENT ONLY*****

Introduction

You have been invited to participate in a focus group with other ISIS participants because you are a participant in the ISIS research study. A focus group is a discussion among a small group of people about a specific set of topics. Focus groups are led by a focus group leader. The comments made by the focus group participants are studied by researchers to learn more about what the participants believe concerning the topics that they discuss in the group. The purpose of this focus group is to help us learn more about some of the community and life factors that are faced by the women who live in your neighborhood. Approximately ten women from four of the communities that are participating in the ISIS research study will participate in each focus group. We will conduct between two and six focus groups in each of these communities. The information gathered from these focus groups will be combined with the rest of the information that is collected during this research. We will use all of that information to learn more about HIV and women in the US. We hope this information will help to reduce HIV rates in women who live in the US in the future.

Procedures

The focus group will be led by a member of the research team. The questions will cover a broad range of issues, including topics such as income, mental health, substance use, and domestic and sexual violence. To minimize that discomfort and to protect your privacy the focus group leader will help the group establish ground rules prior to the start of the focus group discussion. Those rules will include reminders about privacy and confidentiality. Participants will also be encouraged to use a made-up name during the focus group. If any of the questions make you upset the focus group leader may ask you to leave the room, or may stop the focus group meeting all together. You will also be provided with contact and referral information if any of the questions raise issues that you would like to address at this or some later time.

[To be modified to reflect site practices: The focus group will take place in a location that the study staff have determined will provide you with privacy and confidentiality during the study visits, such as the clinic, or other appropriate public places. The study team will talk with you about this so you know where to go for the focus group. ***]***

To help assure that we get the best understanding possible from the focus group participants answers **the focus groups will be recorded**. After the focus group is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript.

- ***[To be modified to reflect site practices:*** The focus group **will take between 1 to 1 ½ hours** to complete.***]***
- There will be **no cost to you** to participate in the focus groups.
- **You will receive *[insert local compensation amount]*** for your time and effort.

What Are the Potential Benefits?

There may be no direct benefits to you for participating in this focus group. We hope that the benefit from these interviews will come in the form of information that might help reduce the risk of HIV among women in your community.

What Are the Possible Risks or Discomforts?

A possible risk to you in participating in this focus group is that some of the questions may make you feel embarrassed or worried. The focus group procedures described above are designed to maximize participant confidentiality and to minimize discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. This is because confidentiality is limited in a focus group setting, since other participants are present during the discussion. Additional steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

If you participate in the focus group, your session will be recorded. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript. After this research study has been completed all of the interview recordings will be destroyed.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH)) and their representatives, local regulatory authorities, ***[insert name of site]*** IRB, study staff and study monitors.

To help study staff keep your personal information confidential, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects

researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

Your participation in this focus group is voluntary. You are not required to participate in this focus group in order to remain in the rest of the research project (ISIS). Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time.

What are Some Reasons Why You May Be Withdrawn From the Study without Your Consent?

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

- The research study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.

What Happens If You Are Injured by This Research?

All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. However, you may have to pay for this care. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

Persons to Contact for Problems or Questions

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

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

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

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

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

FOCUS GROUP INFORMED CONSENT (WOMEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

**APPENDIX VI: OPTIONAL VERBAL SCREENING INFORMED CONSENT
(MEN)**

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

OPTIONAL VERBAL SCREENING INFORMED CONSENT FORM (MEN)

INVESTIGATOR OF RECORD: [insert name]

PHONE: [insert number]

****FOR SITES PARTICIPATING IN QUALITATIVE COMPONENT ONLY****

Interviewer Script:

Hi, my name is [interviewer's name] and I work at [name of institution]. We are conducting a research study in this community and 9 other communities around the United States. The research project is called ISIS. Four of the ten communities include participation of men such as yourself. As part of the study, we would like to learn more about what men in your community think about HIV testing and counseling. Do you mind if I ask you a few questions about your sex life, drug/alcohol use, incarceration and STI history and sex partners to see if you might be eligible to participate?

Patient Information Sheet (to be offered to all men who are willing to screen).

CLINICAL RESEARCH SITE [insert name and address]

INVESTIGATOR OF RECORD: [insert name]

PHONE: [insert number]

Purpose: The purpose of this part of the study is to help researchers learn more about why people in your community do or do not get tested for HIV.

Commitment: Men who are eligible and agree to participate will take part in one focus group that will last about 1 to 1.5 hours. This focus group will be audio recorded.

Benefits: There may be no direct benefits for participants, however information learned in this study may help others in the future. Participants in the study will be offered free condoms.

For more information contact: [insert name and number]

The study will take place at: [insert site address]

APPENDIX VII: FOCUS GROUP INFORMED CONSENT (MEN)

HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Sponsor: NIAID, NIDA, NIMH, NIH

FOCUS GROUP INFORMED CONSENT (MEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

Why is this study being done?

You are invited to take part in a clinical research study conducted by researchers at the *[insert institution]*. This study is called HPTN 064: The Women's HIV SeroIncidence Study (ISIS). The United States National Institutes of Health (NIH) is funding this study. Women from 10 communities throughout the US will participate in this study (2,000 women total). 200 women per community will be enrolled in this research study. Although the majority of people in this study are women, we are also interested in talking to men like you. You are being asked to take part in this research study because you are a man and have stated that you live in *[insert name of area]*. Because *[insert name of area]* has a high rate of people living with HIV, we are interested in receiving information from people such as yourself who might be able to help us understand more about what can be done to lower the risk of future HIV infections among your neighbors.

The purpose of this study is to help researchers do three things:

- First of all, this study will help estimate the number of women who get new HIV infections. This is known as *HIV incidence*. Unfortunately, we do not have enough information on HIV incidence in women, so it is hard to design clinical studies that try to prevent new HIV infections in women.
- Secondly, this study will help researchers understand why some women are more at risk of becoming infected with HIV than others. While certain sexual and drug use behaviors are known to be risks for HIV (such as unprotected sex with an HIV infected partner), some women who are infected with HIV report very few risk behaviors. Learning more about these characteristics may help researchers prevent new HIV infections in women.

- Finally, this study will help researchers learn more about future HIV prevention trials and if women would be willing to participate in future studies related to HIV prevention.

In addition, women and men from four of the study communities may be invited to participate in a study interview or focus group. Thirty women from each of the four communities that are participating in the ISIS research study will be interviewed. Sixty women from each of the 4 communities that are participating in the ISIS research study participate in a focus group. A focus group is a discussion among a small group of people about a specific set of topics. Focus groups are led by a focus group leader. The comments made by the focus group participants are studied by researchers to learn more about what the participants believe concerning the topics that they discuss in the group. The purpose of this focus group is to help us learn more about why people may or may not get tested for HIV. Twelve men from each of the four of the communities that are participating in the ISIS research study will be asked to participate in each focus group. We will conduct between two and six focus groups in each of these communities. The information gathered from these focus groups will be combined with the rest of the information that is collected during this research. We will use all of that information to learn more about the HIV counseling and testing in the US. We hope this information will help to reduce HIV rates in the US in the future.

Before you can make an informed decision about whether to take part in the study, you should understand the possible risks and benefits of being in this study. That process is called ***informed consent***. This informed consent document will give you an idea of what will take place during the study and provides you with detailed information about this research study. This consent form might contain some words that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. If you state that you understand the study and have decided that you want to participate you will be asked to read, sign, and date this form. You will also be offered a copy of this form to keep.

What happens if you do not want to be in the study?

Before you learn more about the study it is important that you know the following:

- You do not have to be in this study if you do not want to.
- You may decide not to complete the study, or to withdraw from the study at anytime, without losing your regular medical care.
- If you decide not to complete the study you can still join another research study later, if one is available and you qualify.
- Some people may not be able to join the research study because of information that is provided during the screening process.
- You will be told of any important new information in the study that may affect your safety or your choice to continue study participation. If you choose to continue in this study, you will be asked to sign a new (revised) Informed Consent form to document that you have been informed of this new information and do in fact want to continue in the study.

What Will Happen During This Study?

If you are eligible to join this study and you decide to enroll, your participation will last for one focus group. When you enroll, the site will tell you how long you will be in the study.

[To be modified to reflect site practices: The focus group will take place in a location that the study staff have determined will provide you with privacy and confidentiality during the study visits, such as the clinic, or other appropriate public places. The study team will talk with you about this so you know where to go for the focus group. *]*

Screening Visit- You will be asked a short list of questions related to your sexual activity, drug/alcohol use, incarceration and STI history and partners. We will also ask you what neighborhood you live in. We will use this information to decide if you may be eligible to participate. We will also ask for your contact information. If you are not eligible, staff may not tell you the reason why. *[Sites can delete this language if they will only be using verbal consent for screening procedures. Sites should leave this language in the consent form if there is the possibility that written consent for screening may be obtained for some subjects.]*

Enrollment Visit- If you are eligible for the study and choose to participate, the study team will ask for your updated contact information so that they can let you know when and where the focus group will be. The focus group will be led by a member of the research team. Prior to the focus group, we will ask you to answer in private some questions about yourself, such as your sex life, drug use and whether you have had an HIV test. In the focus group, we will ask you questions about why men in your community may or may not go for HIV testing and counseling.

To help assure that we get the best understanding possible from the focus group participants answers **the focus groups will be recorded**. The information on the recording will then be typed (called a transcript) by qualified personnel. The focus group participants' names will not be included in that typed record of the groups' answers. After this research study has been completed all of the interview recordings will be destroyed.

- *[To be modified to reflect site practices:* The focus group **will take between 1 to 1 ½ hours** to complete.*]*
- There will be **no cost to you** to participate in the focus groups.
- **You will receive *[insert local compensation amount]*** for your time and effort.

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

What Are the Potential Benefits?

There may be no direct benefits to you for participating in this focus group. We hope that the benefit from these interviews will come in the form of information that might help reduce the risk of HIV among men and women in your community.

What Are the Possible Risks or Discomforts?

A possible risk to you in participating in this focus group is that some of the questions may make you feel embarrassed or worried. To minimize that discomfort and to protect your privacy the focus group leader will help the group establish ground rules prior to the start of the focus group discussion. Those rules will include reminders about privacy and confidentiality. Participants will also be encouraged to use a made-up name during the focus group. If any of the questions make you very upset the focus group leader may ask you to leave the room, or may stop the focus group meeting all together. You will also be provided with contact and referral information if any of the questions raise issues that you would like to address at this or some later time.

The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

If you participate in the focus group, your session will be recorded. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH)) and their representatives, local regulatory authorities, *insert name of site* IRB, study staff and study monitors

To help study staff keep your personal information confidential, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

What are Some Reasons Why You May Be Withdrawn From the Study without Your Consent?

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

- The research study is stopped or canceled.

- The study staff feels that staying in the study would be harmful to you.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.

What Happens If You Are Injured by This Research?

All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. However, you may have to pay for this care. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

Persons to Contact for Problems or Questions

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

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

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

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

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

FOCUS GROUP INFORMED CONSENT (MEN)

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness's Signature and Date

**APPENDIX VIII: AUTHORIZATION TO USE AND DISCLOSE PROTECTED
HEALTH INFORMATION FOR RESEARCH PURPOSES**

**HPTN 064: The Women's HIV SeroIncidence Study (ISIS)
Protocol Version 1.0, 9 July 2008
DAIDS ID: 10705**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute on Drug Abuse (NIDA)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)**

Sponsor: NIAID, NIDA, NIMH, NIH

**AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH
INFORMATION FOR RESEARCH PURPOSES**

INVESTIGATOR OF RECORD: *[insert name]*

PHONE: *[insert number]*

I understand that Federal law requires that researchers, healthcare providers and health plans protect the privacy of information that identifies me. I understand that the privacy law, Health Insurance Portability & Accountability Act (HIPAA) requires that researchers get my permission to be able to use or disclose my protected health information (PHI) for research purposes in the study entitled "The Women's HIV SeroIncidence Study (ISIS)". By signing this authorization, I am giving that permission.

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

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

- Demographic Information
- Contact Information
- Blood storage
- HIV testing
- Medical History
- Current medications
- Sexual History and Related Risk Behaviors

My protected health information will be used for:

For Evaluation of HIV incidence as per the protocol/informed consent and for which my Protected Health Information, and those of others, is required in order to determine the incidence of HIV among study participants.

The Researchers may use and share my health information with:

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

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

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

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

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

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

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

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

This Authorization does not have an expiration date.

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

I have read this information, and I will receive a copy of this form after it is signed.

Signature of study participant

Date

Printed name of participant

Signature of witness (if applicable)

Date

Printed name of witness