

**Project Accept (HPTN 043):
A Phase III Randomized Controlled Trial of
Community Mobilization, Mobile Testing,
Same-Day Results, and Post-Test Support for HIV
in Sub-Saharan Africa and Thailand**

Sponsored by:

The National Institute of Mental Health

The HIV Prevention Trials Network

Note: This is the final version of the Project Accept (HPTN 043) protocol.
Some of the text herein has been updated after the original version
was approved by NIH, IRBs, etc, in order to provide a complete record
of the study as it was actually implemented.

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Version 2.5
July 1, 2013

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LIST OF ACRONYMS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CAP	College of American Pathologists
CBOV	Community-based outreach volunteer
CBVCT	Community-based voluntary counseling and testing
CDC	Centers for Disease Control and Prevention (U.S.)
CEA	Cost-effectiveness analysis
CFR	Code of Federal Regulations (U.S.)
CI	Confidence interval
CWG	Community working group
DALY	Disability-adjusted life year
DSMB	Data and safety monitoring board
EIA	Enzyme immunoassay
FDA	Food and Drug Administration (U.S.)
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HIVNET	HIV Network for Prevention Trials
HPTN	HIV Prevention Trials Network
HPTN NL	HPTN Network Laboratory
IRB	Institutional review board
JHU	Johns Hopkins University
MAA	Multi-assay algorithm
NIH	National Institutes of Health (U.S.)
NIMH	National Institute of Mental Health (U.S.)
OAR	Office of AIDS Research (U.S.)
OI	Opportunistic infection
OSHA	Occupational Safety and Health Administration (U.S.)
PEP	Postexposure prophylaxis
PHS	Public Health Service (U.S.)
PI	Principal Investigator
PLWHA	People living with HIV/AIDS
PMTCT	Prevention of mother-to-child transmission
PPP	Purchasing power parity
PTSS	Post-test support services
QA/QC	Quality assurance/quality control
SAC	Study Advisory Committee
SC	Steering Committee
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SOP	Standard operating procedure(s)
STD	Sexually transmitted disease
SVCT	Standard (clinic-based) voluntary counseling and testing
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
USAID	United States Agency for International Development
VCT	Voluntary counseling and testing

1. INTRODUCTION

1.1 Overview

Achieving significant and lasting reductions in incidence of HIV in countries hit hard by the HIV/AIDS epidemic requires evidence-based approaches to prevention that mobilize entire communities, rather than just focusing on individuals. This is the first randomized controlled Phase III trial to determine the efficacy of a behavioral/social science intervention with an HIV incidence endpoint in the developing world.

Controlled studies of well-characterized approaches to community change are few in number.¹⁻⁴ We propose to test a theory-based, pragmatic, and sustainable approach to community-level change. The approach can be tailored to be culturally appropriate in different countries, as well as sensitive to gender-based issues. Community-level approaches to prevention would need to (a) “tip the scale” to establish as the community norm reductions in behaviors and attitudes (eg, stigma, fears of getting tested for HIV) that lead to HIV transmission, as well as increases in behaviors that help people maintain health (eg, getting tested for and discussing HIV); (b) support early adopters of behavior change so that others are encouraged to follow their lead; (c) ensure that individuals have the information and skills they need to initiate and maintain risk reduction; and (d) establish support systems to promote effective coping for those diagnosed with HIV.^{5,6}

In this prevention trial, 48 communities (10 in Tanzania [Kisarawe], 8 in Zimbabwe [Mutoko], 8 in South Africa/Vulindlela, 8 in South Africa/Soweto and 14 in Thailand [Chiang Mai]) will be randomized to receive either a community-based HIV voluntary counseling and testing (CBVCT) intervention or standard clinic-based VCT (SVCT). The CBVCT intervention has three major strategies: (1) to make VCT more available in community settings; (2) to engage the community through outreach; and (3) to provide post-test support. These three strategies are designed to change community norms and reduce risk for HIV infection among all community members, irrespective of whether they participated directly in the intervention. Thus, a community-level sampling approach is used to evaluate outcomes, as opposed to a cohort design.

1.2 Significance

From a public health perspective, there is no more compelling crisis in the world today than the HIV epidemic in sub-Saharan Africa. There is concern that this magnitude of epidemic burden could devastate part of Asia as well. Since the epidemic began, more than 60 million people have been infected with HIV.⁷ In 2003, AIDS killed 2.3 million people in Africa alone. In addition to death and disease burden, the epidemic has had an enormous impact on economies and life expectancies, and left a legacy of millions of orphans. With an estimated 3.4 million new HIV infections in sub-Saharan Africa in the past year alone, 28.2 million Africans are now living with the virus. Globally, about one-third of those currently living with HIV/AIDS are aged 15-24. Most of them do not know that they are infected. In many developing countries, over 40% of the population is under the age of 15. If communities or environments in these developing countries do not change, then these young people will become adults in the same communities where HIV prevalence will likely continue at the same levels with

the same disastrous impact. From the perspective of national AIDS control planners in these countries, evidence-based strategies that have maximum epidemic impact are critically needed. These planners need interventions that are sustainable and can be adapted to the context of their local cultures. In this prevention trial, we not only test the efficacy of this intervention, but also the incremental cost-effectiveness of implementing such an approach in resource-poor countries. Provided that we can document efficacy with regard to HIV incidence and incremental cost-effectiveness, we expect that resources for widespread implementation of CBVCT will become available from USAID or the new Global Fund. We have worked closely with representatives of national AIDS programs in the host countries to ensure that the intervention is sustainable even in countries with limited resources.

From a scientific perspective, this is the first international randomized controlled Phase III trial to determine the efficacy of a behavioral/social science intervention with an HIV incidence endpoint. Additionally, this is the largest randomized, controlled Phase III study of its kind to be conducted at the community level rather than at an individual level. While the NIH/NIMH Collaborative HIV/STD Prevention Trial is a significant step toward testing the efficacy of a large-scale, community-level (as opposed to individual level) intervention, only behavioral and STD endpoints were able to be collected. This trial is being conducted in sites (South Africa, Tanzania, Thailand, and Zimbabwe) selected because they will allow for testing HIV incidence, thus allowing the study to have both behavioral (HIV risk practices) and biological (HIV incidence) endpoints (to detect an intervention-related difference in HIV incidences with the desired power, the baseline incidences at the sites must be sufficiently high. We chose the participating sites so that the average baseline annual incidence across all communities in the study is likely to reach at least 3%.)

1.3 Rationale for Community-Level Impact

CBVCT is an approach to community change.⁸ Community-level approaches to HIV prevention are important because of the enormous potential for epidemic impact. To date, models to change community norms have largely consisted of social marketing campaigns or structural-level policy interventions. Individual-level behavioral or biological interventions, such as clinic-based VCT and STD treatment, are strategies largely designed to respond to the epidemic one person at a time. A community-level intervention based on changing community norms can change the environmental context in which people make decisions about HIV risk. Community-level approaches have the potential to alter the course of the HIV epidemic in developing countries.⁹ The rationale for this community-based approach is found in diffusion theory,¹⁰ which has been used to study social change, particularly in international development and public health, in various countries. Diffusion is the process by which an innovation is communicated over time among members of a social system. Diffusion theory has been used as the rationale for most community-level interventions in the context of HIV prevention.¹¹ This model focuses on social networks, opinion leaders, and change agents. Although such elements are influenced by global cultural trends such as those portrayed through the media, immediate interpersonal interactions occurring in social networks within specific communities are essential for

inducing and maintaining behavior change. We decided on a community-level intervention because many people in our earlier VCT study in Africa avoided counseling and testing because it was not normative in the community, because of stigma associated with HIV, and because there were no support services available for those who tested. Responding to stigma, discrimination, and inequities requires an environmental or structural intervention to change the context in which individuals and communities respond to HIV.^{5,12,13} The most effective responses to HIV have been those in which affected communities mobilize themselves to fight stigma and discrimination as well as increase community awareness of HIV.¹⁴⁻¹⁸ Thus, the aim of CBVCT is to move beyond individual behavior change to achieve community change. A trial that tests a combined community-level intervention aimed at increasing knowledge of HIV status, changing norms, and enhancing social support could make a significant contribution to the scientific literature and public health practice in developing countries.

1.4 Rationale for Intervention

We hypothesize that this combined intervention will result in a number of positive behavioral outcomes, as well as a reduction in HIV transmission. CBVCT has strong theoretical roots. While the overall community-level approach is based on diffusion theory, each of the components of the proposed intervention has its own rationale. The table below outlines the relationship between theory, intervention, and predicted outcomes.

Theory	Intervention	Assessment
Tipping point for social change – maximizing the proportion of individuals who know HIV status will influence norms mediated by social networks ¹⁹	Easy Community Access to VCT to increase the percentage of the population aware of HIV status through increased availability of VCT in community settings	<ul style="list-style-type: none"> • Behavioral risk • Rates of HIV testing • Social norms of HIV testing • Frequency of discussions of HIV in communities
Diffusion of innovation – early adopters of innovative behavior influence others in their social network ²⁰	Community outreach and mobilization using outreach coordinators and recruiting early testers as community outreach workers	<ul style="list-style-type: none"> • Rates of HIV testing • Social norms of HIV testing • Frequency of discussions of HIV in communities • HIV-related stigma, community level
Social action model – reduction in HIV transmission will be influenced by self-regulatory skills, contextual issues, and mood ²¹	Post-test support through post-test clubs with peer-based social support groups	<ul style="list-style-type: none"> • Social benefits and harm • Frequency of disclosure of HIV status • HIV-related stigma, personal level among those infected • Behavioral risk of transmitting HIV among infected individuals
Combined	Combined	<ul style="list-style-type: none"> • Incidence of HIV infection • Incremental cost-effectiveness

1.4.1 Tipping Point Theory

A “tipping point” occurs when a critical mass of adoption occurs in a social network. It is affected by three factors: (1) the “law of the few”, (2) the “stickiness” of the behavior, and (3) the context of the innovation.¹⁹ The “law of the few” refers to the role that a few core transmitters can have in the diffusion of key factors (such as microbes, behaviors, or beliefs) across a social network. We believe that behavior change among a core of HIV-infected individuals, as well as a change in beliefs among community leaders, will significantly slow the epidemic. The “stickiness” of a behavior refers to the social salience of the behavior, or how important it is deemed to be to the collective community. We believe that increasing the proportion of individuals in a community who are aware of their HIV status will increase the collective awareness that HIV is a real threat and that many HIV-infected people are in the social network. The context of the innovation refers to the physical and social context where behaviors occur; the context of innovations has a strong impact on the readiness to adopt them. We believe that providing VCT in the context of where people live will change social norms around HIV testing, increase the frequency of discussions about HIV in communities, and ultimately decrease behavioral risk.

1.4.2 Diffusion of Innovation

Diffusion of innovation theory contends that within communities there are a small number of people who are innovators. Early adopters then influence others in a social network. Eventually, a threshold of behavioral adoption at the network level is reached that sustains the widespread uptake of a behavior.²⁰ This is similar to what would be explained by the “law of the few” in tipping point theory, but puts greater emphasis on the importance of timing. In particular, diffusion of innovation theory would predict that by enticing opinion leaders early on to adopt an innovative behavior deemed to be adaptive, the speed of uptake of the new behavior is facilitated. Such effects have been documented with regard to changing risk practices associated with adolescent smoking, pregnancy, and sexual risk behavior.²²⁻²⁴ Both negative and positive attitudes towards persons with stigmatized illnesses and behaviors are also influenced by these social dynamics.^{25,26} Thus, we believe that a community mobilization approach that promotes HIV testing among early adopters, particularly if these individuals are influential and central to the larger social network, can begin a process of changing community norms to both increase discussions about HIV in communities and decrease HIV-related stigma.

1.4.3 Social Action Theory

Social action theory²¹ explains health-protective behavior as an interaction among three domains: (1) the self-regulatory capabilities of the individual; (2) the environmental context; and (3) responses to internal affective states. We have used this theory as a guide for

understanding the role of post-test support services. Self-regulatory factors for risk reduction include technical skills (such as condom use), social skills (such as negotiation and partner communication), and interpersonal problem-solving skills. Consistent with previous research, we believe that improvements in self-regulatory capabilities can reduce the likelihood of sexual transmission acts,²⁷⁻³⁰ and that support groups will help build and support the maintenance of these capabilities. Social contextual factors such as relationship status and transactional sex are likely to be linked to transmission acts. For example, injection drug users in Bangkok who believe they are infected have cited a desire to protect partners as a major reason for condom use.³¹ Contextual factors such as relationship issues are logical topics for discussion and problem solving in support groups. Negative affective and arousal states have been associated with decreased self-regulation of sexual behavior in both HIV-infected men³² and women.³³ We expect that support groups will be effective in increasing coping skills (self-regulatory capabilities), as well as decreasing depression and stress (negative affective states) for people living with HIV, particularly if structured around issues likely to be confronted in the local culture (environmental context).³⁴ Thus, we would expect participants in support groups to have reduced behavioral risk of transmitting HIV to others, and less internalized stigma.

1.5 Collaborating Institutions

This project is funded as a National Institute of Mental Health (NIMH) Cooperative Agreement involving Johns Hopkins University (JHU) Bloomberg School of Public Health, the Medical University of South Carolina, and the University of California at San Francisco (UCSF) and Los Angeles (UCLA). The Fred Hutchinson Cancer Research Center in Seattle, University of North Carolina at Chapel Hill, and Charles University in Prague, Czech Republic, are also participating. The host country institutions are Chiang Mai University in Thailand; Human Sciences Research Council in Durban, South Africa; Perinatal HIV Research Unit and the University of the Witwatersrand in Johannesburg, South Africa; Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania; and University of Zimbabwe in Harare, Zimbabwe.

Each institution collaborating on the study holds a Federalwide Assurance, listed below.

<u>Institution:</u>	<u>Assurance #:</u>
Charles University	FWA00000305
Chiang Mai University, Research Institute for Health Sciences	FWA00005355
Fred Hutchinson Cancer Research Center	FWA00001920
Human Sciences Research Council	FWA00006347
Johns Hopkins University Bloomberg School of Public Health	FWA00000287
Medical University of South Carolina	FWA00001888
Muhimbili University of Health and Allied Sciences	FWA00004301
National Institute of Mental Health	M1000
University of California, Los Angeles	FWA00004642
University of California, San Francisco	FWA00000068
University of North Carolina at Chapel Hill	FWA00004801
University of the Witwatersrand/Chris Hani Baragwanath Hospital	FWA00000715
University of Zimbabwe	FWA00001195

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective (Aim 1) of this study is to test the hypothesis that communities receiving 3 years of CBVCT, relative to communities receiving 3 years of SVCT, will have significantly lower HIV incidence. Aim 1 will be evaluated by comparing the post-intervention HIV incidence in CBVCT and SVCT communities. HIV infection status will be assessed in-country using HIV rapid tests (see Section 5.7). The final HIV status may be modified based on the results of Quality Assurance testing performed at the HPTN Network Laboratory (HPTN NL). Annual HIV incidence will be estimated from the post-intervention assessment (cross-sectional survey) using a multi-assay algorithm. This algorithm will most likely include two serologic HIV incidence assays (the BED capture immunoassay [BED-CEIA] and an avidity assay), as well as non-serologic measures (eg, CD4 cell count and HIV viral load). An antiretroviral drug screen may also be used to identify participants who are likely to be on antiretroviral treatment (ART), since these participants are not likely to have recent (incident) infection. Samples from HIV-seronegative individuals may also be analyzed for evidence of early/acute HIV infection.

2.2 Secondary Objective

The secondary objective (Aim 2) of this study is to test the hypotheses that CBVCT communities, relative to SVCT communities, will at the end of the intervention period report significantly:

- less HIV risk behavior
- higher rates of HIV testing
- more favorable social norms regarding HIV testing
- more frequent discussions about HIV
- more frequent disclosure of HIV status
- less HIV-related stigma
- fewer HIV-related negative life events

2.3 Cost-Effectiveness Outcomes

Aim 3 of the study will be to assess whether CBVCT is cost-effective compared to SVCT. Aim 3 will be evaluated in terms of cost per HIV infection averted and disability-adjusted life years (DALYs) saved.

2.4 Qualitative Analyses

The qualitative assessment is designed to describe and compare changes in risk behaviors, norms regarding HIV testing, discussions regarding HIV, HIV serostatus disclosure, HIV-related stigma, and other life events related to HIV among individuals in intervention and control communities. Data will be gathered to describe how anticipated and unanticipated changes in norms, attitudes, and behaviors occur among community members. The specific mechanisms through which the intervention works will be described at the individual and the community level. Psychosocial factors that influence

individual decision-making regarding changes in behaviors, attitudes, and norms will be explored through in-depth interviews conducted with a cohort of 128 community members in each of the three southern African sites, 160 community members in the East African (Tanzania) site, and 112 community members in the Thai site at baseline, 6 months, 15 months, and 36 months. At the level of the community, we will gather ethnographic data through community mapping, participant observations, and key informant interviews to describe networks of interdependence and social support that may prove important pathways through which the CBVCT intervention will function.

3. STUDY DESIGN

3.1 Trial Design

This is a Phase III community-level randomized controlled study, in which 34 communities in four sites in Africa (Zimbabwe, Tanzania, and Soweto and Vulindlela in South Africa) and 14 communities in Thailand will be randomized to either an intervention arm, consisting of community-based voluntary counseling and testing for HIV (CBVCT) plus standard clinic-based VCT (SVCT), or to a control arm, consisting of SVCT alone. As the study is testing a community-level intervention, communities – rather than individuals – are the unit of randomization. The assessment of efficacy is based on changes in communities' risk behaviors, using repeat cross-sectional data collected using household probability samples, as well as community-level HIV incidence determined approximately 3 years after services are introduced in each community. This is different from traditional study designs, namely that we would study individuals receiving the two different kinds of VCT. Rather, our interest is in the impact of community-based VCT on the entire community, relative to standard VCT. Because of this, we must estimate the difference in incident infections between the communities receiving community-based VCT and those receiving standard VCT, and not just follow a preselected cohort of community residents. In addition, if we were to include a baseline assessment of HIV prevalence in the two communities, we would essentially have given everyone the basic intervention.

A baseline behavioral assessment will be conducted in all communities using a household probability sampling technique. Households will be selected at random, and then an eligible member of the household will be selected at random and offered participation in the assessment. Following the baseline behavioral assessment, pairs of communities will be matched using one or more variables; each community in a pair will then be randomized to receive either CBVCT or SVCT (CBVCT communities will be provided with both CBVCT and SVCT services, while SVCT communities will only be provided with SVCT services).

CBVCT combines three main strategies: community mobilization, easy community access to VCT, and post-test support services. The community mobilization phase of the intervention will consist of educating communities about HIV, providing HIV testing, and encouraging discussion in the community with the intent to increase awareness and decrease stigma. Communities randomized to receive CBVCT will receive deployment of a mobile VCT unit comprising VCT counselors, a nurse-counselor, and an outreach worker/driver. The counselors and outreach worker will provide information on HIV/AIDS and the VCT process upon the mobile unit's arrival at a given location to encourage people to consider undergoing HIV testing. Post-test support services facilitated by the study staff will be available to people who have tested at a Project Accept venue or elsewhere, regardless of their test results, to provide support and facilitate health and social service referrals. The combination of community outreach/mobilization, community-based mobile VCT services, and post-test support services will comprise the CBVCT intervention.

In addition to the CBVCT intervention, CBVCT communities will also be provided with SVCT services, outlined below.

Communities randomized to the SVCT arm (the “standard-of-care” arm) will receive the installment of clinic-based VCT services in existing district hospitals, community-based health care centers, or other local health delivery facilities (a version of VCT consistent with the study protocol may be integrated into existing VCT services). Training for the CBVCT and SVCT counselors will be the same; however, no study-sponsored active outreach/community mobilization, mobile VCT services, or special post-test support services will be provided in the SVCT arm (although it is possible that such activities will occur due to local initiative).

A qualitative cohort in each community will be recruited in order to collect data on how stigma changes over time in the communities, and will allow for an assessment of attitudes toward HIV-infected persons, an intermediate outcome of the study.

A post-intervention assessment will be conducted using the same household probability sampling technique as for the baseline behavioral assessment. Recruited individuals from each community will provide biological samples for HIV testing, with a subsample of individuals from each community receiving a second cross-sectional behavioral assessment.

Figure 1 outlines study and consent procedures for each CBVCT study component, including numbers of participants.

Figure 2 presents the organizational structure for the study at each site.

3.2 Rationale for Post-Intervention Assessment of HIV Endpoint

The protocol team deliberated at length and consulted with the biostatistics groups at the Fred Hutchinson Cancer Research Center, UCSF, and Johns Hopkins prior to deciding to assess the primary endpoint using a post-intervention assessment strategy. First, a baseline assessment of HIV incidence, which for ethical reasons would involve state-of-the-art counseling and testing, would provide a key component of the proposed intervention and thus dilute our ability to determine a treatment effect between the intervention and control communities. Second, if a baseline assessment of HIV incidence was conducted that included assessment of HIV infection, and at the same time avoided saturation of the community, excessively large communities would have to be chosen. According to our power calculations, including an incidence assessment in the baseline survey with the same number of people planned for the final sample, and using the estimate to match the communities or to adjust for the baseline incidence, would reduce the power to such a degree that we would need to enroll 50-100% more communities than with our current design. The baseline incidence measurement would have to be based on a huge sample size in order to be useful. The reason is that, in the final analysis, we are merging the estimated effects across all the community pairs; the baseline measurement would have to provide an incidence estimate with a sufficient precision for each individual community. This is not feasible. This is a proof-of-concept study. It is essential

that intervention goals are reached, but also that the study is not overly expensive. Thus, eliminating assessment of HIV from the baseline allows the study to be conducted in reasonably sized communities with the assurance that intervention goals can be reached. Third, a post-intervention-only assessment of HIV rather than a traditional pre- and post-intervention assessment reduces measurement error because the inherent variability (ie, error) in measurement of the primary endpoint occurs only once rather than twice. A cohort design will not work to address the primary hypothesis. If we were studying individual reduction in HIV infection as a result of counseling and testing, we would need to follow a cohort of people who were tested and who were not tested. We are, however, examining reductions in community-level HIV incidence, and this requires that we look at HIV in the whole community. A cohort study would not give us this information because it would not be representative of the entire community. Thus, the design we have chosen is the most optimal, in that it allows us to examine HIV incidence in the community without contaminating the intervention with the assessment.

3.3 Study Duration

The intervention component of the study will last 3 years. The entire study project, from planning work through data analysis, is scheduled to last 8 years. A timeline for the project is presented in **Figure 3**.

4. BEHAVIORAL INTERVENTION

4.1 CBVCT Communities

CBVCT combines three main strategies: community mobilization, easy community access to VCT, and post-test support services. The intervention in each of the countries and sites will be derived from the same theoretical model and contain the same strategies. The operationalization of the elements of the intervention will be tailored to each local culture and context. The CBVCT intervention is based on the premise that HIV sexual risk behavior and HIV incidence will decrease in communities with increased knowledge of HIV status and more supportive community norms. The CBVCT intervention phase consists of four components—Community Mobilization, Community-Based (mobile) VCT, Post-Test Support Services, and Quality Assurance.

In addition to the CBVCT intervention, “CBVCT” communities will also receive provision of SVCT services, outlined in Section 4.2.1.

4.1.1 Community Mobilization

This component of the intervention is based on diffusion of innovation theory, which contends that there are a small number of people in communities who are innovators. Then, early adopters influence others in a social network. Eventually, a threshold of behavioral adoption at the network level is reached that sustains the widespread uptake of a behavior. This is similar to what would be explained by the "law of the few" in tipping theory, but puts greater emphasis on the importance of timing. In particular, diffusion of innovation theory would predict that by enticing opinion leaders early on to adopt an innovative behavior deemed to be adaptive, the speed of uptake of the new behavior is facilitated. Thus, a community mobilization approach that promotes HIV testing among early adopters, particularly if these individuals are influential and central to the larger social network, can begin a process of changing community norms to both increase discussions about HIV in communities and decrease HIV-related stigma.

Community mobilization uses community outreach to enhance the uptake of VCT, thus increasing the rate of HIV testing and frequency of discussions about HIV. This component is also designed to reduce stigma through community education and mobilization. The community mobilization phase of the intervention will consist of educating communities about HIV, providing HIV testing, and encouraging discussion in the community with the intent to increase awareness and decrease stigma. Ultimately, these efforts are intended to increase acceptance and utilization of the mobile VCT component of the study.

4.1.2 Easy Access to VCT

This component of the intervention is based on tipping point theory and is designed to remove practical barriers (fees, inconvenience, waiting for results) and increase safety of VCT (anonymity, high-quality counseling

and post-test support). This ease of access should increase rates of HIV testing, change social norms about testing, and increase the frequency of discussions about HIV in communities. This approach should also decrease behavioral risk for HIV. Mobile vans or temporary units set up at local community sites will provide free, anonymous* VCT in specific, chosen sites where people gather, such as market areas, shopping centers, and community centers. The mobile VCT component of the study is scheduled to operate for three years following the baseline assessment.

** In South Africa, written informed consent is required for HIV VCT. No identifying information will be retained other than the signed consent form, which will not be linked to the participant's HIV test result. HIV and AIDS are not reportable in South Africa, and participant names and HIV results are not communicated to government nor to any other parties.*

4.1.3 Post-Test Support Services

The third component of the intervention is based on a social action model and is designed to build psychosocial support to improve the quality of life for individuals diagnosed with HIV. The expected outcomes include a reduction in social harm, an increase in social support through disclosure to those most likely to provide support, and a reduction in internalized stigma. Social support should also decrease the behavioral risk of further transmission. Our objective in providing post-test support services (PTSS) is to create a culturally appropriate support system for community members following their decision to take part in CBVCT.

4.1.4 Quality Assurance

Both the CBVCT and control arms of this study will use a model of voluntary counseling and testing consistent with recommendations from the Centers for Disease Control and Prevention.³⁵ Quality assurance procedures are detailed in Section 5.4.4.

4.2 Control Communities

Control communities will receive Standard Clinic-Based VCT (SVCT) instead of the CBVCT intervention. Each of these communities will have access to SVCT that reflects local access to health care. The training for VCT counselors will be the same in the CBVCT and SVCT communities; however, no active recruitment for participation in the SVCT services will be made beyond the standard procedures of each clinic for informing patients of services (ie, telling individual patients that VCT is available, posting of a flyer in the clinic announcing VCT availability, etc). As such, no active outreach or community mobilization will be conducted by the study staff in the SVCT settings (although it is possible that such activities will occur due to local initiative). The two major components of the SVCT will be clinic-based VCT and quality assurance.

4.2.1 Clinic-Based VCT

Standard VCT services will be established at existing district hospitals, community-based health care centers, or other local health delivery facilities (a version of VCT consistent with the study protocol may be integrated into existing VCT services). The procedures for counseling and HIV rapid testing will be the same as those in the CBVCT communities, except that referrals will be limited to existing community agencies rather than study-related post-test support services. VCT activities will be implemented in the intervention and control communities simultaneously and run for three years.

4.2.2 Quality Assurance

Both the CBVCT and control arms of this study will use a model of voluntary counseling and testing consistent with recommendations from the Centers for Disease Control and Prevention.³⁵ Quality assurance procedures are detailed in Section 5.4.4.

5. STUDY PROCEDURES

5.1 Baseline Behavioral Assessment

Using predefined criteria, trained study staff or trained staff of a contract survey research organization will conduct an enumeration of households in the community. Households will be randomly selected. The responsible adult who is present at the time of approaching the home for the first time will be identified by approaching the house and asking to speak with "the person in charge of the household right now or other responsible adult that the interviewer may speak with". This person does not strictly have to be the official head of household (de jure), but should be someone identified by the members of the household as an adult who is aware of the ages and genders of all members of the household and, further, who is able to give informal assent for the interview to take place in the home. This is not a substitute for the consent of individuals who will be asked to participate, but rather should be negotiated by the interviewer out of courtesy and to facilitate the ease of the interview. It is important that the interviewer clarify that the "head of household" is someone who is currently living in the home, to distinguish this person from a migrant household member who may only return to the household once every few months. The main purpose of this person is to facilitate access to the home and to enumerate the persons who live in the household. The head of the household will be provided with an explanation of the study and will be asked to enumerate the members of the household.

Enumerated household members will be eligible to participate in the baseline survey if they are aged 18-32 years, have lived in the community at least 4 months in the past year, and sleep regularly in their household at least 2 nights per week. If more than one household member is eligible, one household member will be randomly selected.

If the interviewer is unable to make contact at any step in the recruitment process (making contact with anyone in the household, making contact with the head of the household, making contact with the selected individual), the interviewer will return a minimum of 2 times at each step, until such contact is made. An appointment card may be left for the head of household, to notify them when the interviewer will be returning and to briefly explain the purpose of the survey.

The selected household member will be asked to provide verbal consent. For each assessment taken, the interviewer will document that verbal consent was given. Once verbal consent has been given, the interviewer will administer the questionnaire to the selected household member, question by question, until the assessment has been completed. A subset of participants in the baseline behavioral survey will be invited to participate in in-depth qualitative interviews.

Interviewers will be trained on the importance of ensuring privacy during the interview. Other members of the household will not be permitted to observe the interview, and if the head of household refuses to allow the interview to take place in privacy, the interview may have to be forfeited. Experience in conducting household surveys in these settings has found that very often members of the household are willing to leave to allow the interview to take

place in privacy or the interview can be conducted outside in the yard if there is no space in the home where the interview can be conducted in private.

(Study procedures related to the implementation of the baseline behavioral assessment are described in detail in the *Baseline Assessment Operations Manual*.)

5.2 Community Matching

Communities at each study site will be matched into pairs in order to minimize the differences in the underlying HIV incidence rates between communities randomized to CBVCT and SVCT interventions and thus to increase the chance of detecting a difference in HIV incidence rates due to the interventions. Eight communities at each African site will be matched into 4 pairs; fourteen communities in Thailand will be matched into 7 pairs. Within each pair, one community will be randomized to CBVCT and the other to SVCT.

Each site will propose and document a plan for matching its study communities into pairs. To this end, the sites will use the information on study communities collected during the process of geographic mapping and community ethnography (see Section 5.3.1), and during the enumeration of community households for the selection of the baseline survey sample. The matching plan will take into account the geographic distribution of the study communities so as to assure that matched communities are located close to each other. Factors that may contribute to the matching plan include ethnic composition of the communities (Thailand), housing conditions (Soweto), road accessibility, existence of healthcare facilities, local economic conditions, and other factors. Each site will submit a map identifying the matched community pairs and document what other factors, besides geography, were included in the matching process.

5.3 Qualitative Assessment

Detailed information on qualitative research policies and procedures are included in the *Qualitative Assessment Manual of Operations* and the *Geographic Mapping and Community Ethnography Manual of Operations*.

5.3.1 Community Mapping and Ethnography

Community mapping, participant observation, and key informant interviews will be conducted in each study community to describe the community-level systems and processes that influence how the intervention functions. The qualitative staff will work with community members to develop geographic and social maps of the communities. Existing data on the study communities will be collected and synthesized, and where necessary, geographic maps will be developed, potentially using GPS technology. The communities will be physically mapped by getting tours from a variety of community members and leaders (“participatory mapping”) and by dividing the community into 2-6 grids and having staff explore on foot or by car each grid with a key informant guide (“transect walks”). The maps will include geographic landmarks such as rivers, hills, roads, wetlands, forests, and social

landmarks such as places of worship, markets, bus depots, shops, hotels, and any type of community gathering place. Community members will also be asked to map HIV risk behavior by locating on the map the physical locations where they believe HIV risk behavior tends to take place or where community members are most vulnerable to HIV risk. During the participatory mapping and transect walks, an inventory of social and health services will be made by ethnographic staff. Qualitative staff will also conduct participant observations at least twice in each study community during the intervention period. These observations will be conducted in key locations, such as bus depots and market places, and at key events such as women's group meetings and church gatherings. Staff will observe social interactions and talk to community members about the social networks in which they operate. Finally, the qualitative staff will identify two to three key informants in each site with whom they will develop an ongoing relationship. Through interviews with these informants the staff will describe the networks of interdependence and social support that exist in the community and explore how community members use their social networks for social support around issues of illness, including HIV/AIDS.

5.3.2 In-Depth Interviews

Sixteen community members from each community in the African sites (544 total) and 8 community members from each community in the Thai site (112 total) will be selected for the qualitative assessment cohort. These cohort members will be sampled from among those who complete the baseline behavioral survey. A series of in-depth interviews will be conducted with each cohort member at baseline, 6 months, 15 months, and 36 months. It is anticipated that changes in attitudes, norms, and behavior will occur rapidly as a result of the intervention; therefore interviews have been concentrated earlier in the study period to document and describe this rapid change. An interviewer trained in qualitative research methodology will conduct the interviews with cohort members in a location that is both convenient and private. Informants will select the language for the interviews (English, a national language, or a local vernacular). A semi-structured interview guide listing general topics will be prepared for each interview. Probing will be used to stimulate discussion and follow-up on ideas. Interviews will last approximately one hour and will be audiotaped with the consent of the informant.

5.4 CBVCT Communities

(Study procedures related to the implementation of the intervention are described in detail in the *Community Mobilization Standard Operating Procedures Manual*, the *Community Based Voluntary Counseling and Testing Standard Operating Procedures Manual*, and the *Post-Test Support Services Standard Operating Procedures Manual*.)

CBVCT combines three main strategies: community mobilization, easy community access to VCT, and post-test support services. The intervention in

each of the countries and sites will be derived from the same theoretical model and contain the same strategies. The operationalization of the elements of the intervention will be tailored to each local culture and context. The CBVCT intervention is based on the premise that HIV sexual risk behavior and HIV incidence will decrease in communities with increased knowledge of HIV status and more supportive community norms. The CBVCT intervention phase consists of four components—Community Mobilization, Community-Based (mobile) VCT, Post-Test Support Services, and Quality Assurance.

In addition to the CBVCT intervention, “CBVCT” communities will also receive provision of SVCT services, outlined in Section 4.2.1.

5.4.1 Community Mobilization

This component of the intervention is based on diffusion of innovation theory, which contends that there are a small number of people in communities who are innovators. Then, early adopters influence others in a social network. Eventually, a threshold of behavioral adoption at the network level is reached that sustains the widespread uptake of a behavior. This is similar to what would be explained by the "law of the few" in tipping theory, but puts greater emphasis on the importance of timing. In particular, diffusion of innovation theory would predict that by enticing opinion leaders early on to adopt an innovative behavior deemed to be adaptive, the speed of uptake of the new behavior is facilitated. Thus, a community mobilization approach that promotes HIV testing among early adopters, particularly if these individuals are influential and central to the larger social network, can begin a process of changing community norms to both increase discussions about HIV in communities and decrease HIV-related stigma.

Community mobilization uses community outreach to enhance the uptake of VCT, thus increasing the rate of HIV testing and frequency of discussions about HIV. This component is also designed to reduce stigma through community education and mobilization. The community mobilization phase of the intervention will consist of educating communities about HIV, providing HIV testing, and encouraging discussion in the community with the intent to increase awareness and decrease stigma. Ultimately, these efforts are intended to increase acceptance and utilization of the mobile VCT component of the study. Community mobilization activities will begin as soon as the research team gains access into the study communities. Access will be gained through negotiations with the relevant community leaders and local authorities (community preparedness; see Section 12.1). Mobilization will be an ongoing process and will continue throughout the intervention period. The community mobilization process will be facilitated by three different groups of people who will operate at different levels—Outreach Workers, Community Working Groups (CWGs), and Community-Based Outreach Volunteers (CBOVs).

Community Working Groups: CWGs will consist of community leaders, gatekeepers, and community health workers identified during the preparatory phase of the study. The groups will be trained and monitored by the Community Mobilization Coordinator. Group members will be encouraged to be among early HIV testers so they may in turn mobilize others to get tested. This should motivate the larger community to participate. The purpose of the groups is to inform the research staff about community preferences such as locations for mobile HIV testing and any special issues that may emerge in the course of the study. Some members of the CWGs will be selected to serve on a Study Advisory Committee (SAC). (Selection and role of SACs are discussed in depth in the *Community Preparedness and Involvement Operations Manual*. Where members of CWGs and SACs overlap, the site PI, study project director, and community mobilization coordinator, with assistance from the UCSF Intervention Director, will work together to create a standard operating procedure (SOP) to ensure separation of CWG and SAC roles and responsibilities, including QA duties.) CWG members will not be project staff but may be paid a sitting-allowance for attendance in meetings. The allowance paid may be based on what is standard in local sites.

Community Mobilization Coordinator: The Community Mobilization Coordinator is responsible for overseeing all aspects of the community mobilization work at the site. The coordinator supervises the outreach worker/drivers and assists them as needed in the field to accomplish their duties. He/she will assist the other two Intervention coordinators (VCT and PTSS) and their respective staff with ongoing community outreach activities in their research communities. The Community Mobilization Coordinator will report to the Project Director.

Outreach Workers/Drivers: Each site will have two full-time outreach workers/drivers, supervised by the Community Mobilization Coordinator. The Outreach Workers/Drivers are responsible for carrying out the community mobilization strategy on the ground. This includes recruiting, training, supervising, and monitoring the Community-based Outreach Volunteers. They will also be responsible for driving the mobile VCT teams and other study staff to and from the testing venues. The Outreach Workers/Drivers report to the Community Mobilization Coordinator.

Community-Based Outreach Volunteers: The CBOVs are responsible for diffusing the innovation throughout their social networks and will require a high degree of specialized training to do so. These community volunteers will not be project staff, but may receive a small stipend based on local community standards. These volunteers may be recruited from the pool of people who have participated in VCT, regardless of HIV status, as well as PTSS. Participants with good communication and interpersonal skills and who exhibit enthusiasm will be selected. A gender and ethnic balance in the selection will be maintained. CBOVs report to the Outreach Workers/Drivers.

Unlike Outreach Workers (staff), CWGs and CBOVs will be discouraged from direct contact with study participants at testing venues.

5.4.2 Easy Access to VCT

This component of the intervention is based on tipping point theory and is designed to remove practical barriers (fees, inconvenience, waiting for results) and increase safety of VCT (anonymity, high-quality counseling and post-test support). This ease of access should increase rates of HIV testing, change social norms about testing, and increase the frequency of discussions about HIV in communities. This approach should also decrease behavioral risk for HIV. Mobile vans or temporary units set up at local community sites will provide free, anonymous* VCT in specific, chosen sites where people gather, such as market areas, shopping centers, and community centers. In the case of mobile vans, identification of suitable sites will be a joint effort between the research staff and the community mobilization groups. Permission will be sought from community leaders, local authorities, and entrepreneurs at business centers to park the van and set up a temporary unit in the vicinity. The van will visit each site at on a rotating basis. The fieldwork days will be any combination of weekdays and weekends to ensure that the mobile unit is accessible even to those community members who are employed. A schedule of visits to the mobile testing sites will be distributed by CWGs and CBOVs to the respective communities in advance of the mobile VCT unit visit. Each research site will submit a plan for how to operate the mobile VCT component of the study to the Steering Committee for approval. The mobile VCT component of the study is scheduled to operate for three years following the baseline assessment.

** In South Africa, written informed consent is required for HIV VCT. No identifying information will be retained other than the signed consent form, which will not be linked to the participant's HIV test result. HIV and AIDS are not reportable in South Africa, and participant names and HIV results are not communicated to government nor to any other parties.*

VCT Procedures: VCT services, as well as HIV/AIDS educational materials and condoms, will be available from the van or community venue. People in the vicinity of the van or community center will be approached by an outreach worker and invited to take an HIV test. Those who agree to participate will be invited into the van, where a study counselor will administer informed consent in the client's choice of language. Clients who agree to participate in the study will be assigned a study ID number and receive pretest counseling from the study counselor. If the individual wishes to proceed with the HIV test, the designated staff will collect a venous or finger-prick blood sample that will be used for the rapid HIV tests.

Rapid HIV Testing Procedures: All sites will use tests that have been validated locally and approved by their ministry (or department) of

health. The standard algorithm for Project Accept intervention sites will be simultaneous/parallel running of two rapid tests in the mobile laboratory, with a third test (either a third rapid test or an EIA) used as a tiebreaker for discordant results. All sites must submit their rapid testing algorithm and specific choice of test(s) to the HPTN Network Laboratory. The HPTN Network Laboratory will ensure that all rapid tests chosen by sites are sufficiently sensitive and that rapid testing QA is standardized across all sites. All study sites will adhere to the SOPs elaborated by the subcommittee regarding laboratory practices, biohazard containment, etc.

Post-Test Counseling: The counselor will check with the participant to determine if they are prepared to receive test results. The counselor will then provide the participant feedback of test results and provide post-test counseling. This counseling session will include a condom demonstration, and participants will be offered condoms to take home. Post-test counseling will begin with the disclosure of test results. The counselor will disclose the test result in a direct, neutral tone of voice and wait for the participant's reaction before proceeding. The counselor will assist the participant to understand the meaning of the test results, cope with the emotional impact of the test result, and modify the risk reduction plan as needed.

Regardless of test result, all participants in the intervention communities (ie, those receiving CBVCT) will be referred to Project Accept post-test support services. Referral cards will be developed (and CBVCT staff trained in using them) by the Project Accept Utilization Subcommittee.

For participants who are identified by local testing as HIV positive (two reactive HIV tests out of 3 performed), in addition to referral to PTSS, the counselor will assist in making a safe disclosure plan and will provide appropriate referrals for health and social services. Implications of the positive result for that participant will be discussed; the individualized risk reduction plan will be reviewed with the goal of protecting partners.

For participants who are identified by local testing as HIV negative (two nonreactive HIV tests), the implications of the negative test result will be discussed and the individualized risk reduction plan reviewed with the goal of staying uninfected. The participant will also be referred to PTSS, including psychosocial support groups on staying uninfected.

For participants who are identified by local testing as HIV discordant (one reactive and one nonreactive HIV test), different procedures were followed at the sites. In both South African sites, samples from discordant participants were retested in the reference laboratory (per local practice and guidelines). Participants were asked to return for their HIV results and post-test counseling on a separate visit. In Zimbabwe and Tanzania, a third rapid test was used in the mobile laboratory and results were provided to participants at the same visit.

If a participant so requests, one additional counseling session with the counselor may be permitted—only in exceptional circumstances and only with the approval of the VCT counseling team leader—for additional emotional support; further support of the risk reduction plan; or to assist in overcoming practical, emotional, and interpersonal barriers to changing behavior. These participants will be referred for further counseling and support to Project Accept's post-test support services or other services as needed.

In the event that a participant returns to a Project Accept site for testing (because of the window period or because he/she simply wishes to be retested), the counselor will create a new unique identifying code for the participant and follow all the steps outlined above, as though the participant were new to the study. The participant's previous unique identifying code will not be used to ensure that there are no privacy breaches.

Sites may opt to offer participants a certificate documenting HIV status, to facilitate access to treatment and care. Participants are not obligated to receive a certificate, and no copies or records of certificates issued will be kept by study sites, in order to protect participant confidentiality.

Selection of Counselors: Each site will establish educational requirements for counselors based on local standards. However, in general, individuals who have proven their ability to establish rapport, demonstrate good listening skills, and be supportive, respectful, and nonjudgmental will be chosen as counselors for this study. These individuals should also demonstrate proficiency in basic counseling skills (active listening, reflection, and information gathering), and the basic facts of HIV transmission, antibody testing, and human sexuality.

Training Procedures for Counselors: Counselors will receive a 5-day training program that will be outlined in the *Counselor Training Manual*. Counselors will be required to complete the entire training program. After completion of the counselor training, the supervisor will observe the counselor completing each step of the intervention with a volunteer “participant.” Upon satisfactory completion of observed sessions, the counselor will be certified to conduct the study intervention and will receive a certificate to that effect.

Client-Centered Counseling Approach: The client-centered HIV counseling approach decreases the emphasis on education, persuasion, and test results in favor of personalized risk assessment and the development of a personalized risk reduction plan for each client. The emphasis in client-centered counseling is on developing a risk-reduction plan for each client that takes into account his or her emotional reactions, interpersonal situation, specific risk behaviors, and readiness to change. The content of the counseling sessions and the amount of counseling the participant receives is determined by his or her level of knowledge and specific, personal concerns about HIV/AIDS.

Personalized Risk Assessment: Client-centered HIV counseling is distinguished by the development of a personalized risk-reduction plan for each client. In order to create this plan, the participant's individual risk situation must be assessed. This risk assessment includes gathering information about the participant's sexual and other risk behavior as well as their interpersonal, social, and resource situation. The counselor may initiate the assessment by reviewing the ways in which HIV can be transmitted and asking the participant to discuss possible exposures. Readiness to change risk behavior and perceived self-efficacy to change risk behavior are also assessed. The counselor summarizes the client's risk assessment findings by stating (and listing, if appropriate), for each risk behavior identified, the participant's resources and barriers to change. For example, "You identified having unprotected sex with women other than your wife as an HIV risk for you; you wonder if some of these women are infected with HIV. You have used condoms before, but you aren't sure you can remember to use one or have one handy if you have been drinking."

Personalized Risk Reduction Plan: After the participant's risk behaviors have been identified, the counselor asks the participant if she/he would like to propose any strategies to reduce their risk. At this point the counselor may initiate the discussion of risk reduction by listing several alternative risk-reduction behaviors for the participant to consider. For example, "To reduce the risk that you will contract HIV from having sex with women other than your wife, you could avoid having intercourse with them or you could use a condom when you do. You could also protect your wife by using condoms when you have sex with her."

For each risk-reduction behavior the counselor assesses internal and external barriers to change, perceived efficacy to enact the new behavior, readiness to change, and the availability of resources to change. In supporting the participant's enactment of the personalized risk reduction plan, the counselor will acknowledge and support the participant's strengths (eg, social support, efficacy, previous success in changing behavior) and offer problem solving in areas of concern or expected difficulty in enacting the plan.

Finally, the counselor elicits a commitment from the participant to make specific behavior changes before the next counseling session. When appropriate, the risk-reduction plan can be written and given to the participant to cue and reinforce behavior change. For example, "You said that you would be willing to use condoms every time you have sex with women other than your wife. You have used condoms sometimes before, and that's great, but now you want to use them every time. You mentioned that your friends have started using condoms with other women, too. Would you be willing to carry condoms with you for the next two weeks? Let's see if that helps you to remember to use them, even when you've been drinking."

5.4.3 Post-Test Support Services

The third component of the intervention is based on a social action model and is designed to build psychosocial support to improve the quality of life for individuals diagnosed with HIV. The expected outcomes include a reduction in social harm, an increase in social support through disclosure to those most likely to provide support, and a reduction in internalized stigma. Social support should also decrease the behavioral risk of further transmission. Our objective in providing post-test support services is to create a culturally appropriate support system for community members following their decision to take part in CBVCT.

In establishing Project Accept PTSS, the overarching aim is to ensure that services are accessible to and meet the needs of intervention communities. The Study Site Project Director; Community Mobilization, VCT, and PTSS coordinators; and intervention communities will work together to identify post-test service needs, map existing community social services, and develop the optimal method of establishing Project Accept PTSS. Each research site will develop a plan for PTSS that will be sent to the Intervention Subcommittee and Steering Committee for approval. This plan will include documentation of existing, accessible community services.

At the African sites, PTSS staff will report to the PTSS coordinator. The PTSS Coordinator will oversee all PTSS centers in the intervention communities. Working in concert with the Study Site Project Director and Community Mobilization and VCT coordinators, the PTSS coordinator will negotiate with communities to set up PTSS centers, identify post-test service needs, and map existing community social services (see the Community Preparedness and Involvement Manual for more detail on the needs assessment and mapping processes). The PTSS coordinator will be responsible for monitoring the functioning of PTSS centers and conducting quality assurance of PTSS. The PTSS coordinator will report to the Study Site Project Director. Each intervention community will be staffed for 20 hours a week for PTS Services. The staff will include 2 PTSS team leaders, 2 counselors, and 2 receptionists. Each team will be composed of 1 team leader, 1 counselor, and 1 receptionist. The Thailand site will develop a plan to accomplish these goals with staffing appropriate to their configuration of seven smaller villages randomized to the intervention.

Procedures and Eligibility: Individuals who have undergone HIV testing at Project Accept or other HIV testing venues will be eligible to access the full range of PTSS services, and will be designated as “members”. Those who have not been tested for HIV will be designated as “guests”, and will have access to a more limited range of services. Both members and guests will go through a verbal informed consent process the first time that they come for services. Those who have not tested will be allowed to access the large informational groups offered at PTSS sites, but will not be able to access other PTSS services until they have been

tested. Persons interested in testing will be referred to Project Accept VCT.

Counselors will register members upon their first visit to PTSS and will sign them in on subsequent visits, using the registration logs developed by the Utilization Subcommittee. Counselors will also note whether members were accompanied by family members or friends. During members' first visit to PTSS, counselors will ask them, as well as accompanying family and friends, to discuss their service needs and expectations. PTSS staff will use the findings from this needs assessment to design PTSS activities and ensure that they are responsive to participants' needs. This process will also help to demarcate the difference between (a) the services delivered by Project Accept PTSS and (b) those delivered by non-Project Accept organizations/agencies, thus clarifying where secondary referrals will be necessary. In addition, PTSS staff, working with the Intervention Subcommittee, will conduct ongoing, periodic participant needs assessments through the duration of the research period to ensure responsiveness to participants' needs as well as to facilitate sustainability of PTSS post-Project Accept.

Post-Test Support Activities and Services:

One-Day Coping Effectiveness or "Moving On" Workshops

HIV-positive and HIV-negative PTSS members will be offered the opportunity to participate in one-day "Moving On" workshops that are designed to build skills in:

1. Managing stress
2. Coping effectiveness
3. Identifying post-test social support

The objectives of these workshops, which will involve 8-10 participants, will be to:

1. Optimize mental health outcomes, including ability to manage stress and cope with one's HIV test result
2. Build a core of community members with effective coping skills

We anticipate that the dynamics of the workshop and the interpersonal bonds that are likely to develop among participants will result in a small pool of workshop graduates identified for further skills building in mobilizing their communities around HIV and HIV testing through:

1. Referral to Project Accept's Community Mobilization component as possible candidates to become community-based outreach volunteers
2. Participation in stigma reduction skills building

Ongoing Psychosocial Support Groups

Support groups will comprise 8-10 participants and meet two to four times a month. They will provide an opportunity for participants to meet other people in similar circumstances and to make friends. Group topics will be flexible and based on the expressed preferences of participants as well as staffing availability. Groups may be formed around topics such as:

- For those who are HIV-negative: avoiding HIV acquisition
- Coping with negative or positive HIV test results
- Identifying social support
- Stress management
- Safe and thoughtful disclosure of HIV serostatus to family and friends
- Emotion and feelings
- Serodiscordant couples
- Positive/healthy living
- Adherence to ART
- Gender- and age-specific support groups
- Coping with an HIV-positive family member or friend

Selected support groups members will be trained in support group facilitation so that support groups are led by both PTSS staff and by peers. Such training will also seek to sustain PTSS activities after Project Accept has ended.

Stigma Reduction Skills-Building

We anticipate that the dynamics of the Moving On workshops and the psychosocial support groups, and the interpersonal bonds that are likely to develop among participants, will result in a small pool of graduates/participants, both HIV-negative and HIV-positive, who go on to attend a skills-building course that offers them stigma reduction tools (participants from the Community Mobilization and CBVCT components will also be referred to the course). The main objective of the course will be to prepare individuals *and communities* for public disclosure of HIV status (no one will ever be pressured to disclose his/her HIV status, either privately or publicly.)

The content of the course will focus on building skills in:

- Accurate knowledge of HIV/AIDS and of HIV testing
- Music, dance, and drama for presentations in community venues
- Safe and appropriate public disclosure of HIV status

- Public speaking, including giving testimonials and dealing with radio, newspaper, television, and other media
- Advocacy, covering national laws and policies regarding the rights of PLWHA, access to antiretroviral treatment, and community resources designed for PLWHA
- Problem solving to deal with stress and burnout

Graduates of the skills-building course will be referred to the Community Mobilization Coordinator, who will be responsible for monitoring their activities.

Counseling

The two PTSS counselors will provide counseling sessions to individuals and couples by appointment. Given our staffing limitations, individual and couples counseling will primarily be geared toward crisis management. Counselors will focus on channeling participants to other, less resource-intensive PTSS activities, including our coping effectiveness “Moving On” workshops, psychosocial support groups, informational groups, and recreational activities. Counselors will also provide referrals to non-Project Accept health and social services within the community.

Informational Groups

These will be larger group meetings formed around specific age groups, serostatus, or other characteristics/topics. PTSS staff, a non-Project Accept guest lecturer, or PTSS participants may facilitate these groups. Possible groups may revolve around:

- Nontesters: preparing to take an HIV test
- How to put on condoms and negotiate their use
- Health and nutrition for PLWHA, including OIs
- Physical exercise
- Relationships, including sexual relationships
- Life planning
- Legal issues and policies related to HIV infection
- Spiritual issues
- Resources for family members and friends
- Communication for development (writing grant proposals, securing funding, developing and sustaining community PTSS)
- Health and social services offered in the community (presented by representatives of community organizations)

Facilitation methods will include lectures, ie, formal talks given on a specific topic. Participants may identify a topic of interest relevant to their situation and the PTSS team leader will invite a guest speaker with expertise in that area. Another method will be group discussion, wherein participants share information, ideas, and opinions under the guidance of a facilitator. (Note that all sites will also aim to have a resource area with Information-Education-Communication [IEC] materials available for participants' use.)

Group Recreational and Social Activities

PTSS staff or participants may facilitate these groups/activities. Facilitation methods may include:

- Brainstorming: Facilitator takes spontaneous responses from participants without evaluating the responses.
- Group Work: This is a structured group activity. The facilitator prepares an activity related to the participants' needs and asks participants to work in small groups to generate a solution for the problem. Groups report back in a plenary session for further discussion (5-10 participants in each group).
- Interactive games to help identify and mitigate HIV/STD risks in sexual relationships.
- Role plays: Participants simulate a real-life situation.
- Drama: Participants act out roles and problems faced in everyday life and generate solutions. Unlike role-play, drama is rehearsed.
- Case Studies: Facilitator presents facts about a relevant situation that participants analyze and discuss.
- Storytelling.
- Demonstrations and return demonstrations: Facilitator demonstrates an activity or skill to participants who repeat the procedure while facilitator observes. Participants learn by doing.

All the above activities will be characterized by flexibility and responsiveness to participants' needs. To that end, activities may be modified over the research period. In addition, other site-specific activities may be introduced to meet participant and community needs.

Referrals to Non-Project Accept Organizations/Agencies

Because PTSS will not have the capacity to meet all participants' needs, counselors will make referrals to non-Project Accept organizations/agencies so that members can have immediate, practical needs met. As discussed above, PTSS staff will identify and map a core of community-based health and social service

providers to which participants will be referred. The PTSS coordinator and team leader will negotiate with the relevant service organization about the nature of services to be provided to PTSS participants.

Participants may need referrals for:

- Food aid
- Welfare/disability grants
- Housing assistance
- Other material and financial support (eg, clothing, cash)
- Income-generating projects
- Violence prevention programs, domestic violence counseling
- Alcohol and substance abuse counseling
- Local clinics or hospitals for medical evaluations and services (eg, OIs, TB, STDs)
- PMTCT
- ART
- ART adherence support
- Home-based care
- Local religious organizations or traditional healers for spiritual counseling

See also Section 10.10, “Linkages to Care”.

5.4.4 Quality Assurance

Quality assurance and supervision will occur on two levels. Day-to-day monitoring, supervision, and support of counselors will be carried out by the intervention coordinator (or counseling supervisor), who will periodically observe counseling sessions (with the permission of all participants). Counselors will also be expected to attend weekly/semimonthly individual and group meetings to discuss their counseling experiences, and to receive the support that they will need to provide effective counseling. The counseling supervisor will be expected to identify skills-training needs and organize relevant in-service skills training.

A visiting evaluator assigned by the UCSF Intervention Coordinating Center will visit each of the sites twice a year to evaluate the quality and consistency of the study procedures. The following strategies will be used to evaluate the quality of counseling: a) observation of counseling sessions (with permission of the participant) and recording observations on the Counseling Session Evaluation Form; b) periodic audiotaping of counseling sessions (with the permission of the participants) and reviewing the tapes with a checklist to evaluate the counselor’s performance in delivering the intervention; c) reviewing Counselor Contact Forms for each session and; d) conducting brief Exit Interviews

with some of the clients after receiving VCT to assess their perceptions of the quality and effectiveness of the service.

5.5 Control Communities

Control communities will receive Standard Clinic-Based VCT (SVCT) instead of the CBVCT intervention. Each of these communities will have access to SVCT that reflects local access to health care. The training for VCT counselors will be the same in the CBVCT and SVCT communities; however, no active recruitment for participation in the SVCT services will be made beyond the standard procedures of each clinic for informing patients of services (ie, telling individual patients that VCT is available, posting of a flyer in the clinic announcing VCT availability, etc). As such, no active outreach or community mobilization will be conducted by the study staff in the SVCT settings (although it is possible that such activities will occur due to local initiative). The two major components of the SVCT will be clinic-based VCT and quality assurance. VCT activities will be implemented in the intervention and control communities simultaneously and run for three years.

5.5.1 Clinic-Based VCT

Standard VCT services will be established at existing health centers, district hospitals, or alternative sites. Each research site will propose a plan to the Steering Committee on how to establish SVCT appropriate to communities being randomized in the trial. These plans will vary depending on whether VCT is currently available in communities or the service needs to be established where none exists, as well as feedback from the community-preparedness phase of the study. The procedures for counseling and HIV rapid testing will be the same as those in the CBVCT communities (see Section 5.4.2), except that referrals will be limited to existing community agencies rather than study-related post-test support services. In South Africa where SVCT is not provided by the study, procedures for counseling and HIV rapid testing are not the same. Testing is conducted using serial rapid tests, and counseling does not follow the individualized risk-reduction model.

5.5.2 Quality Assurance

For sites that lack existing SVCT facilities and will be creating their own as part of the study, quality assurance and supervision procedures in SVCT venues will reflect those in effect at the CBVCT venues as closely as possible.

For sites that will rely on existing SVCT facilities, study-determined quality assurance and supervision cannot be guaranteed. These sites will work closely with the SVCT venues to determine what is feasible, and the site will provide training and recommendations in this regard. Sites will carefully document the type of QA and supervision provided at the SVCT venues, whether or not it ultimately follows the recommendations made by the Project Accept site.

5.6 In-Country HIV Testing

HIV antibody testing will be performed to determine the HIV serostatus for participants accessing VCT services through the study. HIV antibody testing will also be performed for participants in the post-intervention assessment in order to evaluate the HIV endpoint. HIV antibody testing algorithms will be approved by the HPTN NL, with the goal of providing >99% of subjects with an accurate diagnosis of HIV at the time of testing, and that HIV infection endpoints can be confirmed and validated. More than one HIV testing algorithm will be allowed, as dictated by local constraints. Validation of the sensitivity and specificity of the testing algorithm used, or documentation of validation of the algorithm in the country where it will be used, will be required prior to the implementation of testing.

Participants accessing VCT through the CBVCT and SVCT interventions will receive rapid HIV testing with same-day results. All sites will use tests that have been validated locally and approved by their Ministry (or Department) of Health.

The standard algorithm for Project Accept intervention sites will be parallel runs of two HIV rapid tests in the mobile laboratory, with a third test (either a third HIV rapid test or an enzyme immunoassay (EIA) for HIV) used as a tiebreaker for discordant results. Sites may use fingerpricks or venous blood for specimens for the rapid tests. For those sites using an EIA for the tiebreaker test, venous blood specimens will have to be collected, specimens labeled with a unique numeric indicator, and participants given appointments for return-for-results visits with a process that maintains anonymity. All sites must submit their HIV rapid testing algorithm and specific choice of test(s) to the HPTN Network Laboratory. The HPTN NL will ensure that all rapid tests chosen by sites are sufficiently sensitive and that rapid testing QA is standardized across all sites. All study sites will adhere to the SOPs elaborated by the HPTN NL regarding laboratory practices, biohazard containment, etc.

Participants in the post-intervention assessment will have a blood draw after pretest counseling and giving informed consent. Individuals who participate in the post-intervention assessment will be offered rapid VCT and post-test counseling from project staff trained in VCT procedures. The biological samples will be collected in one 5 ml CD4 stabilization tube or one 5ml EDTA tube for measurement of the CD4+ cell count, and one 10 ml EDTA tube for collection of plasma. For each participant, the laboratory will perform two HIV rapid tests in parallel. Testing in Thailand, Tanzania, Zimbabwe, and the Soweto site in South Africa will be performed using whole blood; testing at the Vulindlela site in South Africa will be performed using plasma. If both HIV rapid tests are non-reactive, the participant will be considered to be HIV uninfected. If both HIV rapid tests were reactive, the participant will be considered to be HIV infected. If one of the two HIV rapid tests was reactive and one of the two HIV rapid tests was nonreactive (if the HIV rapid tests results were discordant), a third diagnostic test (tie-breaker, either an EIA or a third HIV rapid test) will be performed to determine the participant's HIV status. EDTA tubes will be centrifuged and plasma will be separated and aliquoted in 1.0 ml aliquots. These procedures will be the same for all participants and all specimens collected.

Specimens will then be assessed for the endpoint. CD4 assays will be performed on all participants who have one or more reactive HIV rapid test results.

All HIV testing performed locally in all components of the study (VCT in CBVCT and SVCT communities; post-intervention assessment) will occur in conjunction with high-quality counseling and referrals.

5.7 Quality Control Testing at the HPTN Network Laboratory

Stored plasma samples will be shipped to the HPTN Network Laboratory. Further tests will be performed to confirm the HIV infection status of study participants. This may include use of 3rd- or 4th-generation enzyme immunoassays (EIAs), Western blot testing, HIV viral load assays, qualitative HIV RNA assays, and other tests. This testing will be performed to confirm the infection status for all participants who had at least one reactive in-country HIV rapid test and for a subset of participants who had all non-reactive in-country HIV rapid tests. Based on this testing, participants will be classified as either HIV-infected or HIV-uninfected. Participants who are confirmed to be HIV infected will be further classified as having acute HIV infection (HIV RNA positive, HIV antibody negative), early HIV infection (HIV RNA positive, HIV antibody positive, Western blot indeterminate), or established infection.

Other tests may be performed at the HPTN Network Laboratory to characterize the viruses in stored samples (eg, analysis of HIV diversity, HIV subtype).

Results of laboratory testing performed at the HPTN Network Laboratory will not be returned to study sites or study participants.

5.8 HIV Incidence Assessment at the HPTN Network Laboratory

Stored plasma samples from the cross-sectional survey will be used to estimate HIV incidence. This estimate will be based on identification of participants who are likely to have been recently infected at the time of sample collection (ie, those with incident HIV infections). This assessment will involve testing samples from participants with established HIV infection using serologic assays (eg, the BED-CEIA assay and an avidity assay), as well as assays for non-serologic biomarkers (eg, HIV viral load, presence of antiretroviral drugs). CD4 cell count results obtained locally may also be used to assess HIV incidence. These assays will be combined in a multi-assay algorithm to identify incident infections. Participants who are classified as having either acute or early infection (see Section 5.7) will also be counted as incident infections in HIV incidence estimates. Further information on the post-intervention assessment of HIV incidence can be found in Section 7.1.

Results of laboratory testing performed at the HPTN Network Laboratory will not be returned to study sites or study participants.

5.9 Post-Intervention Assessment (PIA)

As in the baseline behavioral assessment, trained study staff will conduct an enumeration of households in the community using predefined criteria. Households will be randomly selected. Each randomly selected household will be approached, and a head of the household will be provided with an explanation of the study. A minimum of three visits to the household will be made, on different days and/or times, until contact with a head of the household is made. An enumeration of the members of the household will be conducted with the head of household or other responsible adult. At the time of enumeration of the household members, one of the eligible persons in the 18-32 year age range will be randomly selected for the behavioral assessment, and all other eligible household members will be asked to conduct the biological assessment (short survey and blood draw).

For each eligible household member who will be recruited to participate in the PIA; a minimum of 3 repeat visits will be made until contact can be made with the eligible household member(s).

5.9.1 Post-Intervention Biological Assessment

All eligible household members will be asked to provide separate written consent for HIV testing and a short survey. Once consent has been given, the participant will provide a blood sample (15 ml) for the biological assessment. Staff will be trained to set up this procedure such that if the household member decides to decline participation, that decision would be confidential and not known to the head(s), or other members, of the household. All participants included in the biological assessment will be asked to respond to a short demographic and risk behavior questionnaire (duration approximately 20 minutes). The behavioral assessment (see section 5.7.2) will be given to a subset of this study population.

All individuals who participate in the post intervention biological assessment will be offered their test results at a later date. Pre- and post-results counseling will be offered to all participants from Project Accept staff trained in VCT procedures. In sites where it is not possible to return the results of the PIA, all participants will be offered full VCT, using rapid HIV tests, including pre- and post-test counseling. Participants who learn that they are HIV infected will be given counseling and referrals in keeping with standard practice for high-quality VCT. Participants who test HIV negative will also be given standard counseling and referrals.

5.9.2 Post-Intervention Behavioral Assessment

A subset of participants in the post-intervention biological assessment will be randomly selected to participate in the post-intervention behavioral assessment. The post-intervention behavioral assessment will be very similar to the baseline behavioral assessment and will assess the secondary outcomes of the study. An interviewer will administer the questionnaire to the selected household member, question by question, until the assessment has been completed.

5.10 Cost-Effectiveness Analysis

Cost data will be collected at each field site using standardized cost worksheets developed by the Cost-Effectiveness Committee. The cost worksheet will be forwarded to the study sites and will be completed and returned to the Data Coordinating Center for data management. These will be reviewed and cleaned in consultation with staff at each field site. Michael Sweat, PhD, will visit each site to finalize the collection of cost data.

For each site, and across sites, we will estimate the total and average costs for the CBVCT and SVCT interventions, and the incremental cost difference between CBVCT and SVCT. We will estimate the full costs of the interventions, assuming no cost sharing, volunteer labor, or donated commodities. We will derive our cost estimates using a micro-costing methodology such that resource consumption is determined by identifying, measuring, and valuing all incremental costs needed to provide the interventions. Detailed cost worksheets will be utilized to collect these data, and will be adapted from our previous cost analysis from the multisite VCT trial we conducted. These estimates will be compared with project budgets and reviewed with project staff to assure accuracy. Data include: (1) Conversion rate of local currency to U.S. dollars at 6-month intervals over the life of the project; (2) estimated buying power of the currency at the beginning, midpoint, and end of the project based on the World Bank's Purchasing Power Parity (PPP) Index³⁶; (3) costs of all commodities used in the intervention; (4) labor costs for intervention workers; (5) promotional and advertising costs; (6) average time clients spent with intervention; (7) local wages of target population; (8) rent; (9) maintenance; (10) incentives to participants; (11) volunteer activities; (12) user fees; (13) value of donated goods and services; and (14) other relevant costs. Additionally, for analysis taking the societal perspective we shall also include the cost to clients in terms of lost time, wages, childcare, and other relevant opportunity costs. To assess these issues we will ask participants what expenses and opportunity costs they incurred to receive the interventions in the surveys already planned for the project. We will also collect data on the average cost of medical care associated with HIV infection and AIDS through literature review and interviews with health care officials in each country.

Cost data will be entered into a detailed spreadsheet database that will include a range of costs for each item, with high, low, and mean costs at the onset, midpoint, and completion of the study. This will allow us to examine natural variations in costs. Included in the database will be currency conversion rates (local currency to U.S. dollars) over the life of the project, as well as a general estimation of the value of the currency in terms of its buying power. Currency conversion rates are available from the World Bank. The estimate of buying power across study sites using the Purchasing Power Parity Index will be performed to examine any artificial fluctuations in the currency conversion rate.

Cost-effectiveness analysis will be used to examine the value of the intervention in terms of the impact on secondary outcomes, such as stigma, social norms, and behavior. We will have the capacity to rather easily replicate our primary cost-effectiveness analyses for different utilities than just the primary outcome of the cost per disability-adjusted life year (DALY) saved. Once the primary cost-

effectiveness model is developed, we will be able to replace the outcome of disability-adjusted life year saved with other study outcomes, such as the reduced incidence of stigma and negative social outcomes of HIV testing, and increases in such outcomes as condom use and partner reduction across study arms. Such analyses could have significant policy implications in lieu of a null finding on the impact of the intervention on reduced HIV incidence, and associated reductions in the cost per DALY saved.

More detailed information on cost-effectiveness analysis is available in Section 7.3.

6. STUDY POPULATION

6.1 Communities

6.1.1 Countries, Sites, and Communities

Our team has considerable experience in multi-country studies, which require local tailoring while remaining faithful to a centralized protocol to allow cross-country data analysis. Examples are the Voluntary HIV-1 Counseling and Testing Efficacy Study,⁴¹ and the NIMH Collaborative HIV/STD Prevention Trial.⁵⁵ We determined, on the basis of the power analysis, that 40 communities are needed to test the primary study hypothesis (see Section 9). The sample size is driven upward because we are not assessing incidence at baseline and needed protection against varying incidence rates in matched communities (see Section 3). We decided that it was not feasible to conduct the study within one country, as it would be difficult to find 40 distinct communities in one country, and the logistics of carrying out the study in one place would be enormous. Generalizability would also be limited.

6.1.1.1 Selection of Countries

The countries and sites participating in this study were chosen to meet the criterion that HIV incidence could be used as the primary endpoint. To detect an intervention-related difference in HIV incidences with the desired power, the baseline incidences at the sites must be sufficiently high. We chose the participating sites so that the average baseline annual incidence across all communities in the study is likely to reach at least 3%.. The various sites in sub-Saharan Africa met this criterion, but we also wanted sites in Asia to extend the generalizability of the intervention. The only location in Asia with sufficient incidence at the community level is in ethnic minority communities in Northern Thailand, where HIV incidence is currently in excess of 7%;³⁷ thus they were invited to participate as well. Our final selection of sites combines rural (Tanzania, Zimbabwe, Thailand, and KwaZulu-Natal) and an urban (Soweto) location. The cultural circumstances between the sub-Saharan African sites vary widely. While the primary hypothesis will be tested by combining data across all sites, we will be able in secondary analyses to examine variations in outcomes due to country, urban vs. rural location, and intervention implementation (see Section 9.1.1.3). We will be able to test the impact of the intervention on behavioral outcomes in each country separately (see Section 9.1.2.2).

6.1.1.2 Definition of Community

Each of the three southern African sites (Harare, Zimbabwe; and Soweto and Vulindlela, South Africa) selected eight communities, the East African (Tanzanian) site selected 10

communities, and Thailand selected 14 communities (see Section 9.1.1.1). Community has been defined as groups of individuals who live next to one another and participate in common practices; depend on one another; make decisions together; identify themselves as part of something larger than the sum of their individual relationships; and commit themselves to the group's well-being.^{38,39} The communities we selected for this study represent units of organization that reflect these dimensions of communality. They are of a population size of approximately 10,000 (slightly fewer in some communities in Tanzania and Thailand), which fosters social familiarity and connectedness, and they are geographically distinct. Communities are defined primarily geographically for operational purposes for the study, taking into account these dimensions of social communality. The communities chosen within each country and site are selected to be sufficiently distant from each other so that there would be little cross-contamination or little possibility that individuals from a control community would benefit from the activities in the intervention community. Cultural tailoring of the intervention in each site will ensure that the three strategies (easy community access to HIV VCT, community outreach, and post-test support services) are feasible and acceptable in those communities, and also targeted to reach individuals at high risk of transmitting or acquiring HIV. Extensive community preparedness activities will be conducted prior to communities' participation in the study and throughout the duration of the study (see Section 12.1).

6.1.2 Community-Level Randomization

Although individual participants will access services through the SVCT and CBVCT interventions, and will participate in the baseline, post-intervention, and qualitative assessments, this study is of a community-level intervention where communities—rather than individuals—are the unit of randomization. The assessment of efficacy is based on changes in communities (repeat cross sectional data on household probability samples) as opposed to difference in individuals who may have actually received the intervention, and thus the impact of the intervention will be measured in a community sample as opposed to a cohort. To ensure transparency, the communities will be involved in the community randomization process (see Section 12.1).

6.2 Baseline Behavioral Assessment

6.2.1 Participant Eligibility

The eligibility criteria for participation in the baseline behavioral assessment are described below.

6.2.1.1 Inclusion Criteria

Persons may be included in the baseline behavioral assessment if they meet all of the following criteria:

- Reside in a community selected for the study
- Are randomly selected and invited to participate from households that are themselves randomly selected and invited to participate
- Aged 18-32 years
- Has lived in the community at least 4 months in the past year
- Sleeps regularly in their household at least 2 nights per week
- Able and willing to provide verbal informed consent

6.2.1.2 Exclusion Criteria

Persons will be excluded from the baseline behavioral assessment if they meet any of the following criteria:

- Are not a member of the study community or are not randomly selected to be offered to participate
- Are below 18 or above 32 years of age
- Has not lived in the community at least 4 months in the past year
- Does not sleep regularly in their household at least 2 nights per week
- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process or otherwise contraindicate participation in the assessment

6.2.2 Recruitment

Using predefined criteria, trained study staff or trained staff of a contract survey research organization will conduct an enumeration of households in the community. Households will be randomly selected. Each randomly selected household will be approached, and a head of the household will be provided with an explanation of the study. A minimum of two repeat visits to the household will be made until contact with a head of the household is made. An enumeration of the members of the household

will be conducted with a head of household. At the time of enumeration of the household members, one person in the 18-32 year age range (who has lived in the community at least 4 months in the past year and sleeps regularly in their household at least 2 nights per week) will be randomly selected. The selected household member will be invited to participate in the study; a minimum of 2 repeat visits will be made until contact can be made with the selected household member.

The recruitment target for the baseline behavioral assessment is 13,000 (300 per community for the 34 African communities and 200 per community for the 14 Thai communities).

6.2.3 Withdrawal from Study

After verbally consenting to participate in the baseline behavioral assessment, a participant may voluntarily withdraw from the assessment at any time during the assessment process and choose not to have his/her assessment responses submitted to the study team.

6.3 Qualitative Cohort

6.3.1 Participant Eligibility

The eligibility criteria for participation in the qualitative cohort are described below.

6.3.1.1 Inclusion Criteria

Persons may be included in the qualitative cohort if they meet all of the following criteria:

- Participated in the baseline behavioral assessment
- Aged 18-32 years at enrollment
- Have not been away from the community for more than two months at a time in the last two years
- Able and willing to provide written informed consent

6.3.1.2 Exclusion Criteria

Persons will be excluded from the qualitative cohort if they meet any of the following criteria:

- Not a participant in the baseline behavioral assessment
- Less than 18 or greater than 32 years of age at enrollment

- Have been away from the community for more than two months at a time in the last two years
- Demonstrate signs of being visibly distraught, emotionally unstable, or under the influence of psychoactive agents that would invalidate the consent process or otherwise contraindicate participation in the qualitative assessment
- Have concrete plans to leave the community, thus removing possibility of follow up

6.3.2 Recruitment

From the roster of participants in the baseline study, a purposeful sample of individuals at each site will be selected and invited to participate in a longitudinal qualitative study. Participants will be selected to represent key subpopulations whose attitudes toward and experiences with CBVCT will differ. The sample will consist of equal numbers of women and men, and will be constructed to include partnered and unpartnered participants in the age groups of 18-24 and 25-32, as well as pregnant women and men with a pregnant partner at baseline.

The recruitment target for the qualitative cohort is 656 (16 per community for the 34 African communities and 8 per community for the 14 Thai communities).

6.3.3 Retention

Qualitative assessment cohort members and key informants will be reimbursed for the transportation costs incurred to travel to the interview site and for the time that they spent in transit to and during the interviews.

6.3.4 Withdrawal from Study

Following enrollment in the qualitative cohort, participants may discontinue participation for the following reasons:

- Voluntary withdrawal
- Withdrawal requested by the site's Principal Investigator. In such cases the Principal Investigator will review the reasons for withdrawal with the Steering Committee and Protocol Biostatistician prior to participant notification. The Principal Investigator may decide to include data collected prior to participant withdrawal in study analyses.

6.4 Intervention

6.4.1 Community-Based VCT

6.4.1.1 Participant Eligibility

The eligibility criteria for participation in the community-based VCT intervention in CBVCT communities are described below.

6.4.1.1.1 Inclusion Criteria

Persons may access community-based counseling and testing (in CBVCT communities) through the study if they meet all of the following criteria:

- ≥ 16 years of age
- Able and willing to provide verbal informed consent

Persons may access post-test support through the study if they meet all of the following criteria:

- ≥ 16 years of age
- Able and willing to provide verbal informed consent
- Having been tested for HIV, regardless of result

6.4.1.1.2 Exclusion Criteria

Persons will be excluded from accessing counseling and testing (CBVCT) through the study (and will be referred to existing alternate services) if they meet any of the following criteria:

- < 16 years of age
- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process or otherwise contraindicate participation

Persons will be excluded from accessing post-test support through the study (and will be referred to existing alternate services) if they meet any of the following criteria:

- <16 years of age
- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process or otherwise contraindicate participation

6.4.1.2 Recruitment

Community mobilization efforts (see Section 5.4.1) will serve, in part, to inform the community of the mobile VCT services. Community-based outreach volunteers (CBOVs) will visit community sites, households, and community centers to disseminate information about the mobile VCT. The CBOVs will be recruited, trained, and supervised by the Intervention Coordinator at each site. These community volunteers, organized into teams of 3-5 persons, may be recruited from the pool of people who have participated in VCT. They will not be project staff, but may receive a small stipend based on local community standards.

The estimate for participation in CBVCT is 92,500 (4,000 per community for the 17 African CBVCT communities and 3,500 per community for the 7 Thai CBVCT communities).

The estimate for participation in post-test support services is 10,750 (200 per community for the 17 African CBVCT communities and 1,050 per community for the 7 Thai CBVCT communities).

6.4.1.3 Withdrawal from Study

Participants may voluntarily withdraw from participation in a given session of VCT or post-test services, or decide not to continue ongoing participation in post-test services, at any time. Should they later decide to once again avail themselves of VCT or post-test services, they will be able to do so.

6.4.1.4 HIV Infection

Participants who learn they are HIV infected by testing at a CBVCT site will be directed to the study's post-test services, which will include counseling, referrals to health care and social services, and other activities. Participants who test HIV negative will also be referred to post-test clubs for further counseling, referrals and support in staying HIV uninfected.

6.4.2 Clinic-Based VCT

6.4.2.1 Participant Eligibility

The eligibility criteria for participation in the standard VCT intervention in both SVCT and CBVCT communities are described below.

6.4.2.1.1 Inclusion Criteria

Persons may access standard clinic-based counseling and testing (in both SVCT and CBVCT communities) through the study if they meet all of the following criteria:

- ≥ 16 years of age
- Able and willing to provide verbal informed consent

6.4.2.1.2 Exclusion Criteria

- < 16 years of age
- Have an obvious psychological/psychiatric disorder that would invalidate the informed consent process or otherwise contraindicate participation

6.4.2.2 Recruitment

No active recruitment for the SVCT services will be made beyond the standard procedures for each clinic for informing patients of services (ie, telling individual patients that VCT is available, posting of a flyer in the clinic announcing VCT availability, etc.)

The estimate for participation in SVCT in SVCT communities is 26,800 (1,000 per community for the 17 African CBVCT communities; and 1,400 per community for the 7 Thai CBVCT communities).

The estimate for participation in SVCT in CBVCT communities is $\geq 26,800$ ($> 1,000$ per community for the 17 African CBVCT communities and $\geq 1,400$ per community for the 7 Thai CBVCT communities).

6.4.2.3 Withdrawal from Study

Participants may voluntarily withdraw from participation in a given session of VCT at any time. Should they later decide to once again avail themselves of VCT, they will be able to do so.

6.4.2.4 HIV Infection

Participants who learn they are HIV infected based on testing at an SVCT site will be given counseling and referrals in keeping with standard practice for high-quality VCT. Participants who test HIV negative at an SVCT site will also be given standard counseling and referrals. No special, enhanced post-test clubs or services will be provided by the study in the SVCT communities, as such services constitute a key part of the intervention.

6.5 Post-Intervention Assessment

The post-intervention assessment consists of a biological assessment (blood draw and short survey), with a subset of the study population also receiving a behavioral assessment.

6.5.1 Participant Eligibility

The eligibility criteria for participation in the post-intervention assessment are described below.

6.5.1.1 Inclusion Criteria

Persons may be included in the post-intervention assessment if they meet all of the following criteria:

- Reside in a community selected for the study for at least 6 months during the past 12 months
- When residing in the selected community, must also sleep in the selected household for at least two nights a week
- Aged 18-32 years
- Able and willing to provide informed consent (written for biological assessment; verbal for behavioral assessment)
- For the behavioral assessment: are randomly selected to be offered to participate from among all eligible household members in the selected household

6.5.1.2 Exclusion Criteria

Persons will be excluded from the post-intervention assessment if they meet any of the following criteria:

- Are not a member of the study community or are not eligible members of selected household
- Are below 18 or above 32 years of age
- Has not lived in the community at least 6 months in the past year
- Do not sleep in the selected household at least 2 nights per week
- Have an obvious permanent physical disability (eg, deafness) or mental disability that would invalidate the informed consent process or otherwise contraindicate participation in the assessment
- For the behavioral assessment: Not randomly selected to receive the behavioral assessment

6.5.2 Recruitment

Using predefined criteria, trained study staff will conduct an enumeration of households in the community. Households will be randomly selected. Each randomly selected household will be approached, and a head of the household will be provided with an explanation of the study. A minimum of three visits to the household will be made on different days/times until contact with a head of the household, or other responsible adult, is made. An enumeration of the members of the household will be conducted with a head of household. All eligible household members will be invited to participate in the biological assessment (blood draw and short survey). At the time of enumeration of the household members, one eligible household member will be randomly selected to participate in the behavioral assessment. The selected household members will be invited to participate in the study. For the one eligible household member who has been selected for the behavioral assessment, this will consist of the biological assessment (blood draw, short demographic and risk survey), and behavioral assessment (long risk survey). All other eligible household members will be asked to participate in only the biological assessment. All participants selected for assessment will be given a minimum of three repeat visits on different days/times until contact can be made with the selected household member.

The recruitment target for the post-intervention biological assessment is 52,240.

Site	Target sample size per community	Number of communities	Expected number of participants
Thailand	500	14	7,000
Zimbabwe	1,430	8	11,440
Tanzania	900	10	9,000
Vulindlela	1,430	8	11,440
Soweto	1,750	6	10,500
	1,430	2	2,860
Soweto – total	3,180	8	13,360
Total			52,240

The behavioral sample is a subset of those participating in the blood draw. The recruitment target for the post-intervention behavioral assessment is the same as the baseline at 13,000 (300 per community for the 34 African communities [8 communities each @ 3 sites, 10 communities @ 1 site; 10,200 total]; and 200 per community for the 14 Thai communities; [2,800 total]) and includes a subset of those individuals providing a blood sample.

6.5.3 Withdrawal from Study

Participants may voluntarily withdraw from participating in the assessment at any time during the assessment process and choose not to have his/her blood and/or assessment responses submitted to the study team.

6.5.4 HIV Infection

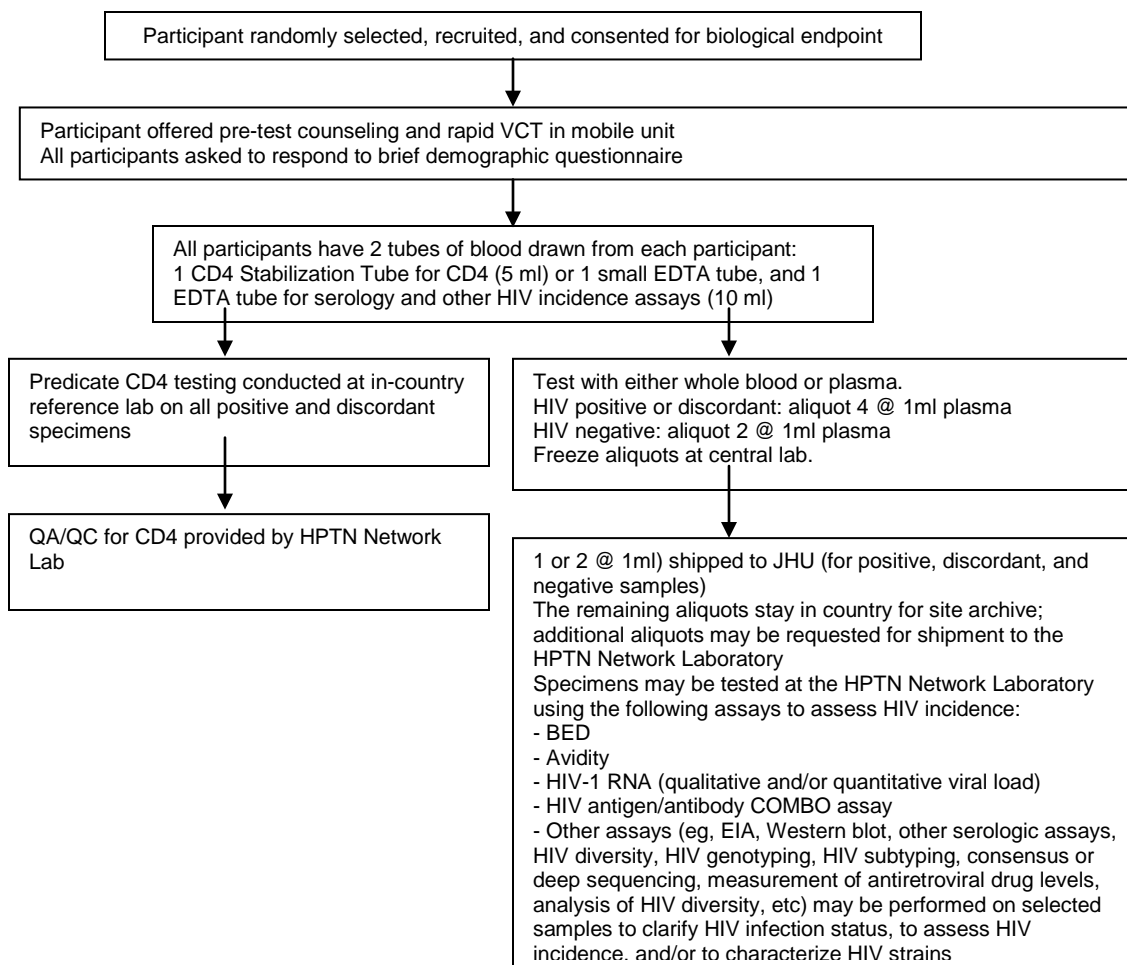
All individuals who participate in the post-intervention biological assessment will be offered their in-country HIV test results at a later date. Pre- and post-results counseling will be offered to all participants from Project Accept staff trained in VCT procedures. In sites where it is not possible to return the results of the post-intervention biological assessment, all participants will be offered full VCT, using rapid HIV tests, including pre- and post-test counseling. Participants who learn that they are HIV infected will be given counseling and referrals in keeping with standard practice for high-quality VCT. Participants who test HIV negative will also be given standard counseling and referrals.

7. EVALUATION OF OUTCOMES

7.1 Primary Outcome

The methods used to assess HIV incidence will be determined prior to endpoint analysis. The final selection of these methods will be determined by the HPTN Network Laboratory, the protocol chairs, and the protocol statisticians; an external expert may also be consulted in this process. These methods may include use of results obtained using the BED-CEIA, an avidity assay, CD4 cell count, HIV viral load, and other measures. The methods may include a combination of assays to estimate HIV incidence

Project Accept Biological Endpoint Flow Diagram



7.1.1 Assessment Algorithm

Once the selected household member(s) have been identified and have agreed to participate in the endpoint assessment, he or she will be asked to provide a whole blood (15 cc) sample drawn into 2 tubes. Participants will be offered free and high-quality VCT as per each site's community-based VCT protocol.

Participants may agree to the biological assessment but choose not to accept VCT. The biological samples (N ≈ 52,240) will be collected in either a CD4 Stabilization tube (5 ml) or an EDTA tube (5 ml) for measurement of the CD4+ cell count; in addition, one 10 ml EDTA tube will be collected for plasma preparation and storage. CD4 stabilization tubes can be stored at ambient temperature (up to 30°C for up to 7 days), preserving cytology for CD4 measures in field settings. For this study, samples will be processed within 30 hours from collection. All specimens will be returned to the Project Accept Labs at each site within 24 hours of specimen collection. EDTA tubes will be centrifuged and plasma will be separated and aliquoted in 1.0 ml aliquots. Either whole blood or processed plasma will be used for HIV antibody testing using two HIV rapid tests. Participants with two reactive HIV rapid tests are designated HIV positive. Participants with one reactive and one nonreactive HIV rapid test are designated HIV discordant; those participants will have a tie-breaker test performed (either a third HIV rapid test or an EIA). Four plasma aliquots from HIV-positive and HIV-discordant samples, and two aliquots from HIV-negative specimens will be aliquoted, frozen, and stored at -70° C.

The final endpoint (HIV incidence estimate) will be based on test results obtained for HIV-positive samples, HIV-discordant samples (after resolving the HIV status at the HPTN Network Laboratory) and HIV-negative samples (all or a subset of the HIV-negative samples will be tested at the HPTN Network Laboratory for evidence of HIV infection; this will include detection of early/acute HIV infection, as well as detection of any false negative test results obtained in country). CD4 cell counting will be performed for all HIV-positive and HIV-discordant participants at each site's laboratory (the CD4 specimen from HIV-negative participants will be discarded). Plasma aliquots will be used to assess HIV incidence (see above); the CD4 cell count may also be considered in the incidence assessment. Assessment for recency of HIV infection will be conducted centrally, at the HPTN Network Laboratory at Johns Hopkins School of Medicine (Susan Eshleman, MD, PhD, Principal Investigator). Plasma will be stored at the sites until shipments are requested, and will then be shipped to the HPTN Network Laboratory on dry ice, analyzed, and stored at -70°C. Having a single reference laboratory conduct assays for HIV incidence assessment will markedly reduce the laboratory variance of the assessment.

The width of recency time window will be determined after the assay or algorithm is selected that will be used for HIV incidence assessment. The duration of the intervention is critical for setting the time window: it may take a year for the intervention to saturate the community and the time window should not include the period when the intervention effect was not yet fully established. On the other hand, a too short time window reduces the power. Hence a 2-year window period would be optimal for a 3-year intervention. However, the window period used for assessment is likely to be 1 year or less, based on currently available data.

The original plan was to apply the BED-CEIA assay to estimate the number of infections occurring within 170 days prior to the assessment.⁵⁶ This method counts the number of HIV-positive samples with normalized optical density (OD-n) below a defined cut-off. A number of recently published evaluations of the BED assay's performance suggest that the resulting incidence estimate is

seriously biased.⁵⁶⁻⁵⁸ This is primarily due to misclassification of non-recent infections as recent. In the context of our trial, the “recent” infections identified by this method would include a number of cases infected before the interventions were started, which would seriously bias the intervention effect and reduce power. Therefore, we will most likely use multiple assays (eg, a multi-assay algorithm that includes the BED-CEIA) and/or alternative assays for the incidence assessment. It is also possible that the BED-CEIA will be incorporated into a multi-assay algorithm as a screening test, with a modified assay cut-off.

7.1.2 Procedures to Reduce AIDS Misclassification Bias

To address the potential misclassification of non-recent infection cases as incident infections, the HPTN Network Laboratory is testing samples from other cohorts with known duration of HIV infection. To date, factors identified that are associated with false recent misclassification include low CD4 cell count and low HIV viral load (due to natural or antiretroviral drug-induced viral suppression). These factors will be considered in selecting the methods used for HIV incidence assessment.

7.1.3 Training, Quality Assurance, and Project Expertise for Lab Studies

QA/QC will be performed using proficiency panels from the College of American Pathologists (CAP). These panels, consisting of 5 blinded samples, will be sent out every 4 months by CAP, and will be run at each site’s lab (including mobile laboratories). Results of the samples will be sent to CAP, who will report back to the HPTN Network Laboratory and to the sites. If any results are incorrect, retraining and review of SOPs will occur to correct the problem. Proficiency panels will be run at CBVCT centers, but not at SVCT clinics. QA will also be performed on each new lot of rapid test kits that arrives at sites by running the controls and testing one positive and one negative sample of known sera. Sites will still need to perform (both at CBVCT and SVCT settings) any local QA/QC procedures required by their governments, and these procedures will be reflected in site SOPs.

Each site has expertise with standard EIA HIV testing. The HPTN NL will coordinate training and QA for the laboratory studies for the project. Study collaborators have significant experience with the proposed techniques.

7.2 Secondary Outcomes: Behavioral Outcomes

7.2.1 HIV Risk Behavior

HIV risk behaviors will be assessed using standardized questionnaire items that have been used previously in international settings. There are several behavioral risk assessments that have been successfully used in a number of multicenter trials supported by the NIH, including the HPTN family of studies (eg, HIVNET 016A, HIVNET 009) in which several of these sites (Zimbabwe and Thailand) have participated. This approach to assessment has also been used in the NIMH Collaborative HIV/STD

Prevention Trial. These questionnaires have been translated for meaning and back-translated with no loss of information, and pretested for validity and reliability in the countries where this study will take place. They are generally easy to administer and assess risk behaviors using a standardized format. Risks include recent (one-month), intermediate (three-month) and longer-term (one-year), and lifetime measures of sexual behavior (by partner gender, type of activity, condom use), using partner-by-partner elicitation (up to 5 individuals). We include measures of transactional sex, association of alcohol and drug use prior to sex (for both partners), and relationship type (spouse, friend, casual acquaintance, commercial, etc). We have developed algorithms to produce easily understood outcome measures (eg, frequency of unprotected intercourse; proportion of acts using a condom).

7.2.2 Rates of HIV Testing

We have three independent strategies for determining rates of HIV testing longitudinally. First, we will include questions in the baseline behavioral “sentinel” questionnaire on history of voluntary HIV testing (first time, last time, number of times total, location, cost, provision of counseling, review of counseling content, rate of returning for post-test counseling, recall of the counseling, obtaining test results) in addition to demographic and risk characteristics to determine a baseline rate of testing and correlates in the community. Second, we will include information on VCT in the ongoing ethnographic assessments at the community level, including in-depth interviews. Third, we will collect ongoing administrative data on VCT utilization in the SVCT and CBVCT arms; as we will have the denominator (population size) of each community, we can estimate age/gender-specific utilization rates over time. Finally, in our post-intervention community sample surveys, we will obtain data similar to the baseline “sentinel” survey to determine change in rates of VCT.

7.2.3 Social Norms

Norms concerning HIV testing will be developed in an analogous fashion to the procedures used to ascertain community norms regarding conversations about sex, HIV/STD prevention, and condom use. In essence, we inquire about behavioral intention to seek VCT, attitudes (fears, worries, resolve, anxiety), self-efficacy to seek VCT, perceptions of abilities to overcome barriers, norms regarding VCT in the community (eg, “most people who are important to me think that I should talk to my spouse about getting HIV tested in the next three months”), and perceptions of support for intentions (eg, “my friends think I should get HIV tested in the next three months”). New items will be constructed, tested for meaning in pilot studies, revised and translated/back-translated for meaning, and compared across sites for comparability.

7.2.4 Discussions about HIV

Questions that capture key elements of community conversation about sex, prevention of HIV/STD, and frequency of discussion with specific individuals (spouse, family, friends, community residents, key opinion leaders) will be adapted from those in the NIMH Prevention Trial baseline questionnaire that were developed for use in five countries (Zimbabwe, Peru, China, India, and Russia).

7.2.5 Disclosure of HIV Status

Disclosure will be measured as it was in prior VCT research in Africa.⁴¹ The instrument asks about the disclosure of HIV serostatus to spouses, sexual partners, parents, children, brothers, sisters, other relatives, friends, landlord, neighbors, religious leaders, community leaders, physicians, and employers. The proportion of participants reporting each disclosure is calculated after eliminating those who say the disclosure was not applicable to them.

7.2.6 HIV-Related Stigma

HIV-related stigma will be assessed at baseline and post-intervention using the Perceived Stigma of HIV/AIDS: Public Views Scale.⁴² This is a 24-item scale (internal reliability: alpha = .90) designed to obtain the participant's perception of what people's attitudes and beliefs are about HIV. In addition, for those who report being HIV infected, we will also use the Perceived Stigma of HIV: Personal Views Scale. This is a 24-item scale (internal reliability: alpha = .87) designed to obtain individuals' views on personal stigma such as shame, guilt, blame, embarrassment, and self-worth. While these measures have largely been used in studies of urban mothers with HIV in the U.S., they have also been adapted for use in India.⁴³ We will be piloting the instrument in Zimbabwe and Thailand to determine if cultural adaptations are needed to measure social stigma and to establish psychometric properties when used in African and Thai sites.

7.2.7 Life Events

Positive and negative life events will be measured as they were in prior VCT research in Africa.⁴¹ Positive life events include strengthening of a sexual relationship and increased support from family, peers, health providers, or employers. Negative events include breakup of a marriage or sexual relationship, physical abuse by a sexual partner, neglect by family, being disowned by family, rejection by peers, and being discriminated by health care providers or employers. The proportion of participants reporting each life event is calculated after eliminating those who say the life event was not applicable to them.

7.3 Cost-Effectiveness Analyses

As with our previous research,^{44,45} we will conduct a cost-effectiveness analysis (CEA) comparing the value of the intervention's effectiveness to other HIV interventions. Our methodology will follow that recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine, which will allow for comparison to other health interventions.⁴⁶ The primary analysis proposed is an incremental cost-effectiveness analysis comparing the incremental costs and benefits of CBVCT to those of SVCT. The CEA analysis adds little cost to the study, but enhances its value enormously. Additionally, this analysis may be of significant assistance to program managers and policymakers who are deciding on which interventions should be supported.

7.3.1 Perspective

The cost-effectiveness analysis requires that data be derived on both cost of the intervention and on the effectiveness in terms of cost per HIV infection averted and Disability Adjusted Life Years (DALYs) saved from the intervention. However, a key question in designing any CEA is "Costs and benefits from whose perspective?" We will conduct this analysis from two perspectives: (1) the perspective of the only in-country payer such as the Ministry of Health, and (2) the societal perspective, which examines all relevant costs and benefits. The payer's perspective is critical, as it is often the primary decision maker regarding whether HIV interventions are implemented. From the payer's perspective we will consider the costs of funding both SVCT and CBVCT in each setting, with the primary benefit being the number of DALYs saved. We shall additionally consider the averted treatment costs associated with HIV and AIDS since this benefit typically accrues to the payer. Because averted HIV/AIDS treatment costs are often difficult to estimate in data-poor environments, we do not expect this estimate to be highly precise. Results will therefore be presented both with and without the estimated savings in HIV/AIDS treatment costs. The societal analysis will take into account the additional economic burden to the client population. This is important not only in understanding the true net benefit of the intervention to society, but also in determining the likely rates of uptake: An intervention can be highly cost-effective from the point of view of the payer, but if the client has to sacrifice a full day of work in order to obtain the services, uptake rates and therefore ultimate impact are likely to be low. Both monetized and non-monetized client costs are crucial factors in determining policy and advocacy support for a broad-based HIV prevention program.

7.3.2 CEA Analysis Framework, Study Design, and Data Management

Cost-utility analysis is a specific type of cost-effectiveness analysis that considers how the intervention affects the quality and quantity of life in addition to the calculation of the number of cases of disease averted. The primary utility for our analysis will be the Disability Adjusted Life Year saved. We will follow Drummond's approach to calculating the cost-utility of interventions.⁴⁷ This involves the following steps: (1)

estimating the cost of the intervention; (2) utilizing estimates of the number of HIV infections occurring in each arm of the study, which will be derived from the study; (3) calculating the DALYs saved; (4) calculating the net program costs; (5) calculating the base case ratios; and (6) conducting sensitivity analysis. Effectiveness data will be collected and managed through the larger study.

For each site, and across sites, we will estimate the total and average costs for the CBVCT and SVCT interventions, and the incremental cost difference between CBVCT and SVCT. We will estimate the full costs of the interventions, assuming no cost sharing, volunteer labor, or donated commodities. We will derive our cost estimates using a micro-costing methodology such that resource consumption is determined by identifying, measuring, and valuing all incremental costs needed to provide the interventions. Detailed cost worksheets will be utilized to collect these data, and will be adapted from our previous cost analysis from the multisite VCT trial we conducted. These estimates will be compared with project budgets and reviewed with project staff to assure accuracy. Data include: (1) Conversion rate of local currency to U.S. dollars at 6-month intervals over the life of the project; (2) estimated buying power of the currency at the beginning, midpoint, and end of the project based on the World Bank's Purchasing Power Parity (PPP) Index³⁶; (3) costs of all commodities used in the intervention; (4) labor costs for intervention workers; (5) promotional and advertising costs; (6) average time clients spent with intervention; (7) local wages of target population; (8) rent; (9) maintenance; (10) incentives to participants; (11) volunteer activities; (12) user fees; (13) value of donated goods and services; and (14) other relevant costs. Additionally, for analysis taking the societal perspective we shall also include the cost to clients in terms of lost time, wages, childcare, and other relevant opportunity costs. To assess these issues we will ask participants what expenses and opportunity costs they incurred to receive the interventions in the surveys already planned for the project. We will also collect data on the average cost of medical care associated with HIV infection and AIDS through literature review and interviews with health care officials in each country.

Cost data will be collected at each field site using standardized cost worksheets developed by the Cost-Effectiveness Committee. The cost worksheet will be forwarded to the study sites and will be completed and returned to the Data Coordinating Center for data management. These will be reviewed and cleaned in consultation with staff at each field site. Michael Sweat, PhD, will visit each site to finalize the collection of cost data.

7.3.3 Identifying and Valuing Outcomes

The primary outcome will be the Disability Adjusted Life Year, or DALY. The advantage of the DALY over direct measures of HIV cases averted is that it accounts for the quality and duration of the life saved due to the intervention. DALYs also include age weights that attempt to

reflect the socioeconomic value of each year of life saved. It is reasonable to examine these factors, as there may be a societal value placed on targeting interventions toward those who have the potential for longer and higher-quality lives. We will use a methodology developed by Holtgrave and Qualls⁴⁸ to first calculate the number of life years saved weighted by the level of disability associated with HIV infection at different stages of illness. This involves deriving estimates of the average age of persons infected, the length of time after infection that persons are unaware of infection status, the amount of time that infected persons are aware of the infection, and the duration of the sequelae of several stages of AIDS. When these are coupled with measures of the quality of life for the different stages just described, it is possible to make a reasonable estimate of the number of life years saved combined with disability prevented that is realized from each HIV infection averted. By applying an age weight function we will then derive an estimate of the number of DALYs saved. The age weight function will be established using formulas and assumptions developed by Murray and Lopez.⁴⁹ Moreover, since the DALY is a standard measure in international health economics, its use will allow comparison of HIV interventions to other health interventions, such as those described in the 1993 World Development Report.⁵⁰

7.3.4 Assessing Effectiveness

The larger efficacy trial is designed to establish an estimate of the number of HIV infections occurring over time in each study arm. Details of the methods for estimation of HIV incidence are described previously in the proposal. Using these estimates, together with the average age of those becoming HIV infected, and the average life expectancy at that age in the absence of HIV, we will be able to derive a direct measure of the effect of each intervention approach in a format needed to calculate DALYs. Note that to estimate a DALY it is necessary to know the average age of HIV infection. Thus, we will establish the intervention effectiveness from empirical data gleaned from the larger study.

7.3.5 Estimating Costs

We will use standard procedures for estimating the cost of interventions.⁴⁶ This will include identification of the various types of resources consumed by the intervention, establishing a unit associated with each type of resource used, estimating the dollar value of each resource, calculating the number of units used, and multiplying the units of resources used by the dollar cost for each. These are summed to derive the cost of the intervention. Both fixed and variable costs will be examined to establish gross program cost. Startup costs will be annuitized over the life of the interventions using a standard annuity function.⁵¹ The discount rate utilized for the annuitization of one-time capital expenditures will be the same as that used in the overall analysis.

Cost data will be entered into a detailed spreadsheet database that will include a range of costs for each item, with high, low, and mean costs at

the onset, midpoint, and completion of the study. This will allow us to examine natural variations in costs. Included in the database will be currency conversion rates (local currency to U.S. dollars) over the life of the project, as well as a general estimation of the value of the currency in terms of its buying power. Currency conversion rates are available from the World Bank. The estimate of buying power across study sites using the Purchasing Power Parity Index will be performed to examine any artificial fluctuations in the currency conversion rate. This will allow us to present constant costs in terms of both conversion rates to U.S. dollars and the value of the currency in its ability to purchase goods and services. The process of estimating costs will include identification of categories of resources used by the intervention, determining the unit for the resource, estimating the monetary value of the resource, and calculating the number of resource units used. With these data it is possible to then multiply the number of resources units used by the monetary value, and then sum the results. All costs will include estimated high, low, and average costs at the beginning, midpoint, and end of the project. Once we have established the program cost, net program cost, and the total number of DALYs saved from the intervention we will calculate "base case" ratios assuming both a donor and societal perspective. The base-case ratio is simply the total number of DALYs saved divided by the cost of the intervention.

7.3.6 Time Preference

An important consideration in any cost-effectiveness analysis is the value given to present versus distant benefits of the interventions being considered. Even with zero inflation, societies typically value intervention benefits incurred sooner over those realized later in time. To account for this it is necessary to discount the future costs and benefits of the interventions under consideration. Following recommendations set by the U.S. Panel on Cost-Effectiveness in Health and Medicine,⁴⁶ we will harmonize the discount rate used for costs with those used for benefits, and utilize a 3% discount rate, with sensitivity analysis conducted with a 0%, 5%, and 7% discount rate. As discussed earlier, we shall also use these same discount rates in the annuity function for one-time capital expenditures and to discount the future health benefits.

7.3.7 Reflecting Uncertainty

The final step is to conduct sensitivity analysis. Sensitivity analysis will allow us to take into consideration any uncertainty that occurs in the data used. We will use sophisticated software programs such as @RISK or Crystal Ball to conduct sensitivity analyses. These procedures work directly in Excel spreadsheets, and are able to apply a variety of probability functions to variables of interest. They use Monte Carlo and Latin Hypercube simulation techniques, and have the capacity to use regression and correlation analysis to examine the sensitivity of model parameters. In a regression analysis the unit of analysis is the iteration. The model is stochastic, so it iterates hundreds to thousands of times

making systematic changes in the input parameters, and derives a dataset from that. The regression is then run on that dataset, which shows in a multivariate way how changes in the inputs affect the selected output. There are also procedures available to find the combination of various probability functions available that produce the best-fit model (with software called BEST-FIT). Additionally, we will also incorporate procedures to correlate the inputs to the model, as in any iteration of the stochastic model the random selection of parameter values across the probability functions defining them can otherwise result in nonsensical combinations of parameter inputs. We will also model the impact of targeting strategies with each intervention project to establish the impact on cost-effectiveness of various targeting strategies. For example, we will be able to identify the targeting strategy that will result in the lowest cost per HIV case averted, as well as model the cost of increasing equity in program delivery. We will derive such ranges based on 95% CIs for biologic and behavioral indices from study data, and from cost worksheets that will include high, low, and average costs for each site.

7.4 Qualitative Analyses

Five social scientists (one from each study site) will convene once or twice during the intervention period and at the end of the intervention period to review interview transcripts and develop a coding scheme that identifies broad themes and subthemes related to the study's research questions. The social scientists will read the transcripts multiple times to refine the codes and will practice using the coding scheme on a selection of transcripts to ensure that all relevant text is captured appropriately by a code. After the coding scheme has been developed, a staff of coders will be trained to apply the codes to the transcripts. To ensure intercoder reliability, a subset of data will be double-coded. The team of five social scientists will resolve coding discrepancies. Codes will be entered into ATLAS.ti. Using these codes, social scientists will retrieve and analyze text relevant to the research study questions.

8. DATA COLLECTION AND ADVERSE EVENT REPORTING

8.1 Data Management Center

The study team at the Medical University of South Carolina will serve as the Data Management Coordinating Center. The Statistical Center for HIV/AIDS Research & Prevention (SCHARP) at the Fred Hutchinson Cancer Research Center will assist the data management team in an advisory capacity. SCHARP provides data management for the HIV Prevention Trials Network (HPTN), and has provided data management support to a host of multisite/multicountry HIV studies with similarly complex study designs, sensitive data, and logistical challenges as this study. SCHARP has pioneered many technical advances in centralizing data management for multisite studies and has a renowned track record in data management, statistical analysis, and field training of developing country colleagues for complex health research studies located in geographically disparate locations.

8.2 Data Management

Both quantitative and qualitative data will be collected, and we have developed a data management plan for each. Quantitative data will include results from the baseline demographic and behavioral survey, utilization data collected over the life of the study, and post-intervention biologic and behavioral results. We have developed a data management plan designed to address key needs of the project, including: (1) maintaining data quality and consistency, (2) pooling of data, as required by the study design and analysis plan, (3) oversight of data management activities by the PIs in host countries and in the U.S., (4) assured timely access to data by PIs in geographically disperse locations, (5) facilitation of data analysis among the study team, and (6) assurance of confidentiality and attention to ethical considerations.

(Study procedures related to data management are described in detail in the *Data Management Procedures Manual*.)

8.2.1 Quantitative Data Management Plan

The DataFax software package will be used for survey instrument design, data collection, and processing. Data from the baseline behavioral survey, exit interview, and post-intervention survey will all be formatted in DataFax and faxed to one of three regional DataFax entry sites (Thailand or South Africa [2]) where the data will be cleaned and validated. Once this step is completed, the validated data will be transmitted to the Data Management Coordinating Center, where data from multiple sites will be pooled. The pooled baseline behavioral data, exit interview data, and post-intervention data will then be transmitted to the Charles University Statistical Center for analysis. Utilization data will be collected and tabulated at individual study sites and then transmitted to the country central office. From the country central office, utilization data will be electronically sent to the Coordinating Center where semimonthly reports will be generated for the purpose of tracking descriptive demographic information and monitoring other site trends.

Data files will not contain identifying information on study subjects, but will contain a study subject ID number to allow for checking of original paper forms for errors that might be identified. All data are cross-sectional, so there is no need to link discrete data points over time.

An experienced fulltime data coordinator will oversee data management activities. At each study site, the Project Director and Field Supervisor have extensive and prior experience managing data on multisite projects that utilized procedures standardized across sites. Each study site will have representatives on the Data Management Committee, which will include the host country PIs, U.S. PIs, the Data Management Coordinator, and Data Managers from each field site. There will be regular conference calls, field visits to maintain quality assurance, training at each field site on data management and analysis, and regular face-to-face meetings of the members of the Data Management Committee. Each site will hire a Data Manager and one to two Data Assistants who will enter, transmit, and maintain the project data.

A set of bylaws for access to and analysis of study data will be codified by the Steering Committee in consultation with the Data Management Committee. We will follow the precedent set in our earlier multisite VCT efficacy trial study where the bylaws stressed several major principles: (1) timely and rigorous analysis and dissemination of study data is a major responsibility the project has to the study participants and the research field, (2) project members should submit brief concept sheets using a standard forms proposing analyses that they wish to take the lead on, (3) other project team members will be given the opportunity to become involved in proposed analyses, with the Data Management Committee coordinating the process, (4) all PIs will be given access to the cleaned data sets, both in the U.S. and in host countries, (5) the major cross-country analysis paper will be published under the authorship of “The Project Accept Study Group” with appropriate recognition given to appropriate team members at all levels, (6) data dispersed to project team members will be blinded of any identifying information to assure confidentiality, (7) there will be an opportunity to review all papers published from the project by all PIs, (8) that there are many important means of dissemination of study results, including publications, presentations at meetings, and also in-country dissemination activities, all which should be supported, (9) that host country team members should be actively supported in analysis and dissemination of study results, (10) that junior members of the overall study team should be given the opportunity to analyze and disseminate data with mentoring by senior members of the team, and (11) that full public access to the raw data should be made in a timely manner once the study has been completed and major papers have been disseminated.

8.2.1.1 Data Collection Forms

8.2.1.1.1 Forms Used

A 45-50-minute behavioral survey instrument will be created and formatted for DataFax software. The survey will be comprised of variables that include, but are not limited to, demographic data, risk behaviors, social norms related to HIV testing, disclosure of HIV status, and stigma. The behavioral survey form will be used for both the baseline and post-intervention data components.

A utilization log will be created for the purpose of gathering demographic data on individuals accessing VCT services in the CBVCT communities, as well for individuals accessing post-test support services in the CBVCT communities. The log form will be present at all sites where CBVCT and post-test support services are provided. The utilization log will involve only a small number of variables.

A DataFax exit interview form will be created to measure overall client satisfaction with study services received. The exit interview form will consist of a series of closed-ended questions.

Forms used for the detuned assay will be determined once the details for the implementation of the assay have been decided.

8.2.1.1.2 Forms Completion and Submission

All DataFax forms will be completed by trained interviewer staff and submitted daily to local field offices. Comment fields will be provided on all forms in case interviewers experience difficulties in filling out a form. Forms will be transferred at least one time per week from local field offices to the country central office, where they will be faxed to one of two regional DataFax centers for processing.

8.2.2 Qualitative Data Management Plan

Qualitative data will be initially analyzed at each of the five host country sites using a standard methodology (see Section 7.4). A Qualitative Analysis Committee with representation across all study sites will be responsible for development of standardized field guides for the collection and coding of qualitative data. These data will be translated from local language into English where feasible (to allow for cross-site

analysis) and then transcribed and typed into computer files for analysis. Transcription machines (Dictaphones) will be procured for each study site for use by staff. Each site will employ two full-time translators/transcriptionists. The data manager will supervise these staff, and there will be regular quality assurance checks conducted to assure consistency in methods of translation and transcription. The final data files will be regularly submitted to the Data Management Coordinator on CD-ROM in order to maintain a central repository and backup of all qualitative data files. Strict security procedures will be followed to ensure confidentiality and security of qualitative data. Study documentation will be kept in locked files in the offices of the Field Supervisor and Project Director. The transcriptionists will be trained to blind any identifying information of study participants as data is entered into textual computer files.

8.3 Adverse Event and Incident Data Collection and Management

All adverse events and incidents associated with the procedures of all components of this study will be reported within the time frames required by the appropriate Institutional Review Boards, and information on adverse events will be provided as frequently as requested to the DSMB. Appropriate action will be taken to address any adverse events or incidents. Field staff at each of the community research sites in both arms of the study will be trained to complete descriptions of adverse events that will then be sent electronically to both the U.S. Principal Investigator and the site Principal Investigator. Thus, adverse events will be monitored at four levels: by the Principal Investigators, the Steering Committee, the IRBs (both U.S. and host country), and the DSMB. Of course, efforts will be taken to minimize the potential for adverse events. Counselor training will stress ensuring confidentiality and avoidance of negative events, and quality assurance/quality control (QA/QC) checks will be performed regularly to ensure adherence to proper counseling techniques and all other relevant SOPs.

Two types of reports will be made involving the conduct of the study. *Adverse Events Reports* will be made using standard forms available from the relevant IRBs for adverse events associated with the study procedures or subject participation. In addition, a studywide Adverse Event Reporting Form will be completed that will be circulated to the Steering Committee and to the DSMB. As the VCT component of the study uses finger pricks, serious adverse medical events are unlikely. Serious adverse medical events are also unlikely in the post-intervention assessment, which involves phlebotomy conducted by trained medical staff.

Incident Reports will also be made of any incidents involving the conduct of the trial (eg, enrolling a participant who did not meet eligibility criteria, needle stick injuries of staff, etc.) These reports will be made in the form of a letter or memo to the Chairs of the relevant IRBs signed by the Principal Investigator.

For the VCT component of the study, we will provide participants with a palm card containing information on how to contact the local research staff to report such events as breaches of confidentiality, HIV-related disruption of families,

acts of discrimination, and physical harm. We will ask VCT participants to return to the research site or otherwise contact research staff in order to make such reports as well as receive referrals to mitigate potential harm. For those participants who enroll in post-test support services, we will be able to track potential negative life events related to HIV testing and report these events. Palm cards will not include identifying information about the study or references to HIV or HIV testing, so that the cards will not have the potential to jeopardize the confidentiality of participants.

If staff members experience occupational exposure to HIV, the incident will be reported and a protocol will be followed to minimize their risk of being infected with HIV that includes the provision of postexposure prophylaxis (PEP) with antiretroviral drugs when indicated. All staff at risk for occupational exposure to HIV will be trained on universal precautions and on the PEP protocol. All staff performing HIV tests will require training and certification on performing the test and on quality assurance.

The Data Coordinating Center will store electronic and faxed copies of adverse event reports using secure systems. Copies will also be maintained at the UCLA Coordinating Center, and at each host-country site.

Adverse events or incidents reporting in this trial have been considered in the context of several important characteristics of the study. First, this is a minimal-risk study as defined in federal regulations—“the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” Second, this is not a cohort study—we do not currently have means of recontacting VCT or post-test support service participants. We have chosen this approach to maximally protect the confidentiality of those volunteering for HIV testing and counseling. Active monitoring of negative life events associated with HIV testing would require the collection of tracking information and making further contacts with study participants. We believe that such an approach would increase rather than decrease the risk of social harm to participants. Third, although no clear guidance is currently provided in regulation for adverse events reporting in behavioral studies such as this one, as opposed to clinical trials of drugs or devices, we are taking the steps outlined above within the context of our study. Finally, the mobile VCT component of the study replicates what is provided as a service in the countries where the trial is being conducted and should not pose added risk by virtue of being more readily accessible.

All study staff/volunteers having potential contact with study participants or data will receive human subjects training as well as training for good clinical practice.

8.4 Security and Confidentiality

Strict security procedures will be followed to ensure confidentiality and security of data for all components of the study. Study documentation will be kept in locked files in the offices of the Field Supervisor and Project Director at each study site. To ensure confidentiality, questionnaires will be saved on password-protected secure computers. All data will be backed up on separate media such as

direct tape backup from the mirrored Raid Level 1 UNIX hard drives. The tape media will then be stored in a secure filing cabinet at the DataFax regional center. Access to security passwords will be given only to the PI and Field Supervisor. Personal identifiers will not be stored in the data set and all computers will be protected by antivirus software.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan

9.1.1 Aim 1

Aim 1 tests the hypothesis that communities receiving 3 years of CBVCT, relative to communities receiving 3 years of SVCT, will have significantly lower HIV incidence.

Primary analysis. The primary hypothesis of no intervention effect on incidence will be tested using a weighted t-test based on differences between estimated log incidence rates in CBVCT community vs. its paired SVCT peer. The incidence rate within a community will be estimated by the ratio of the number of MAA-positive cases divided by the estimated total follow-up (window period times the number of people at risk). For a particular pair, the difference in estimated log rates represents a pair-specific estimate of the intervention effect. The test statistic will be defined as a weighted average of the estimated pair-specific intervention effects divided by the estimated standard deviation of the weighted average. The weights will be proportional to the harmonic mean of the numbers of MAA-positive cases in the paired communities. This procedure adjusts for unequal variances across communities, has a minimal variance among all statistics based on weighted averages and also protects the power against potential unexpectedly low incidence rates at some communities. The null hypothesis of no intervention effect will be rejected against a two-sided alternative if the weighted t-test statistic exceeds in absolute value the 0.975-quantile of the t distribution. The number of degrees of freedom will be adjusted to the unequal weights.

Secondary analysis. In secondary analyses, we will evaluate incidence estimates and test the intervention effects on incidence in subgroups: among males and females, and among subjects under 24 years of age and above 24 years of age. The analysis will proceed by the same methods performed on reduced data sets.

9.1.1.1 Sample Size and Power Calculations

The trial is being conducted in 4 community pairs in Zimbabwe and each of the 2 South African sites, 5 community pairs in Tanzania, and 7 community pairs in Thailand. In Zimbabwe and Vulindlela (South Africa), the sample size for HIV assessment is 1430 per community; in Tanzania, 900 per community; in Thailand, 500 per community. In Soweto (South Africa), the sample size for 6 communities will be 1,750 to increase power due to higher prevalence and incidence there. The sample size in one matched pair (two communities: Thulani and Slovoville) cannot be increased due to limited population size, and hence the sample size will be 1,430 per community. The total number of subjects participating in the incidence assessment survey will be 52,240. The sample size was calculated in terms of the number of randomization units (community pairs) needed to provide at

least 80% power to detect a 35% reduction in HIV incidence in the CBVCT compared to SVCT communities using a two-sided test at a 5% level. The calculation was worked out under the following assumptions: there will be at least 1,000 HIV-negative subjects in the sample from each Zimbabwean or South African community; at least 600 HIV-negative subjects in each Tanzanian community; at least 400 HIV-negative subjects in each Thai community. The window period of the MAA is 170 days; duration of MAA-positive status may vary between individuals, but may not exceed the duration of the intervention. The incidence among the 18-32 year-old population is 3% per year when averaged across all sites. The coefficient of variation between baseline incidences is equal to 0.26. A modification of the formula given in Hayes and Bennett⁵⁹ was used to calculate power. Different community sizes were taken into account by calculating the sample size separately for each site (as one-fifth of the sample size that would be needed if the whole trial was conducted at the site).

Further details on the sample size calculation are provided in Appendix 1.

9.1.2 Aim 2

Test the hypotheses that CBVCT communities, relative to SVCT communities, will at the end of the intervention period report significantly:

- less HIV risk behavior
- higher rates of HIV testing
- more favorable social norms regarding HIV testing
- more frequent discussions about HIV
- more frequent disclosure of HIV status
- less HIV-related stigma
- fewer HIV-related negative life events

Statistical analyses of behavioral and attitudinal endpoints will be performed for each site separately and for all communities combined. Intervention effect will be tested by paired *t*-tests performed on community-wide means. Two analyses will be performed: one will compare post-intervention outcome levels between CBVCT and SVCT communities and the other will compare differences between post- and pre-intervention levels (for the outcomes that were included in the pre-intervention assessment). Subgroup analyses by gender and age will be performed by applying the same methods to a subset of data.

9.1.2.1 Sample Size and Power Calculations

The power is calculated under the assumption of a binary outcome measured at baseline and after the intervention in both

CBVCT and SVCT communities. In a given community pair, the intervention effect is estimated as the difference between the logarithms of two estimated odds ratios: the first compares the odds of a positive outcome pre- vs. postintervention in the CBVCT community; the second odds ratio estimates the same quantity for the SVCT community. The overall treatment effect is estimated by averaging over all community pairs. This approach essentially compares the odds of a positive outcome in CBVCT vs. SVCT communities while adjusting for potentially different baseline levels. When conducting a separate analysis of a single site (4-5 community pairs in an African site with 300 subjects per community or 7 community pairs in Thailand with 200 subjects per community) the planned sample size provides at least 90% power for detection of odds ratios 2–2.5 when the outcome is rare (probability of positive outcome 0.05–0.1) as well as for detection of odds ratios 1.5 or bigger when the outcome is common (probability 0.3–0.5). When conducting a joint analysis of all African sites combined (18 community pairs with 300 subjects per community), the planned sample size provides at least 90% power for detection of odds ratios 1.5 or bigger when the outcome is rare as well as for detection of odds ratios 1.25 or bigger when the outcome is common.

9.1.3 Aim 3

Aim 3 is to assess whether CBVCT is cost effective compared to SVCT. Aim 3 will be evaluated in terms of cost per HIV infection averted and disability-adjusted life years (DALYs) saved. As with our previous research,⁴⁴ we will conduct a marginal cost-effectiveness analysis comparing CBVCT and SVCT to no intervention, and also comparing CBVCT to SVCT. This analysis will allow us to compare the value of the intervention's effectiveness to other HIV interventions and will be of assistance to program managers and policy makers who are deciding on which interventions should be supported. The cost-effectiveness analysis will require that data be derived on both cost of the intervention and on the effectiveness in terms of cost per HIV infection averted and the Disability Adjusted Life Years (DALYs) saved from the intervention. The CEA analysis adds little cost to the study, but enhances the outcomes enormously. Details on cost-effectiveness analysis can be found in Section 7.3.

9.1.4 Qualitative Cohort

In each of the African sites, 16 individuals will be sampled from each of the study communities for the qualitative assessment. In the Thai site, a total of 8 individuals will be sampled from each of the 14 study communities. There are two strata for sampling the qualitative cohort members. First, at the community level we will strive for a 50:50 ratio of participants who are male/female; in partnerships and not in partnerships; and less than 25 years and greater than 25 years. Across communities we will strive for a reasonable representation of ethnicity, religion, SES,

population density of residence, and other salient factors specific to each site.

9.2 Data Monitoring

This study will be monitored by the Data and Safety Monitoring Board (DSMB) convened by NIMH to review this study. Summaries of overall and site-specific trial operations, data, and outcomes will be provided to the DSMB according to its instructions and at the frequency the Board requires.

10. HUMAN SUBJECTS

10.1 Data and Safety Monitoring Board

This study is an NIMH cooperative agreement and as such, NIMH will develop and convene a Data and Safety Monitoring Board (DSMB) with expertise related to this study. The DSMB monitors data from all components of the study (baseline, intervention, post-intervention assessment, and qualitative cohort). The DSMB will review the study protocols and establish clear stopping rules for the trial if adverse events are deemed to reach an unacceptable level.

10.2 Institutional Review

Prior to implementation of any study component at a site, the protocol, SOPs, and informed consent forms governing that component must be approved by the IRB of the host-country institution for the site, as well as its U.S. partner institution. All protocol amendments and amendments to SOPs and any other documents affecting the safety and welfare of study participants must be approved by the US and host-country IRBs prior to implementation. The study site Principal Investigator is responsible for the preparation and submission of all documents and periodic reports required by an IRB.

10.3 Informed Consent

Verbal informed consent will be obtained from each participant in the baseline behavioral assessment, CBVCT counseling and testing*, CBVCT post-test support services, and SVCT counseling and testing*, and post-intervention behavioral assessment prior to participation in that component of the study. Information sheets on the baseline behavioral assessment, CBVCT counseling and testing, CBVCT post-test support services, or SVCT counseling and testing, respectively, will be provided to prospective participants to keep. With the permission of the IRBs overseeing the study at all sites, verbal informed consent for these study components will be accepted, rather than written informed consent, as a signed consent form would link the participant to the study and could jeopardize participant confidentiality.

For the behavioral assessment, there is a section in the Baseline Assessment Household Contact Form that includes "Documentation of Consent and ID Assignment" fields. These are used to document that the study has been explained to the participant, all questions have been answered, and that the participant has been given the information sheet and has given verbal consent to participate. The fields include the interviewer initials, the date/time of consent, the language of consent, and whether others were present.

For community-based VCT, when a participant comes to a CBVCT venue, s/he will go through the verbal informed consent process. To verify that verbal informed consent has been given, the counselor will record the counselor's initials, the date/time of consent, and the language of verbal consent on the CBVCT Service Utilization Form, along with the standard demographic/utilization information we are collecting for each CBVCT participant.

For the post-test support services (PTSS) component of the study, when participants come to a PTSS facility, they will be asked if this is their first visit. If it is, they will go through the verbal informed consent process for participating in PTSS. To document that verbal informed consent has been received, the intake coordinator/counselor will fill out information in a PTSS consent log. This will include the participant's number generated from that day's intake log, whether the participant is a member or a guest, and recording of the counselor's initials. This consent log will be stored in a binder along with that day's intake log.

These documents will all be stored in the requisite regulatory binder/file, and will be available for review by GCP monitors. If verbal informed consent is not documented, this would constitute a protocol violation and data on such participants would not be included in analysis.

Written informed consent will be obtained from each participant in the qualitative cohort and post-intervention biological assessment components of the study, prior to their participation. Participants will be provided with a signed copy of their consent form.

** In South Africa, written informed consent is required for all forms of HIV VCT. No identifying information will be retained other than the signed consent form, which will not be linked to the participant's HIV test result.*

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

Each site has prior experience in obtaining informed consent for prevention trials within the cultural context of each country. The informed consent procedure for this study has been designed to maximize understanding of potential risks. All consent forms will be translated into the local language and back-translated by an independent source into English to ensure correct use of language.

Potential participants will be excluded from participation based on an inability to provide informed consent. After hearing the staff member read the informed consent document aloud, the potential participant will be asked to report back a description of the procedures in his or her own words and explain the reasons why they want to participate to the interviewers. This will ensure comprehension of the informed consent and assist staff in determining contraindications to participation. In cases where the potential participant is unable to provide a description of the study procedures in his/her own words, the Team Leader or Coordinator will be consulted to make the final decision regarding eligibility and inclusion in the study component. This procedure does not involve a formal assessment of mental status, but an assessment of ability to provide informed consent. For any other circumstances in which the staff member requires additional support to determine eligibility, the Team Leader or Coordinator will be consulted.

For components of the study requiring written informed consent, if there are cultural, literacy, or political reasons why signature is not appropriate, individuals will be allowed to mark consent forms with an “X”. At this point, any misunderstandings regarding procedures, risks, or benefits can be clarified. Individuals will be provided with information on how to contact the study staff to report adverse events associated with HIV testing or participation in post-test support services. Study staff will have been trained in the need to ensure individuals provide voluntary informed consent. If a woman wants to get the assent of husband, father, or chief, that is permitted. Such assent, however, may not substitute for her consent.

10.4 Confidentiality

10.4.1 Local Protections

Confidentiality of all study participants will be strictly maintained across all study components. The purpose of the intervention is not to encourage participants to break their own confidentiality; rather, the purpose is to encourage discussion of HIV in communities and thus to destigmatize it. A major objective of the post-test support groups is to help people determine when and to whom it would be safe to disclose their HIV status. HIV testing conducted as part of the intervention and the post-intervention assessment will be anonymous* to afford the highest level of confidentiality.

** In South Africa, written informed consent is required for HIV VCT. No identifying information will be retained other than the signed consent form, which will not be linked to the participant's HIV test result. HIV and AIDS are not reportable in South Africa, and participant names and HIV results are not communicated to government nor to any other parties. We will not keep a record of test results by subject name or identification number. If a subject requests certification of test results, we will provide that certification to the individual at the time when the subject receives test results, but they will not be available to the individual after that time, as we will have no record of test results by individual name or ID number.*

All Site Coordinators and Project Directors attended the one-day Family Health International (FHI) Research Ethics Training Curriculum for Community Representatives conducted by FHI staff during the Training of the Trainers Meeting at the start of the project. A major component of the training involved a presentation and discussion of the principles of research ethics, with emphasis given to confidentiality. In sum, this training provides sufficient background to allow Coordinators to successfully relay the content of the training to their site staff. All staff members are trained on ethics and confidentiality at the start of their employment by their Site Coordinators using the information learned at the FHI Research Ethics Training Curriculum for Community Representatives.

Team members will meet the NIH requirement that all staff conducting research involving human research participants must complete the NIH human subjects training. This free, Web-based course is available through each U.S. institution's IRB. These online courses present information about the rights and welfare of human participants in research, define privacy and confidentiality as it applies to protecting human participants, and describe how these can be maintained throughout the research process. Completion satisfies the NIH human subjects training requirement for obtaining Federal funds. Upon completion, a certificate of completion is printed from the staff member's computer. This certificate is filed in the staff member's personnel file.

Some sites have additional training elements required by the local university. For instance, all research staff at MRCZ in Harare, Zimbabwe are required to attend a 3-day training on ethics and GCP provided by MRCZ. These site-specific requirements are administered in addition to the requirements listed above and do not replace them.

Staff members sign the Project Accept Oath of Confidentiality as well as any confidentiality oath required by their institution. Signing of the oath indicates that the staff member agrees to uphold the confidentiality specific to their work, that all participant information is confidential and shall not be divulged or made known to unauthorized persons, and that a breach of confidentiality may be grounds for disciplinary action or termination of employment. The signed oath is kept in personnel files.

Mobile units in the CBVCT communities will be set up to provide adequate privacy for testing and pre and post-test counseling. In addition, all VCT staff will only be hired from communities other than those being randomized for this study, so that confidentiality is further protected. Procedures have also been developed to make post-test support service participation as anonymous as possible and to remind attendees at each meeting of the need for strict confidentiality.

Participants in the baseline behavioral assessment will be asked to provide verbal consent to participate in the baseline interview. Participants will be informed that they may be recontacted to participate in the qualitative cohort interviews. Upon providing verbal consent to participate in the baseline interview, the participant will provide the baseline interviewer with information to complete a household locator and contact form that includes the participants' initials or a nickname. Once the baseline recruitment is complete, the locator/contact forms will be provided to the qualitative supervisor for recruitment for the qualitative cohort. Once full recruitment for the qualitative study is attained, the household location and contact information for all baseline participants will be destroyed. For the study components in which participants are required to provide written informed consent (qualitative cohort and post-intervention assessment), all study data, laboratory specimens, reports, and study data collection, process, and administrative forms will be identified by a coded number only, to maintain participant

confidentiality. All study data will be stored separately from study records that contain names or other personal identifiers (such as informed consent forms or locator forms). For post-test support services and where written consent is not required for VCT, no identifying information will be collected. In South Africa, written informed consent is required for HIV VCT. No identifying information will be retained other than the signed consent form, which will not be linked to the participant's HIV test result. HIV and AIDS are not reportable in South Africa, and participant names and HIV results are not communicated to government nor to any other parties.

Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information must be stored in a separate, locked file in an area with limited access at the study site headquarters. If participant names and corresponding participant IDs are entered into a computer database, this database must be password protected and must be maintained in a directory separate from any study-specific data. File encryption is encouraged, but not required.

For participants who provided written informed consent, study-related information will not be released without the written permission of participants, except as necessary for monitoring by UCLA's multisite coordinator, the study's statistical/data management team, and/or NIMH.

10.4.2 Statistical and Data Management Center Protections

Access to all study databases housed at the Data Coordinating Center will be password protected to ensure confidentiality of study participants. Any copies of data query forms, utilization logs, and all adverse event reports will be stored in locked file cabinets. Only study PIs and the data research coordinator will have access to secure documents. Any breach in confidentiality protocol will immediately be written up as an adverse event, and submitted to the DSMB. The data sent to the Statistical Center only include anonymous study IDs with no other information identifying the subjects. The databases are stored electronically on university computers protected by a firewall and allow only local access using a password.

10.5 Benefits

10.5.1 Individual Benefits

Participation in the VCT services offered by the intervention and post-intervention assessment components of the study may provide the following benefits for individuals:

- Participants can learn their HIV status. VCT outside this study may be unavailable or difficult to access at some sites because of logistical issues (eg, location and expense). It should be noted that pre and post-test counseling is rarely offered in private

doctor's offices and the quality of the counseling at public VCT sites may be inadequate compared to the protocol standards.

- In addition to enhancing availability of VCT, the intervention will offer individual counseling.
- Knowing one's HIV status may allow participants to plan for their future, particularly in terms of family responsibilities.
- Knowing one's HIV status may afford participants the opportunity to live healthier lives in terms taking better care of themselves—either in staying negative, or if infected, seeking out available care and support services.
- Knowing one's HIV status may cause behavior change that could give participants resolve to protect themselves or prevent HIV transmission to their sexual partners.
- Receiving pre and post-test counseling may answer participants' questions about HIV and its transmission, dispel inaccurate information/beliefs participants may have held, reduce participants' anxieties, and help participants to initiate/maintain behaviors to protect themselves and their partners.
- Participants who access post-test support services may receive beneficial information, support, and/or referrals that assists them in staying HIV negative (if negative), staying as healthy as possible (if positive), protecting their partners, planning for their future, disclosing their status (if they choose to do so), and relieving stress and anxiety.

10.5.2 Community Benefits

- Communities involved in the study will receive free VCT services throughout the intervention component.
- Communities randomized to receive community-based VCT (CBVCT) will receive high-quality, mobile, community-based counseling and testing services, as well as post-test support services, neither of which would be otherwise available to the community.
- Communities randomized to receive standard SVCT will receive clinic-based VCT services or enhancement of current VCT services in existing sites.
- This trial tests the efficacy of a behavioral intervention in reducing the number of new infections in developing countries with high HIV prevalence, which, if successful, would have enormous social benefit. An intervention that is effective, cost-

effective, sustainable, and easily disseminated in developing country settings is critically important, as at present there are no prevention interventions proven to be effective specifically for generalized epidemics (more than 5% of antenatal clinic women infected with HIV).⁵⁴ The countries involved in the study, and other developing countries with generalized epidemics would receive the most direct benefit of the research – not the U.S. or other industrialized countries with concentrated epidemics where this intervention would not be feasible because HIV prevalence is too low. Thus, this study also responds to the ethical principle of justice, as the group exposed to the research risks receives the potential benefit of the research.

The study team at each site will conduct extensive community preparedness activities, including establishment of community advisory boards, prior to communities' participation in the study and throughout the duration of the study (see Section 12.1).

10.5.3 Benefits to Humanity

This study is designed to answer an important scientific question about the ability of a community-based, behavioral HIV intervention to reduce the incidence of HIV in high-prevalence communities. The outcome of this study could have a significant public health impact in communities and countries around the world.

10.6 Risks

10.6.1 Individual Psychosocial Risks

The primary risks to participants are social and/or psychological harm associated with HIV testing, including:

- Disruption of family (eg, breakup of couples following HIV detection)
- Discrimination (eg, a loss of employment or status in community)
- Displacement (ie, loss of housing as a result of HIV status)
- Abuse (eg, acts of violence directed at people who have been diagnosed with HIV)
- Anxiety about testing for HIV or the results of testing
- Embarrassment (eg, being questioned about sexual behavior)

In addition, participation in the baseline behavioral assessment, qualitative cohort, post-intervention behavioral assessment, post-test services, or counseling related to HIV testing involves the risk of:

- Anxiety, discomfort, and/or embarrassment in answering questions related to HIV risk behavior or discussing sexual issues or other personal matters

Participation in any component of the study involves risk of:

- Loss of privacy

10.6.2 Individual Physical/Health Risks

Physical harm may result from abuse related to HIV disclosure as a result of participation in the intervention and post-intervention assessment components. In addition, there may be health consequences associated with loss of housing, employment, or resources caused by displacement or discrimination based on HIV status.

Study participants may experience discomfort associated with blood sample collection. Blood sample collection may be associated with pain during blood drawing or, in very rare instances, local infection. The baseline and qualitative cohort components do not pose any physical or health risks to participants.

10.6.3 Community Risks

Through its participation in the study, the community as a whole may experience stigma, misperceptions, and/or negative rumors. For example, the community may possibly be viewed as having a high prevalence of HIV as the reason for its inclusion in the study. The community may also be perceived to be receiving special benefits beyond those outlined above; it may be perceived as receiving favored treatment. All these may lead to ostracism of and discrimination toward the community and its members by neighboring communities.

10.7 Adverse Event Reporting

All adverse events and incidents associated with the procedures of this study will be reported within the time frames required by the appropriate Institutional Review Boards, and information on adverse events will be provided as frequently as requested to the DSMB. Appropriate action will be taken to address any adverse events or incidents.

Adverse event reporting is discussed in further detail in Section 8.3.

10.8 Study Withdrawal and Discontinuation

The study may be discontinued at any time by NIMH or the NIH.

Study participants will be informed through the process of informed consent that they may withdraw from the study at any time for any reason.

Participants may be withdrawn from the study by the site Principal Investigators if they are found to have:

- An obvious psychological/psychiatric disorder that would invalidate the informed consent process, or otherwise contraindicate participation in the study; or
- Any other condition which in the opinion of the study site Principal Investigator will interfere with achieving the study objectives. In such cases the Principal Investigator will review the reasons for withdrawal with the Steering Committee and Protocol Biostatistician prior to participant notification. The Principal Investigator may decide to include data collected prior to participant withdrawal in study analyses.

10.9 Incentives for Participation

Qualitative assessment cohort members and key informants will be reimbursed for the transportation costs incurred to travel to the interview site and for the time that they spent in transit to and during the interviews. No incentives for participation are provided to VCT participants. A variety of incentives for participation in post-test support services have been developed through site-specific collaborations with local organizations, including the provision of skills training and educational workshops in conjunction with post-test support services. Participants in the post-intervention assessment will be offered US\$5 (or the equivalent in local currency) as compensation for their involvement.

10.10 Linkages to Care

All stages of this trial are planned in the context of recognized ethical principles for protecting human participants in international research. The project also involves a number of strategies to ensure that the trial reflects the needs and concerns of the participating communities and countries. To ensure that participants who test positive for HIV during the intervention and post-intervention assessment can be linked to the highest quality treatment and care available, the study team will track the availability of ART and other treatment and care interventions, and work with the institutions providing this care to construct effective referral mechanisms.

The Cofactors Subcommittee of the study's Steering Committee is charged with the following objectives:

- i. Describe antiretroviral program models as they develop
- ii. Track the implementation of ART distribution programs
- iii. Track the implementation of other interventions that may influence VCT uptake and risk behaviors
- iv. Develop a referral process from VCT services to HIV/AIDS clinical care services

- v. Develop an evaluation framework to measure the impact of ART availability on HIV incidence, VCT uptake, and risk behaviors

Other interventions that may influence VCT uptake include: prevention of mother-to-child transmission (PMTCT) programs, management of opportunistic infections, isoniazid preventive therapy, and cotrimoxazole prophylaxis. Other interventions that may influence risk behaviors include: condom promotion and distribution, microbicides, and HIV vaccines.

In order to track access to the above interventions, we will make a list of all health facilities (public, nongovernmental, private) in each community and will determine which types of HIV-related prevention and treatment interventions are available in each facility by interviewing facility managers at baseline and updating the list annually. This activity will be the responsibility of the Study Site Project Director at each site.

For tracking the number of people on ART in each ART service point, facility records (ART register or pharmacy records) will be monitored by the Study Site Project Director on a quarterly basis.

At the end of the study we will assess if the availability of ART, and if the proportion of eligible people receiving ART, were associated with VCT uptake, HIV risk behaviors, and HIV incidence across sites.

This trial is designed to determine the impact of community mobilization, community-based VCT, and post-test support services, and will not take primary responsibility for providing treatment services for HIV-positive clients. VCT is a widely accepted HIV prevention intervention in all of the study sites, and national governments continue to encourage and support its provision in each host country. It is recognized that VCT, even in the absence of advanced HIV treatment regimens, does provide benefits to clients, and large proportions of client populations in these settings wish to know their HIV infection status.

We shall refer HIV-positive clients to existing HIV clinical services from VCT and from post-test support services. Each VCT site and post-test support service will maintain an up-to-date list of existing health and social support services available in the community and refer clients appropriately. Interventions that are available in each facility will be documented as described above. This will determine what elements of the minimum package are missing. The study team will coordinate with local health authorities and donors to enhance the quality of treatment to the best possible standard. Sites may opt to offer participants a certificate documenting HIV status, to facilitate access to treatment and care. Participants are not obligated to receive a certificate, and no copies or records of certificates issued will be kept by study sites, in order to protect participant confidentiality.

10.11 Inclusion of Women

Women are included as participants in all stages of this trial. While we acknowledge that the risks of physical and social harms are greater for women than men, we do not believe that the exclusion of women from the trial based on

this potential risk could be justified. Because CBVCT is a free service, it is particularly important for economically disempowered women who otherwise would have to negotiate with male partners in order to pay for the service. It is clear that community groups view access to VCT as a human right for both men and women and community groups would not accept the exclusion of women.

We have incorporated a four-point strategy to minimize risk of physical and social harm to women participating in the intervention: 1) Pre- and post-test counseling risk assessment—counselors will screen for a history of abuse in any ongoing relationships and assist the woman in deciding to test or not and, if they decide to participate, to think through the potential consequences of disclosure. 2) Crisis counseling—the post-test support services component of the intervention establishes crisis-counseling services that can be used in case a negative outcome is encountered. Counselors are trained in crisis management, and to seek appropriate supervision in problematic situations. Training also involves assessment and referral for additional services if they are needed. 3) Development of referral services—one of the functions of the post-test services is to identify existing referral services or to develop new ones if they do not exist in the community. Thus, our sites will build capacity for responding to domestic violence in communities. 4) Social support—our post-test services include the option of participating in support groups where the issues of disclosure can be discussed and the individual can learn from peers about high-risk situations for disclosure and how to minimize risk.

10.12 Inclusion of Minorities

This trial is being conducted in four African sites and one Thai site. The intervention component will be applied to all members of the intervention community. In addition, the baseline, qualitative cohort, and post-intervention assessment components of this trial design call for a random sample of persons aged 18 to 32. For example in the baseline assessment, households are randomly selected, and one participant in the eligible age group is randomly selected and asked to participate. The same sampling procedures will apply to the post-intervention assessment. Thus, any tribal minorities in Africa or ethnic minorities in Thailand that reside in the communities being studied will be included in the trial.

10.13 Inclusion of Children

The baseline assessment, qualitative cohort, and post-intervention assessment components of this trial involve children between the ages of 18 and 21. For statistical reasons (see Section 9), the post-intervention random sample is designed for ages 18 to 32 in order to optimize the measure of the HIV incidence. Children who are 16 years of age or older may participate in the VCT and post-test support services provided by the intervention component.

11. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

11.1 HIV Testing

Please refer to Section 5.6 (Study Procedures - HIV Testing) and Section 7.1 (Evaluation of Primary Outcome).

11.2 Biohazard Containment

As HIV and other blood-borne infectious agents can be transmitted through contact with contaminated needles/lancets, blood, or blood products, universal precautions must be employed by all personnel involved in this study. Safety standards should reflect those required by the Occupational Safety and Health Administration (OSHA) and recommended by the CDC. Each site will develop and follow policies for biohazard prevention and response, provision of postexposure prophylaxis for staff members having possible exposures to HIV-infected body fluids, and disposal of biological/hazardous waste.

12. ADMINISTRATIVE PROCEDURES

12.1 Community Preparedness and Involvement

The study team at each site will conduct specific community preparedness activities in all communities being considered for inclusion in the research. The community preparedness activities will commence prior to communities' randomization into the study, and will continue throughout the course of the study, with the goals of preparing communities for possible involvement in the study, maintaining constructive relationships with the communities over the course of the study, and ensuring that the research is responsive to community expectations and needs.

The first step in preparing for the study is for each site to introduce itself and the study concept to both primary and secondary stakeholders. This will begin at the national level and then continue at the provincial, and district levels, and finally continue to the level of the communities in which the research will take place. In order to build a strong collaborative foundation for the research, each site must have a thorough knowledge of all the stakeholders at the various levels that may have an interest in the study or may be able to affect the research outcomes.

After getting to know the communities socially and geographically, the study team can begin to build the community advisory structures, first by establishing the Community Working Groups (CWGs) and the Study Advisory Committee (SAC). For Project Accept, the community advisory architecture is composed of the Community Working Groups (CWGs) and the Study Advisory Committee (SAC). In each study community, the community advisory process is ensured through the development of a CWG. Each research community will establish a CWG and through their participation, the study will ensure information exchange and dissemination between the research team and members of the research communities. The CWG is a group of people selected by the community to foster a partnership between researchers, research participants, and the community. Several members of each CWG will also serve on the overarching Study Advisory Committee (SAC). Although these structures have a common purpose across sites, there may be tremendous diversity in how each site facilitates community participation in the research process. However, the overriding principles in the establishment of the CWGs and the SAC are:

- Parity: Equal opportunity for meaningful input and participation exists among community representatives.
- Inclusivity: The community is represented and involved in meaningful and purposeful ways.
- Representation: Diverse perspectives are sought and ongoing steps are taken to ensure that the research reflects the needs and concerns of the communities' values, norms and behaviors.

The purpose of the CWG is to ensure community input into the research process and to foster partnership between researchers and the community. As CWG members become more familiar and knowledgeable about Project Accept, there

will be greater participation on study-specific issues where members may have a range of suggestions, concerns, and advice to offer. The CWG can include as many members as necessary to achieve appropriate representation of the community. However, very large groups can be difficult to manage and often 20 members is the maximum number for achieving productive meetings and meaningful involvement. Above all, members of the CWG have to be recruited to ensure optimal community representation. The Community Relations and Mobilization Coordinator will be responsible for planning and coordinating CWG meetings and conducting training of CWG members.

The purpose of the SAC is to allow primary stakeholders to exercise leadership at a higher level of study coordination to ensure community involvement not only in the individual communities but also across the communities. The SAC will further facilitate partnership development between Project Accept researchers and the respective research communities and allow a level of networking between study communities that would not otherwise be possible. Networking among study communities will promote a feeling of ownership among all the communities in the study and instill a sense of working toward common goals. The SAC should include at least one representative from each CWG and a back-up representative. Depending upon site needs, there may be more than one representative from each CWG on the SAC but representation from each CWG should be equal. The SAC should aim to represent and reflect the diversity of the study communities including culture, ethnicity, age, and behavioral risk.

Communities will be actively prepared for the initiation of the study. This will include ensuring that the randomization process is as transparent as possible. Extensive explanation of the community randomization process will be conducted with the CWGs. The concepts underlying randomization and its importance in interpreting the study results will be elucidated, and the Statistical Center will provide a lay-language description of the actual steps taken in the randomization process, so that the process is as transparent as possible. The results of the randomization will be provided to the CWGs in a clear manner, and any questions or concerns regarding the results for the randomization will be addressed promptly by study personnel.

Documentation of the community preparedness and involvement process will include creation of workplans, detailed reports of activities, and summary quarterly reports.

A detailed description of implementation policies and procedures appears in the *Community Preparedness and Involvement Operations Manual*.

12.2 Study Coordination

The University of California, Los Angeles (Coates, PI) will serve as the Operational Coordinating Center. In this capacity, UCLA will be responsible for convening the Steering Committee (SC) on conference calls, setting meetings of the SC, setting the agenda for the SC, recording and distributing minutes, setting the timeline, interacting with the DSMB, the NIMH, and the HPTN, preparing the study protocol, and ensuring that the relevant OPHR and IRB regulations are followed. The SC will meet at least monthly via conference call, and meet on a

regular basis during the duration of the study. The SC will also establish a schedule of trainings and quality assurance strategies. There is considerable advantage in meeting at the sites in host countries. It will be quite cost-effective for us to have our meetings at the various sites, as travel will be less expensive for the majority of participating investigators, and it will give the SC the opportunity to visit each of the sites, visit the communities at each of the sites, and discuss and make final arrangements for the study from the vantage point of the actual experience of those sites. Training is usually scheduled to follow an SC meeting, again for cost considerations.

The Principal Investigators, co-investigators, consultants, and other study site personnel may participate in one or more subcommittees or working groups contributing to the design, oversight, analysis, and reporting for various components of the study.

12.3 Intervention Coordinating Center

The University of California, San Francisco, which has extensive experience as the intervention coordinating center for other large HIV prevention trials, will take the lead for training and quality assurance for the proposed intervention. This will include a quality assurance specialist (the intervention director) who will design the training materials for all components of the intervention and be responsible for developing or adapting manuals for each component. The specialist will also develop an intervention quality assurance checklist and make site visits to each of the sites twice a year to evaluate the local quality assurance procedures. The overall goal of the coordinating center is to assure fidelity to all components of the intervention as outlined in the protocols and manuals.

12.4 Statistical and Data Management Coordinating Centers

Charles University (Prague, Czech Republic) will serve as the Statistical Coordinating Center. The study team at the Medical University of South Carolina will serve as the Data Management Coordinating Center. The Statistical Center for HIV/AIDS Research & Prevention (SCHARP) at the Fred Hutchinson Cancer Research Center will provide oversight to the study team at Charles University, and will serve as an advisor to the Data Management Center. SCHARP provides data management for the HIV Prevention Trials Network (HPTN), and has provided data management support to a host of multisite/multicountry HIV studies with similarly complex study designs, sensitive data, and logistical challenges as this study. SCHARP has pioneered many technical advances in centralizing data management for multisite studies and has a renowned track record in data management, statistical analysis, and field training of developing country colleagues for complex health research studies located in geographically disparate locations.

12.5 Study Site Monitoring

12.5.1 Intervention

Day-to-day monitoring, supervision, and support of counselors will be carried out by the intervention coordinator (or counseling supervisor),

who will periodically observe counseling sessions (with the permission of all participants). Counselors will also be expected to attend weekly/bimonthly individual and group meetings to discuss their counseling experiences, and to receive the support that they will need to provide effective counseling. The counseling supervisor will be expected to identify skills-training needs and organize relevant in-service skills training.

A visiting evaluator (intervention director) from the UCSF Intervention Coordinating Center will visit each of the sites twice a year to evaluate the quality and consistency of the study procedures. The following strategies will be used to evaluate the quality of counseling: a) observation of counseling sessions (with permission of the participant) and recording observations on the Counseling Session Evaluation Form; b) periodic audiotaping of counseling sessions (with the permission of the participants) and reviewing the tapes with a checklist to evaluate the counselor's performance in delivering the intervention; c) reviewing Counselor Contact Forms for each session and; d) conducting brief Exit Interviews with some of the clients after receiving VCT to assess their perceptions of the quality and effectiveness of the service.

12.5.2 Data Management

All study PIs will generate a list of criteria to be used for on-site data management quality control and monitoring. PIs will evaluate the successful achievement of defined criteria during site visits and review them with on-site data managers. On-site data managers are responsible for continual monitoring of all data assistants at each study site. Additionally, on-site data managers will be in regular contact with the data coordinator for additional data management monitoring and review.

12.5.3 Documentation

Site staff will receive training in “good clinical practice” (GCP) with regard to the conduct and documentation of all study procedures. Regular monitoring of study documentation will be performed at study sites to ensure adherence to the principles of GCP and the proper recording, reporting, and storage of all study documentation. The study team has developed and approved a GCP plan and GCP monitoring tools (Chart Review Tool and Regulatory File Review Tool). Regulatory staff at the Thailand and Zimbabwe sites will serve as GCP monitors for these sites, while a representative from UCLA's Johannesburg office will serve as the GCP monitor for the Soweto, Tanzania, and Vulindlela sites. GCP monitoring will initially be conducted quarterly; monitoring will move to a semiannual schedule once it is clear no major problems exist. A draft GCP report will be provided by the GCP monitor to the site PI. The PI will have an opportunity to respond, and a final GCP report will then be filed by the monitor (both with the site PI and with the UCLA Coordinating Center).

12.6 Protocol Compliance

This study will be conducted in full compliance with the protocol. The protocol will not be amended without prior approval by the Steering Committee, and receipt of written notice of approval from the UCLA Coordinating Center. Protocol amendments requiring IRB approval must be submitted to relevant IRBs by the study sites' Principal Investigators, and approval obtained prior to implementing the amendment. Approval from the Steering Committee, and written notice of approval from the UCLA Coordinating Center, must be obtained for any additional data or specimen collection in conjunction with this protocol. Requests to implement additional research protocols should be submitted in writing to the UCLA Coordinating Center, who will forward these requests to the Steering Committee.

12.7 Minimizing Risks to Staff

With regard to physical safety, project staff will be escorted by security personnel at all times at the sites where such precautions are necessary. Security is already available at existing clinic sites. A locally hired driver, who will be familiar with safety conditions in the area, will accompany project staff deployed in the community with the mobile caravans. The site Project Director will notify local police of the schedule of the mobile unit and request frequent visits. Local police, CAB members, and merchants will be consulted about safety concerns and their local knowledge will inform decisions about where staff members are deployed. All teams will have access to mobile phones to facilitate communication and to enable them to call for assistance should the need arise. Field staff travel as a group and are trained to respond to threats of violence.

All staff members obtaining and handling blood samples for the study will have received training in proper procedures to minimize risks associated with occupational exposure to blood-borne pathogens. All staff will follow standard safety procedures and will have appropriate supplies available to minimize such risks. Protocols will be in place to provide postexposure prophylaxis (PEP) for any study-related occupational exposures to HIV.

Counselors often have a high risk of emotional burnout. Thus, project staff members, particularly HIV counselors, will have several layers of support. All counseling staff will have access to counseling supervisors for referral in the event of any difficulties. Counseling staff from both arms of the study will be regularly debriefed by a mental health professional, such as a psychologist, who will allow counselors to discuss the stressful and difficult aspects of their work. The psychologist/mentor will also provide continuing, in-service refresher training, allowing counselors to continually update and upgrade their skills.

12.8 Investigator Records

All Project Accept primary source documents will be maintained in a secure location for a period of five years after documents are considered complete and utilized. Primary source documents will be stored both at field office locations as well as the central site offices depending on the type of document and the stage

of data collection. Primary source documents will be made available to authorized personnel upon request.

12.9 Policy on Substudies

Project Accept actively supports the implementation of substudies designed by study sites and/or affiliated investigators, including students.

The Steering Committee will serve as the review committee for evaluating proposed substudies. In addition to evaluating the relevance and scientific rigor of proposed substudies, the Steering Committee must verify that proposed substudies would not have the potential to contaminate main study outcomes or create an undue burden on participants, staff, and/or budgets.

Investigators will submit a brief Substudy Concept Sheet to the Steering Committee using a standard form describing the design and operation of the substudy they are proposing. In general, the criteria to be used in evaluating such proposals will be:

- Importance or significance
- Lack of interference with the answering of main study questions
- Lack of significant participant, staff, or financial burden

12.10 Policy on Data Sharing

12.10.1 Intra-Study Data Sharing

The Data Management Coordinating Center will oversee the intra-study data sharing process, with input from the Data Management Subcommittee.

All Principal Investigators (both U.S. and host country) will be given access to the cleaned data sets. Project data sets will be housed on the Project Accept Web site and/or the file transfer protocol site created for the study, and all data sets will be password protected. Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

12.10.2 Public Data Sharing

Project Accept adheres to the principle that full public access to the raw data should be granted in a timely manner once the study has been completed and major papers have been disseminated. A public area on the Project Accept Web site will be used to facilitate distribution of the data to the public. Data sets will be made available to the public in several different statistical software platforms to facilitate ease of use.

12.11 Dissemination of Study Results

Timely and rigorous analysis and dissemination of study data is a major responsibility the project has to the study participants and the research field. Project Accept recognizes that there are many important means of dissemination of study results, including publications, presentations at meetings, and in-country dissemination activities.

The Steering Committee will serve as the committee on manuscript review and publications, with the goal of ensuring that all manuscripts, publications, and other products generated from the study accurately represent its design, implementation, and analysis. This will provide all PIs an opportunity to review all papers published from the project. Both manuscripts and abstracts will require review by the Steering Committee prior to submission to the journal/conference.

The major cross-country analysis paper will be published under the authorship of “The Project Accept Study Group”, with proper recognition given to appropriate study group members at all levels. Other study group members will be given the opportunity to become involved in proposed analyses and dissemination activities, with the Data Management Coordinating Center overseeing the process. Host-country study group members will be actively supported in analysis and dissemination of study results. In addition, junior members of the study group will be given the opportunity to analyze and disseminate data with mentoring by senior members.

The process for proposing analyses/publications will consist of a “round-robin” that will allow all sites an opportunity to participate. Study group members will submit a brief Dissemination Concept Sheet to the Steering Committee using a standard form proposing analyses that they wish to take the lead on. Once the proposal is approved, authors will have 12 months to submit the product (ie, paper, abstract) to the Steering Committee for review (qualitative papers will be allowed 15 months). If no product has been submitted by the end of this time period, the authors forfeit their claim to the proposed analysis, and the analysis will be assigned to new authors.

Authorship of all study manuscripts will reflect standards of scientific paper authorship, including that all authors have made an intellectual contribution to the design, implementation, interpretation, and/or analysis of the study, and have participated in the study and the preparation of the manuscript sufficiently to assume public responsibility for the content of the manuscript. The Steering Committee will resolve any disputes that may evolve with regard to manuscript development.

All publications, presentations, and deliverables resulting from NIMH Project Accept (HPTN 043) will include the following support/acknowledgment statement (may be adapted as required to meet various journal style requirements):

This research was sponsored by the U.S. National Institute of Mental Health as a cooperative agreement, through contracts U01MH066687 (Johns Hopkins University – David Celentano, PI); U01MH066688

(Medical University of South Carolina – Michael Sweat, PI); U01MH066701 (University of California, Los Angeles – Thomas J. Coates, PI); and U01MH066702 (University of California, San Francisco – Stephen F. Morin, PI). In addition, this work was supported as HPTN Protocol 043 through contracts U01AI068613/UM1AI068613 (HPTN Network Laboratory – Susan Eshleman, PI); U01AI068617/UM1AI068617 (SCHARP – Deborah Donnell, PI); and U01AI068619/UM1AI068619 (HIV Prevention Trials Network – Sten Vermund/Wafaa El-Sadr, PIs) of the Division of AIDS of the U.S. National Institute of Allergy and Infectious Diseases; and by the Office of AIDS Research of the U.S. National Institutes of Health. Views expressed are those of the authors, and not necessarily those of sponsoring agencies.

Acknowledgement statements may also include language to the effect of the following:

We thank the communities that partnered with us in conducting this research, and all study participants for their contributions. We also thank study staff and volunteers at all participating institutions for their work and dedication.

Sources of support will also be disclosed on all statements, press releases, requests for proposals, bid solicitations, and other relevant documents.

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Figure 1: Table of Study and Consent Procedures

Study Component	No. of Participants in <i>EACH</i> Southern African Site (Soweto, SA; Vulindlela, SA; & Zimbabwe)	No. of Participants in East African Site (Tanzania)	No. of Participants in Thailand Site	Procedures	Timeline	Consent Process
Baseline Behavioral Assessment	300 x 8 communities (n = 2,400)	300 x 10 communities (n = 3,000)	200 x 14 communities (n = 2,800)	Behavioral survey with household probability sample	Prior to randomization of communities	Verbal consent; waiver of written consent requested Information sheet
Ethnographic Cohort	16 x 8 communities (n = 128)	16 x 10 communities (n = 160)	8 x 14 communities (n = 112)	Purposeful sampling; qualitative interviews Cohort; tracking information collected	Baseline 6 months 15 months 36 months	Written informed consent
HIV Voluntary Counseling and Testing (VCT)	<p>We estimate that 16,000 individuals will access mobile VCT in the 4 CBVCT communities (approx. 4,000 per community).</p> <p>We estimate that 4,000 individuals will access standard clinic-based VCT in the 4 SVCT communities (approx. 1,000 per community).</p> <p>We estimate that $\geq 4,000$ individuals will access standard clinic-based VCT in the 4 CBVCT communities ($\geq 1,000$ per community).</p>	<p>We estimate that 20,000 individuals will access mobile VCT in the 5 CBVCT communities (approx. 4,000 per community).</p> <p>We estimate that 5,000 individuals will access standard clinic-based VCT in the 5 SVCT communities (approx. 1,000 per community).</p> <p>We estimate that $\geq 5,000$ individuals will access standard clinic-based VCT in the 5 CBVCT communities ($\geq 1,000$ per community).</p>	<p>We estimate that 24,500 individuals will access mobile VCT in the 7 CBVCT communities (approx. 3,500 per community).</p> <p>We estimate that 9,800 individuals will access standard clinic-based VCT in the 7 SVCT communities (approx. 1,400 per community).</p> <p>We estimate that $\geq 9,800$ individuals will access standard clinic-based VCT in the 7 CBVCT communities ($\geq 1,400$ per community).</p>	<p>Voluntary parallel rapid HIV testing and counseling either in clinics (SVCT) or through mobile outreach units (CBVCT).</p> <p>Standard clinic-based VCT will be offered in both SVCT and CBVCT communities, while community-based VCT will only be offered in the CBVCT communities.</p>	36 months, beginning after community randomization	<p>Verbal consent; waiver of written informed consent requested.</p> <p>Information sheet</p> <p>(South Africa requires written release for HIV testing)</p>

Post-Test Support	We estimate that 800 individuals will follow through on referral to post-test support in the 4 CBVCT communities (approx. 200 per community).	We estimate that 1,000 individuals will follow through on referral to post-test support in the 5 CBVCT communities (approx. 200 per community).	We estimate that 7,350 individuals will follow through on referral to post-test support in the 7 CBVCT communities (approx. 1,050 per community).	Voluntary participation in post-test support activities, including psychosocial support groups	36 months beginning in year 2 after community randomization	Verbal consent; waiver of written informed consent requested. Information sheet
Post-Intervention Biological Assessment	1,430 x 8 communities (n = 11,440) in Zimbabwe and Vulindlela; 1,430 x 2 communities + 1,750 x 6 communities in Soweto (n = 13,360)	900 x 10 communities (n = 9,000)	500 x 14 communities (n = 7,000)	HIV testing to detect recent infection; household probability sample	Post intervention	Written informed consent
Post-Intervention Behavioral Assessment	300 x 8 communities (n = 2,400)	300 x 10 communities (n = 3,000)	200 x 14 communities (n = 2,800)	Behavioral survey with household probability sample	Post intervention	Verbal informed consent

Figure 2: Organizational Structure at Each Study Site*

*Adjustments in staffing details may be made at sites, as necessary.

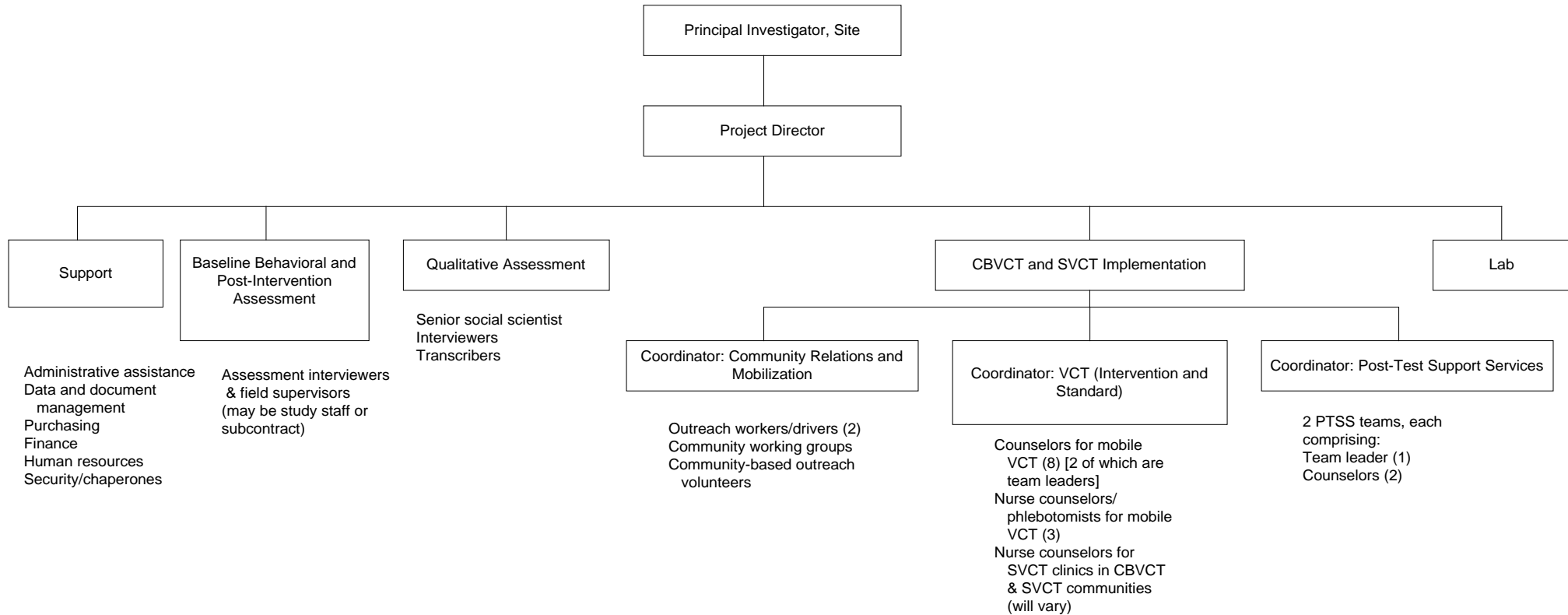


Figure 3: Study Timeline*

Activity	Years 1 – 2 (2003 – 2005)				Years 3 – 4 (2005 – 2007)				Years 5 – 6 (2007 – 2009)				Years 6 – 8 (2009 – 2011)			
	Yr 1 Q 1/2	Yr 1 Q 3/4	Yr 2 Q 1/2	Yr 2 Q 3/4	Yr 3 Q 1/2	Yr 3 Q 3/4	Yr 4 Q 1/2	Yr 4 Q 3/4	Yr 5 Q 1/2	Yr 5 Q 3/4	Yr 6 Q 1/2	Yr 6 Q 3/4	Yr 7 Q 1/2	Yr 7 Q 3/4	Yr 8 Q 1/2	Yr 8 Q 3/4
Planning & Consultation	■	■	■	■												
Instrument Development		■	■	■												
Community Preparedness			■	■												
SOP Manual Development	■	■	■	■												
Staff Training			■	■	■	■	■	■	■	■	■	■	■	■	■	■
Qualitative Assessments			■	■	■	■	■	■	■	■	■	■				
Baseline Behav. Assessment			■	■	■											
Intervention Pilot Testing			■	■	■	■	■	■	■	■	■	■				
Intervention Implementation					■	■	■	■	■	■	■	■				
Pilot of Post-Interv. Asses.											■	■				
Post-Intervention Assessments**													■	■	■	■
Data Cleaning & Analysis			■	■	■	■	■	■	■	■	■	■	■	■	■	■
Study Completion & Closeout															■	■

* Timeline reflects date ranges for study as a whole; timelines at each study sites may vary somewhat.

** Behavioral assessment + biological assessment (determination of communitywide HIV incidence)

Appendix: Statistical Methods

Power calculation

The power calculation is based on the following statistical model: in the i -th community pair, let $\log \lambda_i^T = \mu_0 + \mu_i + \alpha_i + \theta$ and $\log \lambda_i^C = \mu_0 + \mu_i - \alpha_i$, where λ_i^X are incidence rates in the communities ($X = T$ for CBVCT, $X = C$ for SVCT), μ_0 is a fixed overall mean, $\mu_i \sim N(0, \sigma_\mu^2)$ is a random community-pair effect, $\alpha_i \sim N(0, \sigma_\alpha^2)$ is a random deviation of the community log incidence rate from the pair-specific mean $\mu_0 + \mu_i$ (independent of μ_i), and θ is the intervention effect. Given the community and pair effects α_i and μ_i , the number N_i^X of recent infections occurring in a community during a follow-up period of duration τ is distributed as $\text{Po}(\tau n_i^X \lambda_i^X)$, where n_i^X is the number of initially HIV-negative people in the community sample (for $X = C, T$). Denote $r_i^X = N_i^X / (\tau n_i^X)$ the estimated incidence rate in a community. The intervention effect in the i -th pair can be estimated by $\hat{\theta}_i = \log r_i^T - \log r_i^C$.

Conditionally on μ_i and α_i , the distribution of $\log r_i^X$ is approximately $N(\log \lambda_i^X, (\tau n_i^X \lambda_i^X)^{-1})$. Hence, $\hat{\theta}_i$ has unconditional mean $\approx \theta$ and approximate variance

$$\text{var } \hat{\theta}_i \doteq e^{(\sigma_\alpha^2 + \sigma_\mu^2)/2} \frac{1/n_i^T + e^\theta/n_i^C}{\tau e^{\mu_0 + \theta}} + 4\sigma_\alpha^2.$$

When n community pairs are randomized, the estimates $\hat{\theta}_1, \dots, \hat{\theta}_n$ obtained from the n pairs are independent and have the mean and variance specified above. Suppose that n_i^X is the same in every community. Then $\text{var } \hat{\theta}_i$ is the same for all i (denote it σ_E^2). The overall intervention effect estimate is $\hat{\theta} = n^{-1} \sum_{i=1}^n \hat{\theta}_i$ and the distribution of $\sqrt{n}(\hat{\theta} - \theta)$ is approximately $N(0, \sigma_E^2)$. Hence, the sample size needed to achieve the power $1 - \beta$ with a two-sided α -level test of $\theta = 0$ against $\theta = \theta_0$ is given by

$$n = (z_{1-\alpha/2} + z_{1-\beta})^2 \frac{\sigma_E^2}{\theta_0^2} + 2. \quad (1)$$

The sample size is increased by 2 community pairs to adjust for the loss of degrees of freedom due to the estimated variance.

To take into account the varying community sizes at different sites, we propose a stratified approach. Index sites by $k = 1, \dots, K$ and denote $\hat{\theta}_{ki}$ the intervention effect estimate calculated from community pair i ($i = 1, \dots, n_k$) at site k . Let $\hat{\theta}_k = n_k^{-1} \sum_{i=1}^{n_k} \hat{\theta}_{ki}$ be the intervention effect estimator for site k . It follows that $\sqrt{n_k}(\hat{\theta}_k - \theta_0) \sim N(0, \sigma_k^2)$. We propose to estimate the overall intervention effect by a weighted average of the site-specific estimates $\hat{\theta} = (\sum_{k=1}^K w_k)^{-1} \sum_{k=1}^K w_k \hat{\theta}_k$. The most efficient estimator of this form uses weights $w_k = \sigma_k^{-2}$. Its asymptotic variance is $(\sum_{k=1}^K \sigma_k^{-2})^{-1}$. In practice, σ_k^2 have to be estimated from the data. The number of pairs at site k is determined as one fifth of the sample size (as given by Eq. (1)) needed if the trial was conducted entirely at the site. The stratified estimator is drawing one fifth of the total information from each of the sites.

For the sample size calculations reported in the protocol, we assumed that $\exp(\mu_0) = 0.03$, $\sigma_\mu^2 = 0$, $\theta_0 = \log 0.65$, n_i^X was equal to the number of HIV- subjects sampled from the community, and τ was 172 days. Since $E \log \frac{\max(\lambda_{iC}, \lambda_{iT})}{\min(\lambda_{iC}, \lambda_{iT})} = 2\sqrt{2\sigma_\alpha^2/\pi}$, the random effect variance σ_α^2 can be approximated as $\sigma_\alpha^2 \approx \pi(\log \psi)^2/8$ where $\psi \geq 1$ is the expected ratio of the larger and smaller of the two community rates. We took $\psi = 1.45$. The coefficient of variation of baseline incidence rates within the community pair can be calculated as $c \approx \sqrt{2}(\psi - 1)/(\psi + 1)$.

Estimating the number of recent infections

We propose to use a multivariate set of markers W observed on all HIV+ cases to estimate the number of infections having occurred within the time window τ prior to the assessment. To do this, we need a set of validation studies (currently ongoing) consisting in observing W on external cohorts of treatment-naive subjects with approximately known times since infection T . The external cohorts must include all possible times since infection. These studies will provide information on the joint distribution of T and W (perhaps after transformation) in the validation cohorts. The joint density can be decomposed as $f^V(w, t) = f^V(w | t)f^V(t)$ (V refers to the validation population). The marginal distribution of T is population-specific; however, the conditional distribution $f(w | t)$ can be assumed independent of the population (perhaps conditionally on some observed characteristics such as

age, gender, clade). We will estimate $f(w | t)$ by fitting a multivariate normal mixture to the joint distribution of W and T using model-based cluster analysis and calculating the conditional multivariate normal distribution of w given T .

In the community in which we want to estimate the number of recent cases, we will obtain a sample from the marginal distribution of W , which can be written as

$$f^C(w) = \int_0^\infty f^C(t)f(w | t) dt,$$

where C refers to the community. The density $f(w | t)$ is assumed to be the same as in the validation population (where it has been estimated). We are interested in estimating $P[T \leq \tau] = \int_0^\tau f^C(t) dt$. Assuming that $f(w | t)$ does not vary much for t in $(0, \tau]$ and for t in (τ, ∞) , we can simplify the integral equation into

$$f^C(w) = \alpha f(w | T \leq \tau) + (1 - \alpha)f(w | T > \tau)$$

where $\alpha = P[T \leq \tau]$ is the parameter of interest. Given observations from $f^C(w)$, this is a simple mixture analysis problem, which can be solved by the EM-algorithm of MCMC methods to estimate α and get a confidence interval for it. The number of recent infections in the community is estimated by $\hat{\alpha}N^+$ where N^+ is the number of HIV+ cases.

With this approach, the time window τ can be set almost arbitrarily. Given the three-year duration of the intervention, we can set it as wide as two years. This will reduce the variance of intervention effect estimates up to four times. On the other hand, the number N_i^X of recent infections is subject to additional variability of unknown size, which was not acknowledged in the power calculation. The overall effect on the trial power cannot be evaluated until the validation data are collected and analyzed. Nevertheless, the benefit from extending the time window is so huge that it is likely to overcome the uncertainty in the number of recent infections.