Methodological overview of a five-country community-level HIV/sexually transmitted disease prevention trial

NIMH Collaborative HIV/STD Prevention Trial Group*

Objective: To provide an overview of the National Institute of Mental Health (NIMH) Collaborative HIV/STD Prevention Trial taking place in five populations at risk of HIV and sexually transmitted diseases in China, India, Peru, Russia, and Zimbabwe, including the rationale, study management, methods, and proposed data analyses.

Design: The Trial will scientifically evaluate the effectiveness of the community popular opinion leader (C-POL) community-level HIV prevention intervention that was adapted for use in the various cultures within the resource limitations faced by service providers in world regions threatened by high rates of HIV infection.

Methods: The study phases consist of an ethnographic study, pilot studies, an epidemiological study, and a community-randomized trial. The Trial uses the C-POL intervention, which researchers selected on the basis of research that shows the intervention's success in populations vulnerable to HIV risk behavior in the United States, and has the potential to be applied in a variety of international settings.

Results: Trial results will be tabulated by and across country by randomization assignment. Results will include a careful review of data to substantiate original assumptions used in the study design. Data collection will not conclude until August 2007.

Conclusion: Although data collection is incomplete, researchers have learned lessons throughout the development of the study. These include the importance of preliminary epidemiological studies; the close monitoring of biological testing, follow-up rates and process measures at international sites; the tailoring of assessments and interventions to various cultures; regular communication; and a review of the timeline to accommodate Institutional Review Board clearances.

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Introduction

The National Institute of Mental Health (NIMH) Collaborative HIV/STD Prevention Trial is the first multicountry randomized trial of a community-level HIV prevention intervention, and its scope spans four continents. The sites and populations selected for study within the countries represented in the Trial are among those in the world most imminently threatened by HIV infection [1]. The study is powered at a site level to detect change in either HIV/sexually transmitted disease (STD) risk behavior or disease incidence; it is powered at an overall trial level to detect change in both risk behavior and disease incidence. If successful, the Trial will validate an intervention urgently needed to reduce risk behavior in vulnerable high-risk populations in resource-poor countries, and governmental agencies and non-governmental organizations throughout the world can confidently add the intervention to their arsenal of weapons addressing the epidemic.

This paper provides an overview of the Trial, including the rationale, study management, methods, and proposed data analyses.

Background and significance

The HIV epidemic is a global catastrophe that had resulted in over 40 million active infections at the time the study was initiatied [2]. At that time, more than 96% of the world's infections were outside of north America, chiefly

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in developing countries and world regions undergoing difficult social transitions. Therefore, the primary prevention of HIV disease was and still is one of the world's most critical public health imperatives. Consequently, researchers urgently need to develop and scientifically evaluate the effectiveness of community-level interventions that target the populations most vulnerable to HIV, lend themselves to cross-cultural adaptation, and are practical within the resource limitations faced by service providers in world regions facing significant AIDS epidemics.

Community-focused behavioral HIV prevention interventions seek to reduce the prevalence and frequency of high-risk behaviors at a population level by reaching large numbers of vulnerable people with effective, culturally tailored, and theory-based HIV risk-reduction messages. Such programmes encourage behavior change among individual members of the risky population, and create and strengthen social norms to provide sustained peer support for making and maintaining these changes.

In research spanning more than 30 years, Rogers [3] and colleagues examined how technological and behavioral innovations became adopted, accepted, and normative within populations. This research has shown that a subset of population members, called community popular opinion leaders (C-POLs) for the Trial, often originates these innovations. They are the trusted trendsetters whose actions, attitudes, and views influence those of other population members, and they, therefore, are models who others naturally observe and emulate. The theory put forward by Rogers [3] considers opinion leaders to be effective innovators of new behavioral trends, because others like them, they are popular, and they can influence the social norm perceptions of others in the community. Kelly and colleagues [4,5], St Lawrence *et al.* [6], Kelly *et al.* [7] and Sikkema *et al.* [8] have reported several successful studies adapting the popular opinion leader intervention approach to reduce HIV risk behavior among vulnerable US populations.

Researchers selected the C-POL intervention model for evaluation in the Trial for several reasons. The first was the wide-scale potential applicability of this model across multiple countries, cultures, and populations. Second, this model addressed the urgent need to evaluate the effectiveness of community-level HIV prevention interventions that are feasible and cost-effective, and that can be implemented by governments (e.g. ministries of health, local health departments), non-governmental organizations, and others with limited resources.

One data coordinating center (DCC; RTI International) and five cooperating sets of US and international institutions [University of California, Los Angeles (UCLA)–Chinese Centers for Disease Control and Prevention (Chinese CDC), Beijing, China; Johns Hopkins University–Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE), Chennai, India; University of California, San Francisco (UCSF)–UCLA–Cayetano Heredia University, Lima, Peru; the Medical College of Wisconsin–St Petersburg State University, St Petersburg, Russia; and Battelle Memorial Institute–University of Zimbabwe Medical School, Harare, Zimbabwe] were funded to develop a common cross-site protocol, develop common study procedures and supporting materials, engage in site preparation activities, conduct essential ethnographic and epidemiological studies, and implement and evaluate the impact of the common intervention using behavioral and biological outcomes. A data safety and monitoring board (DSMB) appointed by the NIMH has approved the entire protocol and, in many cases, has required substantial additions to the study scope of work and modifications to the protocol (see 'Role of the Data Safety and Monitoring Board in an international trial' [9]). The section on Trial organization describes the organization of the NIMH Collaborative HIV/STD Prevention Trial.

Study phases and objectives

The primary objective of this Trial was to adapt the C-POL intervention to five different cultures, and to test the efficacy of this community-level HIV prevention intervention in a variety of international settings. The Trial consists of a number of phases, each with its own activities and objectives. Specific activities and objectives for the ethnographic study, preparation activities, epidemiological study, and the community-randomized Trial are presented below. A schematic of the design of the Trial appears in Fig. 1.

Throughout the design and implementation of the Trial, investigators paid particular attention to ethical considerations related to conducting a behavioral intervention in the developing world. The translation of ethical principles into daily practice in international research trials is often not a transparent process. Therefore, researchers established a workgroup on protecting human participants during early deliberations. This workgroup included the top US and in-country investigator for each site, the principal investigator of the DCC, the NIMH staff collaborator, and selected consultants with expertise in international ethics deliberations. This group was charged with identifying and implementing optimal procedures for ensuring the ethical and equitable treatment of participants, and with making recommendations to minimize physical, psychological, and social harm to the participants. See 'Ethical issues in the NIMH Collaborative HIV/STD Prevention Trial' [10] for a further discussion of ethical considerations related to the Trial.

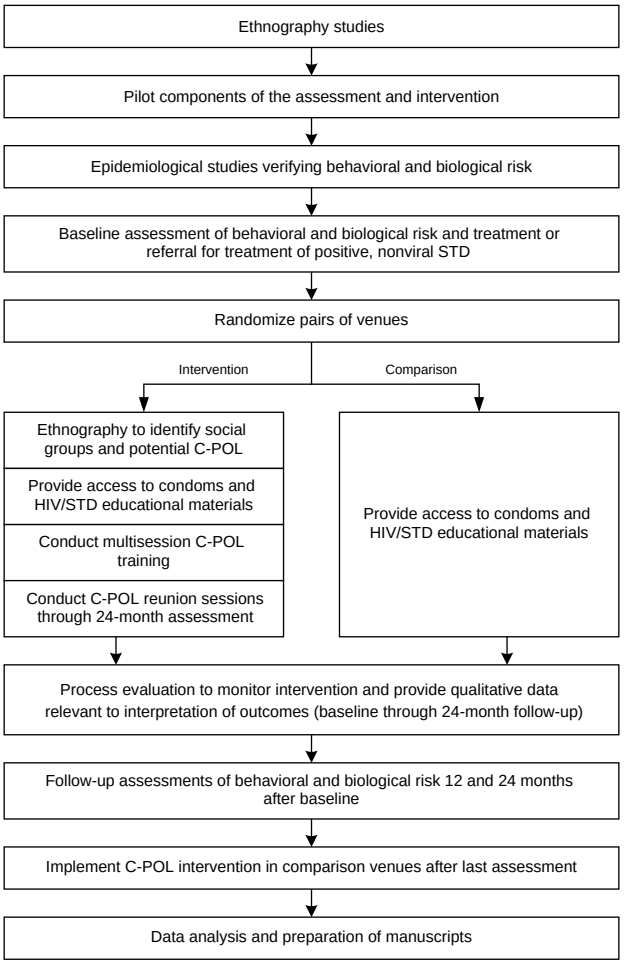

Fig. 1. Design of the NIMH Collaborative HIV/STD Prevention Trial: a two-arm, randomized, community-level efficacy trial. C-POL, community popular opinion leader; STD, sexually transmitted disease.

Ethnographic study

Before the formal ethnography study, an ethnography workgroup developed a common ethnography protocol that was adopted by the steering committee of the Trial and implemented across sites. The protocol: (i) defined the criteria for the selection of venues (individual geographically defined places in the community where members of a high-risk population gathered and could be accessed) for inclusion in the Trial (see 'Selection of populations represented in the NIMH Collaborative HIV/STD Prevention Trial' [11] for venue selection criteria); (ii) outlined standard ethnographic methodologies to be used across sites; (iii) described a list of key topic areas relevant to the objectives of the Trial, to be explored using these methodologies; and (iv) standardized techniques and tools for data collection to ensure quality and enable cross-site comparison. Subsequently, ethnographers conducted detailed interviews and focus groups mostly in the two or more resource venues selected in each site to provide access to target population members without contaminating the venues selected for the Trial. The purpose of these rapid ethnographic assessments was to identify and establish the demographics of risky populations in potential venues in the participating countries, elucidate sexual and other risk factors and nomenclature, develop procedures for identifying C-POLs in the study venues and microvenues (i.e. places within the venues where high-risk individuals socialize), determine the acceptability, content, and format of the C-POL intervention in the venues, and document social norms regarding outcome behaviors. Ethnographic supervisors were centrally trained by the DCC and other study investigators, and returned to their sites to train other local staff. Comprehensive quality control and quality assurance (QC/QA) plans were developed and implemented. QC/QA procedures included random observations of field teams by field supervisors, random checks of transcripts against tapes of interviews and group sessions, random checks of English-translated transcripts against local language transcripts, regular feedback to individual staff members by field supervisors, and regular conference calls between field supervisors and US-based staff. See 'Design and integration of ethnography within an international behavior change HIV/sexually transmitted disease prevention trial' [12] for additional information about the methodology of the ethnographic study.

Data from the ethnographic study informed the selection of venues, microvenues, and biological outcomes for the epidemiological study. Study ethnographers initially identified potential community venues with the following characteristics: (i) population expected to be relatively stable over 2 years; (ii) population believed to engage frequently in high-risk sexual behaviors and to have high STD prevalence; (iii) stakeholders or management supportive of the Trial; (iv) population density sufficient to ensure high exposure to the intervention; and (v) geographical and population separation sufficient to consider each venue independent of the other venues. The ethnographic study also built critical relationships with stakeholders, gatekeepers, key informants, nongovernmental organizations, and other service organizations in the venues and microvenues selected for study. See 'Cross-site ethnographic findings that contributed to the design of the community popular opinion leader intervention in a five-country intervention study' [13] for examples of the findings from the ethnography study and how those findings were used.

Preparatory activities

A number of specific preparatory activities occurred before beginning the epidemiological study and then the randomized trial. First, the steering committee developed and the sites implemented a feasibility study examining the acceptability of data collection using audio computer-assisted self-interviewing, in which a participant uses headphones to listen to interview questions and enters answers into the computer without interviewer assistance.

A subsequent test–retest study compared data collected using audio computer-assisted self-interviewing with data collected using computer-assisted personal interviewing (CAPI), in which an interviewer reads questions from a computer screen and enters the participant's answers into the computer. Although participants were generally not familiar with computer technology, both methods proved feasible in the populations studied. See 'The feasibility of audio computer-assisted self-interviewing in international settings' [14] for a complete description of these studies and their findings.

The sites also pilot tested various components of the assessment and intervention among populations that were similar to those in the venues but that were not going to be studied. Information gathered allowed site staff to tailor study procedures, assessment procedures, questionnaire items, and components of the intervention to the study populations while maintaining fidelity to the Trial protocols.

Supervisors of the assessment, laboratory, and intervention staffs received central training before these activities were initiated. Supervisors returned to the individual sites to train local staff. All staff were certified during site visits by personnel from the DCC.

Epidemiological study

Although each site believed that it had identified venues with sufficient risk, the DSMB required a large-scale epidemiological study in all venues, to ascertain that venue selection and sampling strategies within venues would yield stable populations of high-risk individuals and to provide intraclass correlation coefficients (ICC) for more precise power estimates. Therefore, before the Trial, large-scale epidemiological investigations were conducted in each of the five sites to confirm the prevalence of risky behaviors and STD in the venues identified by the ethnographers and to finalize the assessment and biological protocols, procedures, and questionnaire items. This study consisted of behavioral interviews with and testing biospecimens collected from 7150 individuals across the five international sites (see 'Sexually transmitted disease and HIV prevalence and risk factors in concentrated and generalized HIV epidemic settings' [15] for a description of this study and its findings). When data from two of the sites (India and Peru) demonstrated that the initial sampling strategy did not yield sufficient numbers of high-risk individuals, the DSMB required a second epidemiological study of 1358 individuals in India and 1205 individuals in Peru using a revised sampling methodology focusing on better-defined venues frequented by higher-risk populations. These new venues in India and Peru yielded populations at a much higher risk. The epidemiological studies also piloted the planned QC/QA procedures. This included shipping biological samples from each site to a reference laboratory (Johns Hopkins) to compare STD/HIV outcomes from a sample of participants.

The ethnographic and two epidemiological studies resulted in the selection of the following venues (and microvenues within venues) for the Trial: food markets with individually owned stalls in Fuzhou, China; clusters of wine shops in slums in Chennai, India; gathering points of young, high-risk people in barrios in Lima, Chiclayo, and Trujillo, Peru; trade school dormitories in St Petersburg, Russia; and retail establishments in business centers of growth points in rural Zimbabwe. See 'Selection of populations represented in the NIMH Collaborative HIV/STD Prevention Trial' [11] for a complete discussion of population and venue selection.

Randomized trial

The two-arm, phase III, community-randomized controlled trial involved between 20 and 40 independent community venues in each country where high-risk members of the target population could be accessed. Biological and behavioral baseline data were collected from a cohort of participants recruited in the venues (average number of participants eligible per venue in China, 98; India, 145; Peru, 148; Russia, 92; Zimbabwe, 185). Paired venues within a site were then randomly assigned by the DCC, one venue of each pair to the intervention and the other to the comparison condition. Participants in the cohort who had non-viral STDs on testing at baseline were treated. Although measurements were obtained on individual participants within each venue, the intervention was delivered to the target population in the venue. In comparison venues, access to HIV and STD educational materials and condoms was ensured. In intervention venues, these materials were available, and the C-POL intervention was undertaken. In intervention venues, staff observation, peer nominations, and gatekeeper (a person who controls access to the venue) nominations identified C-POLs from among the population members who frequented the venue. Between 15 and 20% of study population members regularly present in the venues were recruited and trained as C-POLs. Groups of C-POLs attended a series of four or five weekly sessions that provided training on how to communicate effective, theory-based, risk-reduction messages to friends and other acquaintances and guidance on having these conversations with others between sessions. The efforts of the C-POLs were supported with project logos and other 'conversation starting' tools. After their initial training, C-POLs attended reunion (booster) sessions six to nine times per year during the 2 years after the baseline assessment to reinforce and support continued conversation efforts. Both 12 months and 24 months after baseline data collection, behavioral interviews were repeated, and biospecimens for HIV/STD testing were

obtained from members of the cohort originally assessed at baseline. At both timepoints, cohort members were treated if they tested positive for non-viral STD.

Site staff transmitted all data to the DCC on an ongoing basis, and the steering committee monitored Trial progress biweekly. The DCC and the DSMB monitored all biological and behavioral data on an ongoing basis, but site investigators remained blind to study outcomes until the end of the Trial. The DCC was responsible for all data analysis and reports to the DSMB. In addition, the DCC worked with investigators to provide analyses for manuscripts approved by the steering committee as data were released.

Each site developed and implemented detailed strategies for retention and reassessment. QA procedures, implemented within and across sites, monitored the quality and fidelity of the assessments, intervention delivery, and adherence to ethical procedures and informed consent activities. The DCC coordinated the cross-site QA procedures for all assessment, laboratory, and intervention activities on an ongoing basis. Each site demonstrating protocol deviations implemented procedures to remediate processes as necessary.

Specific aspects of the randomized trial are provided in the following sections.

Research questions

The primary aims of the randomized trial are to test the hypotheses that, across all sites (countries), populations in venues that have received the C-POL intervention ($n = 69$ venues) relative to comparison venue populations ($n = 69$ venues) will: (i) have a lower overall observed incidence of STDs [chlamydia, gonorrhea, syphilis, trichomonas (women only), HIV, and herpes simplex virus 2 (HSV-2)] as detected by biological specimens collected at the 12 and 24-month follow-ups; and (ii) have fewer population members who report unprotected sexual acts with non-spousal partners during the 3 months before the 24-month follow-up point, measured as a change from baseline.

The secondary aims of the Trial are: (i) to test the hypothesis, across all sites, that populations in venues receiving the C-POL intervention, relative to comparison venues, will also report fewer unprotected sexual acts with non-spousal partners during the 3 months before the 12-month follow-up assessment; (ii) to test the hypotheses, separately within each country site, that populations in venues receiving the C-POL intervention, relative to comparison venues, will have either a lower overall observed incidence of STD as detected by biological specimens collected at the 12 and 24-month follow-ups, or will have fewer population members reporting unprotected sexual acts with non-spousal partners during the 3 months before the 24-month follow-up point, measured as a change from baseline; and (iii) to test the hypothesis, both within and across sites, that populations in venues receiving the C-POL intervention, relative to comparison venues, will, at 24 months' follow-up, report greater exposure to HIV prevention messages, more STD treatment seeking, lower stigma regarding HIV and STD, and lower substance use associated with sexual behavior.

See 'Challenges and process of selecting outcome measures for the NIMH Collaborative HIV/STD Prevention Trial' [16] for further discussion of the outcomes chosen for the Trial.

Study design

Randomization of venues

Pairs of venues within a site were matched on the basis of site-specific characteristics (e.g. STD prevalence in Russia, city and STD prevalence in Peru, language and time of assessment in Zimbabwe). For each pair of venues, the DCC randomly assigned one venue to the intervention and the other to the comparison condition, immediately after baseline assessments were conducted for those venues.

General considerations for sample size

The data from the epidemiological studies were used to determine the sample size and to estimate power for detecting effects within and across sites using the following primary biological and behavioral endpoints: individuals with any new cases of chlamydia, gonorrhea, syphilis, trichomonas (women only), HIV, or HSV-2 at the 12 or 24-month follow-ups (Y/N), and individuals with unprotected sexual acts with non-spousal partners during the last 3 months before the second follow-up assessment (Y/N) measured as a change from baseline. In computing the sample sizes for each country site, the venue unit of randomization was taken into account, because a component of variation would be attributable to venues. Specific power calculations provided by Murray [17] for group-nested cohort designs were used to compute sample sizes (e.g. number of venues and number of participants per venue) for each site using the epidemiological study data. In addition, data from the epidemiological studies provided information on the degree of migration into and out of the venues that allowed follow-up rates to be estimated and provided information for the matching of venues for randomization.

In particular, the primary biological outcome assumed baseline treatment for any existing cases of chlamydia, gonorrhea, syphilis, and, for women, trichomonas. For sample size calculations, rates of new cases at the 12 and 24-month follow-ups of these four STDs were estimated in the comparison group as those observed on the epidemiological assessments. Furthermore, the percentage of all new cases of HIV or HSV-2 at the 12 or 24-month follow-ups was estimated in the comparison group as the

Table 1. Sample size requirements by country.

Country	Powered on primary endpoint	Participation rate (%)	Follow-up rate (%)	No. of venues	No. of participants approached per venue
China	Biological	95	84	40	124
India	Behavioral	96	90	24	163
Peru	Biological	89	90	20	190
Russia	Behavioral	90	85	24	99
Zimbabwe	Biological	85	86	30	171

slope coefficient from the linear regression of HIV/HSV-2 (Y/N) on age ($\times 2$ years) using epidemiological study data. The ICC within each country for the primary biological outcome was taken as that for the composite of the four infections from the epidemiological data: chlamydia, gonorrhea, syphilis, or trichomonas (women only) without regard for HIV or HSV-2. No relevant incidence data were available on HIV or HSV-2 for inclusion of these items in the ICC estimation.

Cross-site statistical power

The cross-site intervention effect on the primary biological outcome can be detected using a type I error rate (two-sided) of 5%, with 97% power using at least 20 venues per site and 50 participants per venue, if there is a 33% lower STD incidence in the intervention venues versus the comparison venues within each site. This intervention effect translates into a common odds ratio (i.e. odds ratios computed for each site and averaged) of 0.63 using the data from the epidemiological studies to estimate the outcome rates in the comparison venues and 33% less to estimate the outcome rates in the intervention venues. Also, for this cross-site power analysis, the ICC was taken as the average of the ICC within sites from the epidemiological study data.

A cross-site intervention effect on the primary behavioral outcome can be detected using a type I error rate (two-sided) of 5%, with 99% power using at least 20 venues per site and 50 participants per venue, if there is an absolute difference of 10% in the change in high-risk sexual behavior between the intervention and comparison venues within each site. This intervention effect translates into a common odds ratio of 0.65 using the data from the epidemiological studies for India, Peru, and Russia to estimate the outcome rates in the comparison venues and 10 percentage units less to estimate the outcome rates in the intervention venues. Also, for this cross-site power analysis, the ICC was taken as the average of the ICC within these three sites from the epidemiological study data.

Within-site sample sizes

The study was initially designed so that each site would have at least 80% power to detect the relevant effect for either the primary biological or the primary behavioral endpoint (using the specific risk data for each site from the epidemiological studies) and operating with a type I error rate (two-sided) of 5%.

Table 1 summarizes the results of the within-site sample size calculations. These calculations use the epidemiological study data to provide estimates of the ICC, participation rates, and follow-up rates for each site and the proportion having sex in the past 6 months for Peru and China. The calculations assume that 20% of the study participants in the cohort are C-POLs and will be excluded from the primary analysis.

Recruiting, screening, and accessing a cohort in each venue

In each venue, staff met with stakeholders and gatekeepers in the community to gain support for the study and to gain access to the venue or to microvenues (specific areas or stores where members of the population gather) within it. The DCC worked with staff at each site to develop site-specific recruitment procedures based on the size of the population and the source of participants. Sometimes participants were approached as they entered one of the microvenues (e.g. a wine shop in India or a retail store in Zimbabwe) and recruited for the cohort. In other cases, a list was created (e.g. market stall owners and employees in China, dormitory rooms in Russia), and the DCC specified the order in which to approach those on the list for inclusion in the study. An average of between 92 and 185 eligible participants per venue were randomly or purposively selected from the population of all individuals present in the venue using the site-specific sampling protocol established by the DCC.

Eligibility

Generally, participants were eligible if they were between the ages of 18 and 30 years, although age ranges were expanded at some sites based on the STD and HIV epidemiology of the country (e.g. 18–49 years in China). Participants had to live, work, or socialize, as appropriate, in the selected venues or microvenues, and they had to plan to remain in the venue for at least the next year. In all sites, participants were excluded if they could not give informed consent or if they had a permanent disability (e.g. deaf, mental retardation). China excluded participants who reported no sex in the past 6 months and who did not have an STD at baseline. Peru excluded those who reported no sex in the past 6 months at baseline. Russia excluded students who were in their last year of school at the time of recruitment for the Trial. Zimbabwe excluded those who had lived in the venue for less than 2 years and those who lived in the venue for less than 9 months a year.

Informed consent

All sites had Institutional Review Board (IRB)-approved, culturally appropriate, informed consent procedures, including a signed consent form. In some sites, consent information was initially presented through a video. Both assessment participants and C-POLs always met individually with a staff member to review all study procedures, review the benefits and risks of participation, discuss the option to discontinue participation at any time without penalty, and receive methods to contact the investigator and the local IRB if questions about participation in the study arose. Finally, signed informed consent was obtained. Substantial ethnographic research informed the design of consent forms and procedures at the sites. In some sites, the behavioral risk assessment instrument was framed as a general health questionnaire in order to develop rapport with the research participant and reduce stigmatization.

Reimbursement

Study participants received modest reimbursements covering the time and expenses related to study participation. These reimbursements varied from country to country to reflect local economic conditions and the proximity of the assessment site to the venue. For the baseline assessment, reimbursement for time spent (in US dollars) was approximately $3 in China, $4 in India, $6 in Peru, $15 in Russia, and $6 in Zimbabwe. Transportation to the assessment site was generally provided, as was food if the assessment occurred during mealtime. Reimbursements were similar in scope at follow-up.

Baseline interview

The objectives of the assessment activities were to identify, recruit, and train assessment staff; to conduct a baseline assessment to document risk behaviors and HIV/STD prevalence in intervention and comparison venues before the intervention was initiated; to treat or refer positive cases of non-viral STDs; to refer cases of viral STDs on the basis of a site-specific plan; and to conduct outcome assessments 12 and 24 months after the baseline assessment to document the prevalence of risk behaviors and the incidence of HIV/STD in intervention and comparison venues after the intervention was initiated.

The behavioral assessment questionnaire was designed to take approximately 45 min to administer and included up to 300 questions. The following domains were assessed: demographic characteristics; mobility; self-reported sexual risk behavior; opportunities for social interaction; recognition of the project logo; exposure to HIV/STD prevention messages; general health and healthcare seeking behavior; HIV testing; substance use; and stigma. Interviewers administered the assessment using a CAPI program and a standard protocol to minimize variability within and across the five sites, as well as to reduce interviewer bias. Site staff used a decentering approach [18] to translate the assessment to local languages: Mandarin in China, Tamil in India, Spanish in Peru, Russian in Russia, and Shona and Ndebele in Zimbabwe. This approach focused on translation for meaning into language levels that participants could understand, and did not use a literal, word-for-word, translation process. The DCC arranged for backtranslation of the assessments, and discrepancies were resolved through discussions between DCC and site staffs. Staffs at both the DCC and study site tested the CAPI programs in the relevant language before they were finalized.

After completing the interview, participants received HIV pretest counseling following national guidelines and provided blood, urine and, for women, vaginal swab specimens. During this part of the evaluation, participants completed an STD symptoms questionnaire while talking with a health professional. If the responses indicated that STD symptoms were present, researchers provided syndromic treatment for participants with discharge or ulcers immediately after the biospecimens were collected, or these participants were referred to local clinics for treatment (depending on the country). Treatment procedures followed local, World Health Organization [19], or Centers for Disease Control and Prevention guidelines [20], as appropriate. Participants also received HIV/STD education when the biospecimens were collected.

Biospecimens were tested in study laboratories in each country following standardized laboratory protocols. Urine from men and vaginal swabs from women were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* using polymerase chain reaction. HSV-2 testing was performed using enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA). HIV testing was performed using EIA or ELISA and repeated using a different EIA/ELISA. Positives were confirmed using Western blot, except in Zimbabwe where a positive result on both ELISA tests is considered confirmatory and a third ELISA or Western blot test was used only to confirm HIV status in the case of discordant results on the initial two. Syphilis testing was performed by rapid plasma reagin (RPR) and confirmed using the *Treponema pallidum* particle agglutination test. Vaginal swabs were cultured for *Trichomonas vaginalis* using the InPouch TV test.

Once local laboratory results were available, participants were given the opportunity to receive their test results and post-test counseling. If a result was positive and the participant had not been treated or referred for the disease on the basis of symptoms at the time of the assessment, the protocol specified that he or she was to be treated for non-viral STDs or referred for treatment by the study, treated for episodic HSV-2 in China, India and Zimbabwe, and, for positive HIV results, referred to local agencies for HIV counseling and treatment. In Zimbabwe, pregnant women who were HIV positive received vouchers to ease access to treatment near the time of delivery in order to reduce the chance of mother-to-child transmission.

Intervention and community popular opinion leaders

The primary objectives of the intervention activities were to identify, recruit, and train intervention staff; to identify or develop appropriate HIV/STD educational materials for distribution in the intervention and comparison venues at each site; to recruit, train, and deploy C-POLs in the intervention venues; to conduct between six and nine reunion sessions for C-POLs during each of the next 2 years; to assist C-POLs to co-facilitate reunion sessions during the second year of the study in order to enhance sustainability; and to conduct the C-POL intervention in comparison venues after the 24-month outcome assessment was completed.

The presence of certain core elements distinguishes the C-POL intervention from other types of general peer education approaches [21]. The following core elements reflect the theoretical base of the model implemented at the sites: (i) the intervention is directed to an identifiable target population in well-defined community venues where the population's size can be estimated; (ii) techniques are systematically used to identify cadres of individuals, C-POLs, who are popular, well-liked, and trusted by others in their everyday social groups; (iii) over the life of the programme, at least 15% of the target population in the intervention venues are trained as C-POLs; (iv) the programme teaches C-POLs skills for sharing HIV risk-reduction messages with others in everyday conversations; (v) the training programme teaches C-POLs the characteristics of effective behavior-change messages targeting risk-related attitudes, norms, intentions, and self-efficacy, and teaches C-POLs personally to endorse the benefits of safer behavior and to recommend practical steps needed to implement change; (vi) small groups of C-POLs meet weekly in sessions that use instruction, facilitator modeling, and extensive role-play exercises to help C-POLs refine their skills and gain confidence in delivering effective HIV prevention messages; (vii) C-POLs set goals to engage in risk-reduction conversations with friends and acquaintances in the target population between the weekly training sessions; (viii) the conversational outcomes of C-POLs are reviewed, discussed, and reinforced at subsequent training sessions; and (ix) logos, symbols, or other devices are used as 'conversation starters' between C-POL and others.

C-POLs were initially identified by ethnographic and intervention staff observation, through interviews with key informants, and by self-nomination. Participants were recruited as C-POLs by emphasizing, in a culturally appropriate manner, how they were selected and how they could help their communities. C-POLs were informed of their ethical rights, provided voluntary informed consent, and were invited to attend four or five weekly training sessions, depending on site requirements. Reimbursements varied, were based on local economic conditions, and reflected the time involved in training at the local site (items worth the equivalent of US$1.45–$15 per session). C-POLs understood their commitment to provide social messages to social group members in their venues with the aim of preventing the spread of AIDS. Each C-POL training session lasted 90–150 min. Sessions were led by a team of two to three facilitators in a convenient location.

Groups of 10–20 C-POLs attended the four to five weekly training sessions. In the first session, C-POLs were introduced to the programme and were encouraged to think of themselves as an important vanguard in efforts to prevent HIV, STD, and AIDS in their community by talking with others about prevention. The threat of AIDS, national and local epidemiology, risk behaviors, and prevention steps were discussed. In the second session, C-POLs were taught how to correct myths and misconceptions held by friends about the disease, and began to learn the characteristics of effective health communication messages applied to HIV risk reduction. Because risk behavior reduction is a function not only of one's knowledge about AIDS but also of attitudes, beliefs, intentions, skills, and peer norm perceptions, C-POLs were taught to develop and practice communication messages that focus on these determinants. Specific messages used in training were based on findings that emerged from the ethnography with each site's populations. In subsequent sessions, C-POLs continued practising conversations in the group. They also discussed and planned how, when, and where they would initiate conversations with other members of the target population, and they set goals at the end of each session to talk with a specified number of friends and acquaintances. Outcomes of the conversations were discussed and reinforced in the next group meeting, and any problems encountered and their potential solutions were discussed. The objective was for C-POLs to engage in increasing numbers of conversations with others each week.

Reunion sessions were held to build a sense of camaraderie and to enhance the perceptions of C-POLs that they are HIV/STD prevention leaders in order to sustain their delivery of prevention messages. In addition, the reunions provided support, reinforcement, and encouragement for C-POLs to continue in their HIV/STD prevention advocacy roles. See 'The community popular opinion leader HIV prevention programme: conceptual basis and intervention procedures' [22] for additional information about the intervention.

Assessment of outcome in the cohorts

All participants in the baseline cohort were followed, and those located were administered follow-up CAPI and STD symptoms interviews, and were asked to provide biospecimens for STD testing 12 and 24 months after the date when they completed the baseline measures. (India had difficulty maintaining IRB approval and completed its follow-up assessments at 18 and 30 months.) The

CAPI questionnaire measured the same domains as the baseline assessment, although some questions were modified to reflect the 12 months elapsed since the last study assessment. The plan for treatment of those with positive STD results was the same as at baseline. All sites used procedures developed in conjunction with the DCC that were designed to minimize attrition and the loss of participants at follow-up.

The Trial was powered assuming a greater than 80% follow-up rate across the 2 years. Each site aimed for a 90% follow-up rate. Staff would make at least eight attempts on different days and at different times of the day to locate each cohort member who was eligible for follow-up. In addition, once follow-up for a venue began, staff used up to 6 months to locate cohort members from that venue. After 6 months, cohort members who had not been located were considered lost to follow-up for that assessment round. In each site, participants who left the study area could be followed by telephone if they could be located, even if biospecimens were then not available. To ensure satisfactory retention rates, staff at all sites were trained to address participants' concerns, obtain multiple types of locating information, and use reimbursements to compensate for participant's time as appropriate.

Implementation progress

Figure 2 presents the number of participants who completed the baseline interview in each of the sites, indicates the subsequent randomization, and shows that the 12 and 24-month follow-up assessments are in process. Since the trial is in process and volunteers continue to be recruited and trained as C-POLs, we cannot, at this time, report the numbers of C-POLs successfully recruited and trained in each country.

Quality control and quality assurance procedures

QC for this Trial focused on developing procedures that ensured that data were collected in a standardized way, comparable measurements were valid, data were maintained in a secure and confidential manner, and the intervention was implemented in a similar fashion across sites. QA procedures addressed adherence to the study protocol and ensured that QC procedures were being implemented consistently across all participating sites, given the necessary country-specific tailoring.

The components of the QC/QA model adopted for this Trial were divided into three major categories: (i) manuals for the Trial (overall operation, assessment, biological specimen collection, intervention, data management system, laboratory management system, and laboratory procedures); (ii) personnel (including selection criteria, job descriptions, training, and certification procedures); and (iii) ongoing monitoring of adherence to study procedures including ethnographic activities, assessments, intervention training, and collection and analysis of biological specimens. Each site sent samples selected by the DCC to the reference laboratory at Johns Hopkins for QA. Specific activities for various areas appear below.

Documentation

Documentation of standard study procedures is one of the most important aspects of any trial. Documentation for this trial began with careful specification of the overall trial design and procedures in the study protocol. Once the protocol was fully specified, investigators began developing and pilot testing components of study

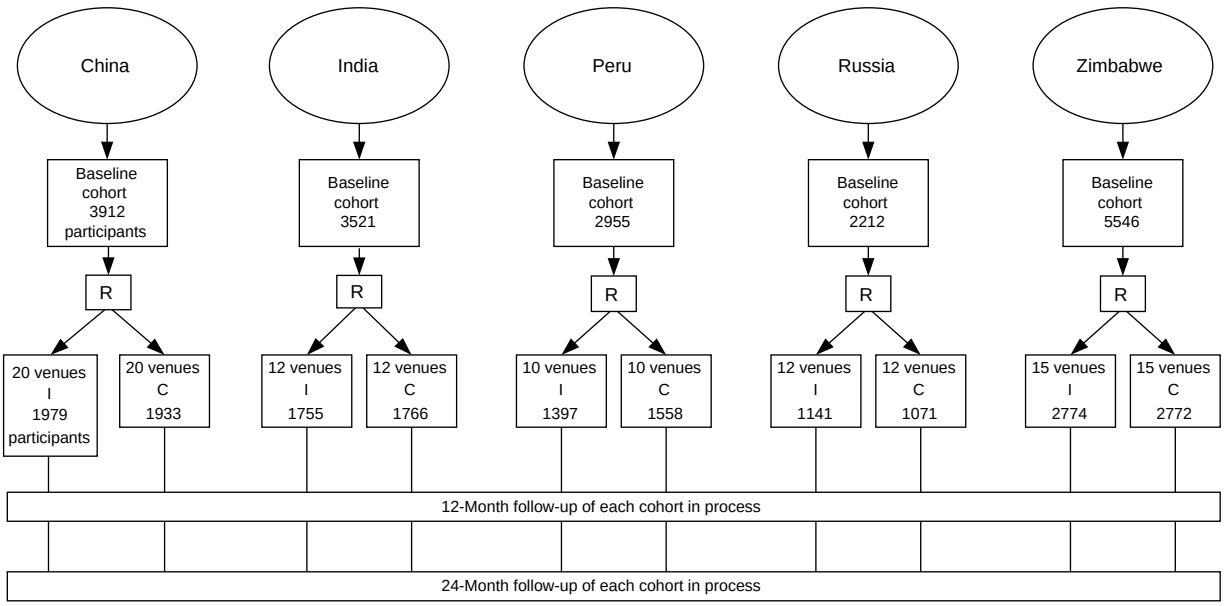

Fig. 2. Assessment implementation. C, comparison; I, intervention; R, randomization within pairs of venues.

instruments, study procedures, training manuals, and other manuals documenting various study activities. Any instrument, procedure, or activity that needed to be implemented in the same manner across all sites was documented. When necessary, these documents were translated into the languages of the local countries, and elements were adjusted within protocol guidelines to reflect the content and procedural changes required to reflect the cultures and regulations of the five countries participating in the Trial.

In addition to the CAPI system that captured assessment data from individual participants, the DCC developed three intricate systems for monitoring the study: a data management system; a laboratory management system; and a process evaluation data collection and management system. The computerized data management system was designed to collect and monitor data from the assessment activities. This system monitored participant recruitment, assessment, and follow-up, including participant contacts and the accumulation of assessment and laboratory data other than the interview data collected via CAPI. The computerized laboratory management system monitored the location, testing, and results of biological samples obtained during the interviews. The process evaluation system collected and managed the data collected as part of the process evaluation. Each of these systems could easily produce reports that aided project staff in monitoring activities recorded in the system. Extensive manuals documented the purpose and use of each of these systems.

Study personnel

Selection criteria, job descriptions, and training procedures for study personnel were standardized across the sites. Selection criteria for each of the major study roles ensured that personnel with similar levels of training, experience, and ability were performing similar study functions across sites. The specific activities required in certain roles (e.g. assessment team members) could, however, be parsed among individuals in various ways. For example, in some sites, the same individual conducted the assessment interview, administered an STD symptoms questionnaire, and collected biological specimens, whereas in other sites, these activities were split among different team members.

Standardized job descriptions ensured that study personnel (e.g. project coordinators, assessors, facilitators, laboratory personnel) engaged in similar activities in a consistent manner across sites, except for local modifications approved by the steering committee. These formal job descriptions also ensured that certain functions could not be combined or overlap with other functions. For example, the duties of facilitators who trained the C-POLs could not be combined with those of the assessors, for this overlap could potentially bias the assessment of the effect of the intervention.

Central training for the local trainers of ethnographers, assessors, biospecimen collectors, laboratory personnel, and intervention facilitators also helped ensure the standardization of Trial procedures. Because of the travel expense required to bring staff from five countries to the United States and the differences in language and customs among those sites, a train-the-trainers model was used. Under this model, three or four senior staff in each area came to a central training session in the United States. The initial central training session also enabled the translation and tailoring of the training manuals, so that site staff implemented the principles and study procedures in a standard manner across all the sites. The trained supervisors then returned home, completed translating the training manual into the local language (or languages), and trained in-country staff. Bringing together senior personnel from the five sites had the added benefit of reinforcing the fact that they were key staff in an international, multisite trial and that common implementation of the elements of the protocol was critical to the success of the study.

Trainees who demonstrated competence were certified on the basis of a standard set of criteria for each function across the sites. Personnel who did not achieve certification were barred from undertaking the activity (e.g. collecting ethnographic data, administering the behavioral assessment, collecting or analysing biospecimens, training C-POLs) without additional training. Certification provided a strong motivation to meet required standards. This process also facilitated the rapid training of new staff.

Because the data and laboratory management systems were tailored to reflect nuances related to recruiting and maintaining the participants at each site and the correct installation of the systems was critical to their use, training in these systems was conducted at the sites during data management system site visits rather than centrally.

Quality assurance for assessments

Quality for all assessments was reinforced through five types of onsite and central monitoring procedures: (i) monitoring the behavioral risk assessment version and administration; (ii) monitoring biospecimen collection, storage, and analysis; (iii) monitoring data and laboratory management systems and operating procedures; (iv) monitoring IRB knowledge, procedures, and documentation; and (v) monitoring local laboratories. Annual visits to each site were conducted by QC/QA specialists from the DCC and the biological reference laboratory.

Quality assurance for biospecimen testing

The QA process for biospecimen testing was extensive. Senior laboratory staff from each country were trained at the reference laboratory to follow the protocols that specified standard biospecimen collection, storage, and

analysis procedures. Panels of approximately 200 samples were sent to site laboratories for analysis by appropriate assay, and annual site visits were conducted to review laboratory procedures. A 20% sample of specimens collected in each country and selected by the DCC, including all positive samples (if less than 10%, or a random sample of positives up to 10%) and a random sample of negatives, were shipped by the five site laboratories to the reference laboratory for retesting during the first year each laboratory operated. Once laboratories were certified through that procedure, the sampling rate for HIV, HSV-2, and syphilis dropped to 5%, whereas the rate for chlamydia and gonorrhea remained at 20%. All discordant results were initially checked for data entry or interpretation errors, and study data were corrected as needed. Remaining samples with discordant results were retested by the sites and reference laboratory, but study data were not changed on the basis of these results. Finally, panels (HIV, chlamydia and gonorrhea, HSV-2, and syphilis) assembled by the College of American Pathologists, were sent to the site laboratories several times per year for analysis.

Quality assurance for the intervention

The two sources of ongoing QA for the intervention were a process evaluation and central QA by a consultant experienced in the C-POL intervention model. These efforts are briefly described below.

The process evaluation was designed to provide feedback for intervention delivery, and document the reasons for intervention effects. The five specific objectives of the summative process evaluation are to assess: (i) the number and content of messages delivered by C-POLs; (ii) adherence to the training protocol; (iii) the spread of messages to the target population; (iv) community exposure to other sources of information related to outcomes; and (v) problems and challenges in the field related to the intervention/message or characteristics of a specific subpopulation. The instruments developed to collect these data include: (i) a C-POL recruitment form that documents the number of people approached to be C-POLs, how they were identified, their basic demographics, and whether they agreed to participate; (ii) an attendance form that monitors which of the C-POLs attend training and reunion sessions, the number of conversations reported when homework is reviewed, and the number of those conversations that occurred in the venue; (iii) a C-POL demographic assessment that gathers basic demographic information about each C-POL; (iv) a generic C-POL session observation checklist, completed by a session observer, which is designed to assess fidelity to the training protocol, to improve the training sessions and to document what was covered during training; (v) a form to record facilitator notes documenting events during intervention delivery; (vi) a monthly log that records numbers of C-POL logos posted and worn in each venue and the number of other HIV/STD health education messages posted and worn in each venue; (vii) a form that documents other HIV/STD prevention messages and activities in a specific venue; (viii) a form that monitors other HIV/STD prevention messages and activities across the site; and (ix) process evaluation questions on the behavioral assessment that assess exposure to the project logo, participation in conversations on topics targeted by the intervention, and stigma related to HIV.

On an annual basis, the DCC consultant with expertise in implementation of the C-POL intervention visited each site, observed training and reunion sessions, interviewed each facilitator regarding the intervention protocol, and interviewed a selection of C-POLs in an intervention community when culturally appropriate. The monitor completed the ratings described in the site visit protocol and discussed areas in which improvement was possible with site supervisors and staff.

Data analysis plans

Data collection will not conclude until August of 2007. Therefore, plans for analysis are presented below.

Analyses of baseline data

Baseline results pertaining to primary and secondary outcome measures will be tabulated by and across venues by country, and compared by intervention assignment. In particular this will include: individuals with any case of chlamydia, gonorrhea, syphilis, trichomonas (women only), HIV, or HSV-2 (Y/N); individuals with any unprotected sexual act(s) with non-spousal partners during the past 3 months (Y/N); individuals with any case of chlamydia, gonorrhea, syphilis, or trichomonas (women only), (Y/N); the proportion of sexual acts with non-spousal partners by an individual during the past 3 months that were unprotected (with abstinence coded 0%); the number of unprotected sexual acts with non-spousal partners by an individual during the past 3 months; and the number of partners during the past 3 months. The prevalences of individual STD and HIV will also be analysed.

A careful study will be made of data to substantiate original assumptions used in the design. In particular, the following will be tabulated: participation rates for the assessment and collection of biospecimens by and across venues by country; the frequency of missing data for critical assessment questions by and across venues by country; the length of time until treatment for positive test results on chlamydia, gonorrhea, syphilis, and trichomonas by and across venues by country; the length of time between baseline assessment and implementation of study intervention by and across intervention venues by country; ICC estimates within country; and the HIV/HSV-2 rate of change with age. Finally, QC results for the laboratory data will be summarized.

Analysis of primary endpoints at follow-up

An intent-to-treat analytical approach will be used, in that any venue assigned to the intervention will be considered treated, whether or not the C-POLs were active in that venue. The intervention effect for the biological endpoint will be estimated as the difference in incidence rates between intervention and comparison venues at the 12 and 24-month follow-ups. Cases (defined by a positive test result) of chlamydia, gonorrhea, syphilis, and trichomonas (women only) were to be treated after each assessment. Existing baseline HIV and HSV-2 cannot be eliminated. An individual will thus be classified as a new case of any of the six infections at the 12 and 24-month follow-ups if there is a positive test at either of the follow-ups for chlamydia, gonorrhea, syphilis, trichomonas (if female), HIV (if not positive for HIV at baseline), or HSV-2 (if not positive for HSV-2 at baseline). To be considered a new case of syphilis if syphilis was documented at baseline, documentation will be required both that the syphilis at baseline was treated, and that the follow-up test at 12 months was negative. Otherwise, an individual who was positive at both baseline and 12-month follow-up and who has a fourfold or more RPR titer decline from baseline to 12-month follow-up and a fourfold or more RPR titer increase from the 12 to 24-month follow-up will be considered a new case. If the above conditions are not met for the six biological measures, the individual will be classified as negative for the composite outcome if at least two-thirds of the tests used in the individual's assessment provide definitive results (i.e. positive, negative, or indeterminate but not missing). For example, if the individual is a man, positive for HIV and negative for HSV-2 at baseline, the outcome assessment will be based on chlamydia, gonorrhea, syphilis, and HSV-2. At least three of the four test results must not be missing. If there are no new positive tests and more than a third of the individual's tests are missing, the composite variable will be set to missing. Prior to analysis, a panel of experts will meet to review laboratory and treatment data from selected cases to ensure that new cases are classified correctly.

The intervention effect for the behavioral endpoint will be measured as differences between intervention and comparison groups in the change scores from baseline to follow-up. Data will be gathered on the number of sexual acts during the past 3 months with non-spousal partners and the number of these occasions in which a condom was used, in order to compute indicators, numbers, and proportions of unprotected sexual acts with non-spousal partners. Individuals in the sample reporting no sexual acts with non-spousal partners will be assigned a proportion of 0%. See 'Challenges and process of selecting outcome measures for the NIMH Collaborative HIV/STD Prevention Trial' [16] for additional discussion of the outcome measures.

For the primary analyses, hypotheses regarding the study endpoints across countries will be evaluated using permutation tests (randomization tests) on unadjusted summary statistics (e.g. the difference between intervention and comparison venues on the percentage of participants with a new STD/HIV at the 12 and 24-month follow-ups). Permutation tests require far fewer assumptions than traditional model-based approaches, and seem appropriate for a trial with such diversity both within and across countries. The permutation tests will account for the fact that venues were randomly assigned and that this randomization involved pair-matching of venues in each country. For example, within a country with 10 matched pairs of venues (i.e. randomization to intervention and comparison within each of 10 pairs of venues), the permutation test for a specific endpoint involves computing the mean of the 10 pairwise differences between intervention and comparison venues calculated for each of the 2^{10} (1024) ways that the intervention could have been randomly assigned to the 20 venues. The rank of the observed mean among the 1024 possible means will give the significance level. This same procedure will be used across countries. Test-based confidence intervals can be constructed on the basis of the permutation tests.

An advantage of the randomized assignment of intervention is that baseline covariates will be balanced on average (in expectation) between intervention and comparison groups. Any imbalances that occur by chance are accounted for by the significance test. The greater sample size for the primary analysis across all sites makes large chance differences unlikely. By performing adjusted analyses (particularly for site-specific analyses), however, the effect of chance imbalances can be investigated. In this regard, the DCC will examine the comparability between intervention and comparison venues for several baseline variables at all sites. Permutation tests on adjusted summary statistics will be used as secondary analyses. In general, the covariates used for adjustment may not be the same in each country because of the diversity of the study populations (e.g. Zimbabwe has little injection drug use, whereas injection drug use may be higher in other countries). Mixed-model regression analyses will be run as secondary analyses if these models prove to be reasonable.

As in the across-countries analyses, hypotheses regarding the within-country study endpoints will be evaluated using permutation tests on both unadjusted and adjusted summary statistics. In general, the unadjusted summary statistics will be the primary analyses, and the adjusted summary statistics (e.g. adjusted for baseline level of risk, age, sex) will be used as secondary analyses. Also, mixed-model regression analysis on each endpoint will be secondary analyses.

Statistical models

When using statistical models to analyse the study endpoints, the analysis must reflect the group-randomized design (e.g. nested cohort design). It is anticipated that

a mixed-model regression analysis on each behavioral outcome will be used to include fixed effects (e.g. as a result of intervention and time) and several random components of variation (e.g. as a result of venue nested within intervention and individual nested within venue). The interaction of intervention with time will assess the effectiveness of the intervention [7]. As distinguished by Murray and Hannan [23], the general nested cohort design will include a fixed effect for time that is crossed with intervention, venue and individual, and a random effect for individual that is nested within venue. For the biological endpoint, it is not appropriate to use this model, because the endpoint is a composite of new HIV/STD cases. In this case, the mixed model is a main effects model for intervention. For all of these models, additional levels of nesting may be specified, for example to combine results across countries (if it appears that using a statistical model across countries is feasible) and to take into account matching (e.g. pairing of venues within a country for randomization to intervention versus comparison). Regression adjustment for covariates may also be applied to account for baseline differences and to improve power. Before testing the hypotheses using mixed models, it will be necessary to determine if variable transformations are required. Experience in related studies has indicated that some of the self-reported behavioral outcomes (i.e. number or proportion of times) may be skewed. Box–Cox plots [24] will be generated to determine the most appropriate transformation. The SAS/STAT [25] MIXED procedures alone or in combination with the SAS macro GLIMMIX will be used to fit the mixed regression models. MIXED assumes a Gaussian error distribution for all random effects. The SAS macro GLIMMIX allows for different specifications of the residual error distribution [26]. Binary outcomes (e.g. the composite biological outcome) may be modeled with binomial error, whereas frequency of occurrence measurements (e.g. the number of unprotected acts) may require Poisson error or Gaussian error on a transformed scale. In addition to using the mixed regression models approach, it may be useful to explore a population-averaged approach via the generalized estimating equations methods of Liang and Zeger [27]. This method is more robust to misspecification of the covariance structure. The generalized estimating equations method is available in SAS/STAT GENMOD and the SUDAAN software product of Research Triangle Institute [28]. Each of these approaches will be explored for possible model-based analysis.

Other analyses

The primary results will probably need to be substantiated with a sensitivity analysis of the results to missing outcome data (e.g. losses to follow-up). To some degree, the need for a detailed sensitivity analysis will depend on the results of the primary analysis, the degree of loss to follow-up, and any intervention-dependent pattern to the missing data. A first step will be to look for patterns by comparing observed characteristics of participants who are lost to follow-up with those having complete data. Then, both non-parametric and parametric approaches will be undertaken to account for missing data. In the non-parametric approach, the participants will be stratified for characteristics thought to be related to outcome or the probability of missingness (e.g. venue, sex, age, intervention condition, and baseline and 12-month measures), and outcome values will be imputed within strata using the observed outcomes. This will be followed by a permutation test analysis. For the parametric approach, a mixed-effects model that includes covariates associated with outcome or the probability of missingness will be fit. The exact specifications will require investigation of the available data. Both approaches assume that the probability of missingness does not depend on the missing values, but only the observed data used appropriately in the stratification or modeling.

Additional analyses will be performed to explore the relationship of process measures to the magnitude of intervention effect. For example, to analyse a measure of extent of intervention in a venue, the correlation of this measure (recorded for each intervention venue) with the difference in outcome between the venues in each matched pair will be investigated. Regression models will be used to investigate the relationship of multiple process measures with outcome. This type of analysis can be performed both within and across countries. The interaction of process measures by country may be of interest. Process measures that can be used for this analysis include attendance at C-POL training sessions, the number of relevant conversations that C-POLs reported occurring during the 7 days before the training or reunion sessions, and the number of C-POL logos that are observed within each venue on one day each month.

Lessons learned from implementing this Trial

Many lessons have been learned from implementing this international, multisite HIV/STD prevention trial. These include the following.

Preliminary epidemiological studies are required to: (i) determine if the populations being studied are at risk; (ii) identify the STD/HIV and behavioral risk prevalences in each country; and (iii) provide preliminary data to use for sample size calculations.

Close monitoring and training of staff for biological testing in foreign laboratories is required including ensuring that they always have the proper equipment and supplies (e.g. test kits) available.

A sustained effort must be directed to meet the challenge of taking a common intervention and tailoring it to ensure cultural relevance across diverse cultures while still

ensuring that the same basic approach is being tested in all countries.

The intervention content must be tailored to multiple at-risk populations in different countries while ensuring adherence to core principles.

The implementation of a behavioral intervention must be carefully monitored through ongoing supervision, process measures, and periodic site visits to ensure that the intervention is comparable across sites.

Assessment measures must be carefully translated and adapted to maintain consistent meanings in multiple languages.

Be prepared to react to the loss of venues over time as a result of natural disasters, political upheaval, or business factors.

Each site must develop a plan for follow-up activities, monitor those activities, and be prepared to adjust the plan if retention rates are lower than anticipated.

Regular meetings and conference calls of the steering committee and workgroups are essential throughout the Trial.

The timeline must always reflect the extended time involved to obtain IRB clearances from multiple IRB for each site and the DCC.

In conclusion, this Trial provides an opportunity to test rigorously a behavioral intervention in five countries, which increases the generalizability of the results. The Trial will evaluate the efficacy of the C-POL community-level HIV prevention intervention that was adapted for use in the various cultures, within the resource limitations faced by service providers in world regions threatened by high rates of HIV infection. On the basis of data from ethnographic and epidemiological studies conducted preceding the randomized trial, investigators tailored both the assessment and the intervention to the diverse cultures while still ensuring that the same basic approach is being tested in all countries. Venues (and participants within venues) were selected on the basis of risk behaviors, thus permitting recruitment of a core age group, but still targeting those with high-risk behaviors in each country. For example, high-risk individuals in the Fuzhou markets in China included older individuals than the dormitories in Russia, and the age range was expanded to reflect this difference. The use of randomized allocation provides a valid comparison of intervention and comparison conditions, thus avoiding bias, providing balance (on average) in factors predictive of outcome, and providing a valid basis for statistical tests of significance. As is necessary for this type of community-level trial, the sample size and statistical power calculations, as well as the analysis plan, account for the randomization of clusters (venues). Efficacy will be assessed using both behavioral and biological outcome measures; the primary biological outcome is an innovative composite measure of the incidence of six STDs, providing a single measure that can be used across sites with variable burdens of different STDs. The results of the Trial will provide important information for addressing this major public health problem.

Trial organization

The NIMH Collaborative HIV/STD Prevention Trial was supported using the cooperative agreement mechanism. The National Institutes of Health use this mechanism to support large-scale, multisite, phase III randomized controlled studies when substantial resources are required and when the funding institute wants both to participate actively in the scientific development of the study and provide administrative oversight.

Figure 3 presents an organization chart for the Trial. The components of the organization are described below.

National Institute of Mental Health

The Division of Mental Disorders, Behavioral Research, and AIDS at the US NIMH funded the study. Division staff actively participated in all aspects of the study, with primary input provided by the NIMH senior scientist and the NIMH project officer.

The NIMH senior scientist had substantial scientific input, in collaboration with award recipients, both in planning and conducting the study, and was a voting member of the steering committee (see below). The senior scientist assumed a major role in developing the study protocols, specifying QC/QA procedures, informing data analysis and interpretation, and preparing publications.

The NIMH project officer had overall responsibility for budget negotiations and for monitoring the conduct and progress of the project. The project officer carried

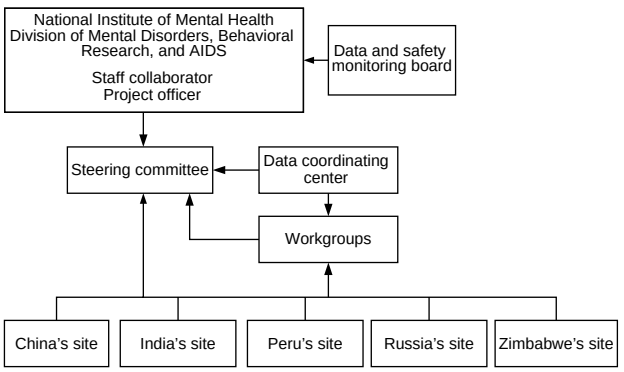

Fig. 3. Organization chart.

primary responsibility for periodic review, approval of the protocol in relation to stated objectives, and made recommendations regarding the continuation of the programme at critical decision points. The project officer oversaw the DCC, received all required reports, and determined that satisfactory progress was being made. The project officer sought advice from the DSMB on issues concerning the conduct and progress of the study.

Sites

Sites were located in China, India, Peru, Russia, and Zimbabwe. A site consists of a US institution and the foreign institution paired with it. The sites performed all of the research activities needed to implement the protocol, and were responsible for the daily conduct of the study at the foreign location. The sites participated in the design of study protocols, then implemented the ethnographic and epidemiological studies; adapted and translated the model intervention; trained staff; conducted baseline and follow-up assessments; selected, recruited, and trained the C-POLs; implemented on-site QC/QA procedures, helped interpret study results; and assisted in the preparation of reports and publications. The sites agreed to abide by the Trial design and policy recommendations developed by the steering committee and any requirements NIMH established in the terms and conditions of the cooperative agreement.

Data coordinating center

The DCC provided overall study coordination, including data management, data analysis, and training in common procedures, and ensured the distribution of necessary materials to all sites. It coordinated pilot testing of the protocol for assessment and full implementation of the Trial. DCC staff purchased and installed computer servers in each of the foreign sites, and the DCC retained a network manager to maintain these systems at each site. The DCC developed computer-assisted interviewing and other data capture programs to ensure efficient, accurate, cost-effective data collection. They developed and maintained a common data repository containing data files needed by many study participants. The DCC funded and monitored the activities of the core laboratory for the study. They arranged teleconferencing and other technical means (e.g. E-mail, a project web site) to facilitate rapid and easy communications among all staff from participating institutions. The DCC participated in QA activities, including site visits monitoring information technology, ethnography, behavioral and biological assessment, and intervention activities. The DCC conducted all data analyses required to prepare reports and manuscripts and participated in manuscript preparation. When requested, the DCC presented a written or oral progress report to the DSMB.

Steering committee

A steering committee provided scientific direction to the study and ultimately made decisions at the operational level. The steering committee was composed of the US and in-country principal investigators of each site, the principal investigator of the DCC, and the NIMH senior scientist. It had primary responsibility for developing the protocol, facilitating the conduct of the study, and reporting the study results to the project officer, the director of the NIMH Division of Mental Disorders, Behavioral Research, and AIDS, and the DSMB. The steering committee also developed policies on data sharing and on access to data and materials subject to NIMH review. The steering committee met on a regular basis to ensure that the Trial proceeded in a timely, systematic, and orderly fashion. The steering committee established workgroups to consider such topics as adoption/adaptation of the intervention, assessment measures, biological outcomes, ethnography, data collection and analysis, and protecting human respondents and ethical responsibility. Publications were written and authorship decided using the procedures specified in the protocol and approved by the steering committee. The steering committee, working with the DCC, prepared reports for submission to the project officer, the director of the NIMH Division of Mental Disorders, Behavioral Research, and AIDS, and the DSMB.

Data and Safety Monitoring Board

The director of the NIMH Division of Mental Disorders, Behavioral Research, and AIDS and the project officer established a DSMB to serve as an independent and external board providing expert consultation to NIMH. The DSMB assisted NIMH in reviewing the final trial protocol and recommended modifications during the conduct of the study in order to meet scientific objectives. In addition, the DSMB monitored progress on the data and technical aspects and assisted the NIMH project officer in dealing with operational aspects of the study. Finally, the DSMB monitored safety issues related to the Trial.

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