Ethical issues in the NIMH Collaborative HIV/STD Prevention Trial

NIMH Collaborative HIV/STD Prevention Trial Group*

Objective: To develop decision rules regarding key ethical dimensions in scientific protocols for the National Institute for Mental Health (NIMH) Collaborative HIV/STD Prevention Trial taking place in five countries (China, India, Peru, Russia, and Zimbabwe).

Design: Countries had HIV rates from 27 to 0.1%, the standard of care varied from access to antiretroviral drugs to no availability, and the reporting of sexually transmitted diseases (STD) to government agencies was mandatory in some countries and not in others. These variations presented challenges when developing decision rules that could be uniformly adopted across countries and simultaneously follow the ethical principles of beneficence, respect, and justice.

Methods: We used several strategies to identify and resolve ethical dilemmas for this international HIV prevention trial. First, we identified key principles, especially those derived for clinical therapeutic, biomedical preventive, or device trials. We convened a 'workgroup on protecting human participants' and charged them with identifying and implementing optimal procedures for ensuring the ethical and equitable treatment of participants and making recommendations to minimize physical, psychological, and social harm to the participants. Each site had a community advisory board, essential in identifying local ethical issues and possible resolutions to them. The NIMH established a data safety and monitoring board with ultimate responsibility for adjudicating ethical dilemmas and decisions. The protocols were deliberated thoroughly by the Trial steering committee, and approved by nine United States and five in-country institutional review boards.

Results: We summarize the decision rules adopted to resolve the ethical dilemmas identified. Especially important were the translation of clinical trials principles for a behavioral intervention trial, strategies for ensuring confidentiality and informed consent, dilemmas relating to partner notification of sexually transmitted infections including HIV, minimizing the risks of social harm, establishing community partnerships, ensuring equity among United States and in-country principal investigators, and building capacity for additional research.

Conclusion: We document our processes and decisions, and their underlying rationales, and hope they contribute to the development of further thinking and practice regarding the ethics of social and behavioral HIV and STD prevention trials in resource-poor settings.

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Introduction

The ethical conduct of HIV prevention research, especially in less-resourced countries, continues to evolve rapidly [1–5]. Its evolution is marked by major differences of opinion [6–8], trials being held up or halted [9,10], and attempts to design and conduct trials to benefit participants and the communities and countries in which they reside [11,12]. Hopefully, the results of these trials will have broad application to protect others at risk of HIV infection [13]. This paper focuses on the ethical issues identified and resolved from 2000 to 2003 while designing the National Institute of Mental Health (NIMH) Collaborative HIV/STD Prevention Trial ('the Trial'), which is assessing the efficacy of an international, community-level, social diffusion HIV prevention

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intervention designed to influence both behavioral and biological endpoints. Our goal in writing this paper is to document our processes and decisions, and their underlying rationales, and thus contribute to the further development of this important area of thinking and practice regarding the ethics of prevention trials in resource-poor settings. Some may disagree with the decisions that we made; others may argue that our decisions are outdated, superseded by subsequent research findings. Our goal is to articulate what we did and why, so that others may discuss and follow or change our procedures if their reading of ethical principles leads them to different conclusions or compelling new evidence leads to new practices.

The Trial's steering committee established a workgroup on protecting human participants and ethical responsibility to ensure the highest level of protection of human participants during this Trial and to provide a forum for resolving issues related to ethical responsibility. The workgroup was composed of the steering committee [highest ranking US and host country investigators for the five sites; the principal investigator of the data coordinating center; and the NIMH senior scientist] augmented with experts on the ethics of conducting international prevention and biomedical trials.

The workgroup 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. The workgroup reviewed all informed consent procedures, assessed the risks and benefits associated with participation, and established procedures for fairness in the selection of participants. In addition, the workgroup identified ethical dilemmas, addressed in this paper, which arose or reasonably could be expected to arise during the course of the Trial. Because of the ethical imperative of equity for all study participants, the intervention is being delivered in the comparison venues once the final follow-up endpoint data are collected. Expansion of the intervention to the comparison venues will permit, in some sites, an evaluation of technology transfer to governmental and non-governmental organizations capable of continuing this effort after the conclusion of the Trial. If results indicate that the intervention is successful, researchers will encourage local organizations to sustain it in the sites.

We convened a series of consultations to ensure that ethical standards for this research adhered to evolving international standards relevant to the conduct of a behavioral trial. The most extensive of these was a workshop involving international leaders in the ethical conduct of HIV trials in London in September 2000. In addition, ethical consultations were sought and received from other developed and developing-country experts. We were guided in these deliberations by the findings of the US National Bioethics Advisory Commission [14].

The NIMH also established a data safety and monitoring board [15], which not only monitored the safety of individual participants but also raised larger ethical questions about the responsibilities of US investigators undertaking international research. In addition, the protocols were reviewed and approved by nine institutional review boards (IRB) in the United States and one IRB in each of the participating countries (a total of five more).

It should be noted that the local IRB were in place before the start of the study. Furthermore, it should be noted that gaining consensus among so many different regulatory bodies for a large-scale multisite trial is not an easy task. We had to take into account both the judgements of the US institutions, including the funding agency and the body acting on behalf of the participants (the data safety and monitoring board), but also the in-country IRB and regulatory bodies. In the latter case, although all bodies wanted to adhere to the highest standards of clinical research, the local IRB were also clear that it was important that we not impose standards for research that contravened local laws or regulations, or that skewed local best practices in order to provide undue inducement to participate in the research study. These issues are discussed below, especially in relation to the provision of antiretroviral therapy for individuals with HIV and partner notification or contact tracing.

Ethical standards for behavioral research

The fundamental principles guiding the conduct of all clinical trials were followed during the Trial. The first code of ethics, the Nuremberg Code, emerged from the Nuremberg trials in 1946 in response to the abuses of human research subjects during World War II. The World Medical Association's Declaration of Helsinki followed this in 1964. The Declaration of Helsinki has been revised many times over the past 40 years, most recently to include a provision that 'medical research is only appropriate if there is a reasonable likelihood that the populations in which research is carried out stand to benefit from the results of the research' [16]. Applied to the Trial, this required that the interventions being tested could be implemented reasonably and cost-effectively, and would benefit the participants and countries involved in the investigation both during and after the Trial.

Regulations governing the standards for all research involving human participants in the United States have evolved over time. Following the disclosure of the Tuskegee experiments in 1972, the US Congress amended the Public Health Service Act to require the Secretary of Health, Education and Welfare to develop standards for research involving human participants. The first regulations, issued in 1974, established the US Office

for Protection from Research Risk. Consequently, the Ethical Conduct of Research with Human Participants, the Belmont Report [17], was developed in 1979. The Belmont Report outlined the principles, respect for persons, non-malfeasance, beneficence, and justice, by which federally funded research is conducted in the United States. These principles became the basis for federal regulations, which have been revised several times over the years, most recently in 2000 with the establishment of the US Department of Health and Human Services' Office for Human Research Protections (OHRP). The OHRP directly oversees all human research funded by the National Institutes of Health (NIH), including international collaborative research involving US institutions.

Drug trials versus behavioral trials

Although different ethical dilemmas may arise during behavioral research trials than during medical intervention trials, the ethical principles governing medical trials still apply. Namely, such research must ensure adequate informed consent, a favorable risk–benefit ratio, and the just distribution of the benefits and burdens of the research. Whereas the focus in medical intervention trials is primarily on protecting participants from physical harm, the focus in behavioral trials is largely on protecting participants from psychological or social harm. Groups deliberating ethical standards, such as the US National Bioethics Advisory Commission, have focused predominantly on medical intervention trials [3,5]. The development of ethical principles guiding international social and behavioral HIV/sexually transmitted disease (STD) prevention research has thus lagged somewhat behind the principles governing international trials of drugs or devices. Our efforts were designed not only to guide this specific trial, but also to foster the evolution of the principles for social and behavioral HIV/STD prevention efforts more generally. We also believe that issues related to psychological and social harm can and should apply to medical intervention trials, but are often not considered in the development of research and ethics protocols for those studies.

Ethical standards for behavioral research developed as a result of public attention focusing on controversial research conducted in the 1960s. In 1971, the American Psychological Association (APA) promulgated 'Standards for the conduct of research with human participants' [18]. This document was based on a content analysis of ethical dilemmas encountered by APA members when conducting behavioral research. Other professional associations, such as those for sociology, anthropology, social work, and psychiatry, have developed similar guidelines. The guidelines governing behavioral research have focused primarily on protecting participants from deception and potential social harms that may result from a breach of confidentiality. Such social harms might include embarrassment (e.g. being questioned about sexual behavior), stigma and discrimination (e.g. being identified with an AIDS or STD-related study) [19], disruption of family (e.g. detection of infidelity) [19], suspicion of being a commercial sex worker [20], injection drug user [21], or blood donor [22,23], loss of employment (e.g. if illegal drug use becomes known to an employer), and legal exposure (e.g. if HIV status becomes known in the context of an arrest or court case) [24]. All of these issues were relevant to our study.

The APA continues to review its ethical guidelines as new dilemmas arise. The latest example is developing guidelines addressing the conduct of research using the Internet [25].

Standard responsibilities of trial investigators

The principles regulating research with human participants require that the dignity of all participants and communities be respected, equality be promoted among participants, vulnerable populations not be unfairly burdened, and risks be minimized. These principles translate into the need for the strict protection of confidentiality, an appropriate risk–benefit ratio, clear strategies for minimizing risk, close attention to informed consent processes and procedures, and training and monitoring for staff involved in the study.

Confidentiality

We collected information on HIV/STD knowledge, attitudes, and risk behaviors, i.e. self-reported sexual risk, including the number and types of partners (regular partner/spouse, casual partners, and commercial partners), the use of alcohol and drugs, and condom use, in a cohort at baseline and 12 and 24 months later. We also obtained biological specimens for the assessment of chlamydia, gonorrhea, HIV, herpes simplex virus 2 (HSV-2), and syphilis in all participants, and trichomonas in female participants only.

Participants in the Trial faced the risk of social harm if behavioral data or biological test results were inadvertently revealed to others. Therefore, a number of traditional measures were taken to protect confidentiality. These included assigning a unique participant code to data rather than using names or other common identifiers, ensuring secure storage of research data, limiting the number of individuals in the study staff with access to sensitive information, and requiring that all participant counseling take place in private settings. Under US

federal law (Privacy Act of 1974), it is a misdemeanor to breach confidentiality during applicable data collection activities. Because similar protections did not necessarily apply in the host countries of the Trial, the investigators worked, where needed, to find ways to increase confidentiality protections through protocol design. This was a particular problem in Russia, which requires the reporting of all STD to the state and required clearly outlining reporting responsibilities at the time of recruitment, as well as altering the strategy for informing participants of positive results of an STD.

Potential risk could have been eliminated completely had the samples and data been analysed with no identifiers (unlinked data), but we decided against this for various reasons. The investigators believed that it was unethical to identify HIV and STD in voluntary participants without informing the participants of test results and treating the bacterial STD. Linked results allowed individual counseling for all participants and treatment or referral for positive results. Moreover, linked data allowed researchers to measure the incidence of HIV, HSV-2, and syphilis in the study cohort because baseline test status and treatment can be linked to data for the same participant 12 and 24 months later. Third, linked data allowed the identification of the types of individuals who were influenced by the persuasive messages and the types who were not (intervention effect).

The Trial faced potential consequences if STD could not be tracked by individuals and if treatment was not provided to those who tested positive at recruitment for bacterial STD. Without these steps, it would not be possible to know whether infections were new incidences or if bacterial STD were untreated from the time of recruitment to 12 or 24 months later. Substantial arrangements were thus made to ensure that participants could access their results. In Russia, participants in the Trial had to contact the researchers to be informed about their HIV status by accessing a personalized, confidential number known only to each participant, and were provided access to cell phones to make these calls at their convenience. The clinic staff never had the names of the participants, only matched identifying numbers informed the research staff of the Russian sample's STD results. This system allowed participants to learn of their bacterial STD through their own initiation via a numbered system and to receive free treatment while the study tracked incident bacterial and viral STD infections over time, without the clinic knowing the status of any specific participant and requiring the reporting of incident STD by participant name to the state.

The HIV and STD testing conducted by the study was thus confidential. These laboratory tests, with pre and posttest counseling, were offered to all participants and to partners of participants with positive laboratory results. All test results were made available at no cost to participants and their partners. Although participants were strongly encouraged to return for test results, no attempts were made to contact individuals in a way that might be stigmatizing. Participants were encouraged to notify their partners of results, and they were offered couples counseling by the study or by referral at the study's expense. Also, participants were given basic counseling and education when results were returned; if more extensive counseling was required, an appropriate referral was made at the study's expense.

Pregnant women identified as HIV positive through this screening programme were referred for appropriate counseling and prophylaxis to prevent vertical transmission. The rationale on whether the study was to provide prophylactic regimes to pregnant women is outlined more fully below under the topic of antiretroviral and antibiotic prophylaxis.

Partner notification

Previous studies of HIV transmission and prevention [26], have been criticized for failing to notify uninfected individuals of their sexual partner's infection. We did not engage in partner notification in this study, for two reasons. First, even in the United States, where sexually transmitted infections might be reportable and public health authorities need to engage in contact tracing, the confidentiality of the infected individual is always respected and people cannot be contacted if the infected individual does not reveal names [27,28]. Second, not all of the countries where the study was being implemented require the reporting of infections, and the places that do require reporting do not necessarily require name reporting. Some countries have specific laws against breaking participant confidentiality, and not all countries allow partner notification nor do they necessarily have the resources to do it. Therefore, we concluded that the most ethical strategy, and one that would not have us run foul of local laws and regulations, was to follow in-country laws and regulations, the country-specific standard of medical practice established by the country's Ministry of Health, and the standard established for other HIV/STD prevention studies in that country. This is consistent with the Joint United Nations Program on AIDS and World Health Organization guidelines [29]. We encouraged disclosure when appropriate, and also encouraged infected individuals to refer their partners for testing, counseling, and treatment or referral at the study's expense if needed.

Treatment for bacterial STD was provided to partners of study participants for free. In China, where all medical treatment is fee based, single dose treatment for all bacterial infections except syphilis was provided to the participant for their partners at the time of receiving the assessment results. If syphilis was identified, a coupon for free treatment was provided to the Chinese participants for their partners, as well as themselves. In other countries

these procedures varied, depending on the availability of treatment in the local environment. In some countries, we documented a high rate of reinfection for some STD [30], suggesting that this strategy was not completely successful. Future studies might examine additional strategies to enhance partners' awareness and treatment, while respecting participant confidentiality [30–39].

Assessing the risk–benefit ratio

One of the guiding ethical principles in the protection of human research participants is the requirement that the research be justified on the basis of a favorable risk–benefit ratio (US CFR 45). Therefore, IRB and scientific reviewers are asked to judge whether the risks to study participants are outweighed by the potential benefit to the individual participant and the importance of the knowledge to be gained from the study (i.e. the Trial's 'social benefit').

Many research studies, such as phase I drug trials, offer no direct benefit to participants while at the same time posing more than minimal risk. Such studies are, however, deemed to have a favorable risk–benefit ratio if the importance of the knowledge to be gained from that trial may provide significant social benefits. In addition, substantial evidence indicates that assessing their own behavior benefits many participants. An old public health adage states that 'the quickest way to stop an epidemic is to study it'. Across studies, the behaviors being addressed in the assessment improve by 15–30%, presumably because of the repeated examination of one's own behavior. Also, participants frequently comment that they found the study very helpful, even when they were enrolled in the control group and received no intervention.

Beyond the benefits of repeated assessments, the NIMH Collaborative HIV/STD Prevention Trial is testing the efficacy of a social diffusion intervention in reducing the number of new HIV infections and STD in various international contexts. If successful, the social benefit would be enormous because this intervention is inexpensive, could be adopted widely, and could limit the further spread of the epidemic. We expect this intervention to be effective, cost effective, sustainable, and easily disseminated in international settings. The primary risk to participants is social harm associated with HIV and STD testing: disruption of family (e.g. breakup of couples after HIV/STD detection or the revelation of infidelity); stigma and discrimination (e.g. being associated with a morally or socially disqualifying condition, with a consequent loss of employment or status in community); physical harm (e.g. acts of physical violence directed at individuals who have been diagnosed with HIV); or embarrassment and distress as a result of being questioned about sexual behavior.

Strategies for minimizing risk

Although almost all research involves some risk to participants, protocols should be judged on the basis of the overall risk–benefit ratio and the extent to which research-related risk is minimized. Obtaining individual informed consent, maintaining strict standards for confidentiality, and providing appropriate referral services may minimize the previously described risks to participants. In this protocol, we made a special effort to ensure that risks of social harm were explained as clearly as possible to potential participants during the informed consent process. Many of these same concerns were addressed in pretest counseling, when the participant's motivation for testing and preparedness for a positive test result were explored. The training of counselors for both pre and posttest counseling included confidential assessment and direct referral for crisis services. Counselors were trained to seek immediate consultation with a second counselor in any problematical situation. The intervention in this protocol also involved providing information regarding where participants could receive posttest referral services through the existing health system.

Informed consent

Informed consent is an essential part of minimizing risk to potential participants [40]. IRB accept differences among sites in informed consent procedures as long as the required information is conveyed and the differences are necessary to conform to local laws, regulations, or customs. The countries participating in this study have adopted a requirement for informed consent procedures at various times in the past, although some do not have a well-established tradition in this regard. The social meaning of consent depends on local cultures and traditions, and public perceptions about what is good or fair (particularly in a balance between individual and community) vary across cultures. Furthermore, conflict exists in some places about who can give consent. According to the OHRP guidelines for research on adults, only the research participant himself or herself can give consent to participate in the research. Permission to participate may sometimes be needed from the prospective participant's head of household or others in the community. Study implementation thus required extensive discussions about how to ensure that the ethical guidelines adopted reflected a multicultural understanding, rather than an imposition from one culture to others where a study commonly must first be endorsed by other members of the household or by local officials. Work with community advisory boards and others was required to ensure that communities accepted the requirements of informed consent, and understood the differences between permission, assent, and informed consent. Informed consent procedures and forms were validated in each country to ensure that they accomplished similar goals in each setting.

The language of consent forms often appears to be complex, legalistic, and difficult to understand for all populations, but especially for vulnerable populations in

international settings. Potential research participants may be very suspicious of any document that looks formal to them. Also, written, signed, informed consent forms may be impractical in sites where: (i) literacy levels are low (e.g. signing with 'X' or a thumb print is common); (ii) documents may symbolize undesired bureaucratic interference; (iii) even signing one's name to a consent document might pose a risk to confidentiality; or (iv) the content of the form itself may disclose important information such as serostatus [4,41]. The most important aspect of the informed consent process is not the signed document itself, but that the field staff honors the principles of respectful and protective treatment of study participants, and that the individual clearly understands the study and has agreed to participate in the research effort. The participant must feel free to refuse participation based on an understanding of what he or she is being asked to do and know that there are no implied or actual negative consequences of refusal.

Because we were concerned that individuals might feel coerced into participating, especially in countries with authoritarian histories, the Trial protocol required that the consent process involve a face-to-face discussion between the research participant and the field staff member obtaining informed consent. In some countries, videotapes were made locally demonstrating the procedures and activities that would follow and outlining the responsibilities and potential benefits and costs to participants (e.g. in China). Even when videotape orientations were used, a one-on-one meeting with a research interviewer was held. The study procedures and the risks and benefits of participation were explained carefully to the potential participant in simple language, and the individual had the opportunity to have any questions answered. Every effort was made to make the information conveyed clear and easy to understand, and not so long that parts of it were forgotten before the form was signed or so long that it overwhelmed potential participants. Participants were provided with contact information for in-country personnel who could answer any questions that arose in the future. Individuals were assured that their participation was entirely voluntary. We made every effort to ensure that no authority, in the markets in China, in the wine shops in India, in the barrios in Peru, in the dormitories in Russia, or in the growth point villages in Zimbabwe, was involved in recruiting individuals into the study or obtaining consent from them. No one except study personnel and the participants knew who did and who did not agree to participate.

Informed consent for the collection of biological specimens for HIV and STD testing must include a statement of the potential risks of such testing to participants. The following elements describing this risk were used in the consent forms adopted by each site: (i) HIV and STD tests may cause anxiety regardless of the test results; (ii) a positive HIV result means that the individual has been infected with HIV, but other tests will be necessary to determine the extent to which the disease has progressed; (iii) it may be possible to treat an STD identified through laboratory testing; (iv) receiving a positive HIV or STD test result may cause psychological distress (e.g. anxiety and depression) and may affect partner relationships; (v) if other people learn about an individual's positive test result, it could affect the way family and friends treat the individual; and (vi) if the individual's test is negative, it is still possible that the individual could become infected with HIV or another STD in the future.

Improving confidentiality through staff training

The NIH requires education on the protection of human research participants for all investigators and their key personnel (both national and international staff), including all personnel who have responsibility for the design and conduct of the study or direct contact with human participants. The Trial went further, however, by requiring that all personnel supported by project funding be certified on the protection of participant confidentiality before data collection began. Certification involved participation in a workshop on ethical principles and their application and signing an agreement through which staff agreed to abide by the international principles for the protection of human participants adopted by this study. This included receptionists, drivers, and clerical workers to ensure that they maintained the confidentiality of those participating in the study.

Because of the major harm that staff could do in small communities by inadvertently revealing personal information about research participants, extra steps were taken to ensure confidentiality. In addition to certification, sites developed and adopted procedures to ensure adherence to ethical principles by interviewers and other personnel involved in research contact with participants. Mechanisms included proficiency testing, field supervision, group discussions, and other appropriate techniques to ensure adherence to all protocols, including those involving human participants. Finally, the ongoing quality assurance procedures implemented by each site, and the external monitoring system, provided additional oversight and assurance that participant protection procedures were being followed. For example, on a random basis, supervisors in each site would visit recruitment venues and check that all procedural guidelines to assure informed consent were being followed. Case vignettes were generated across countries and project staff had the opportunity to discuss ethical dilemmas experienced by other country teams, examples that helped teams proactively to address potential problems. For example, the study resources to health examinations were considered so valuable in some countries that a few participants encouraged their friends to impersonate them to get free services. Protocols to protect both the

participant's confidentiality and the study's integrity were constantly updated as such new obstacles were encountered.

Challenges unique to international collaborative research

The challenge of collaborative research

The NIMH Collaborative HIV/STD Prevention Trial was established as collaborations between US academic institutions and host country counterparts. Such collaborative research between international and US researchers has the potential to benefit both parties. Research in host countries that is sponsored by a resource-rich country has the potential to exploit vulnerable international populations, and has thus been the subject of extensive recent debate [14]. Lo and Bayer [2] have further challenged investigators conducting research in host countries to meet certain guidelines for collaboration, including the following: (i) research must be responsive to the needs of the host nations and consistent with their priorities for healthcare; (ii) lower standards of care offered in host countries, compared with standards of care normally offered in the United States, need a special ethical review; (iii) reasonable efforts need to be made to secure access to experimental interventions proved effective after the Trial is over; and (iv) sponsors and researchers from the United States should build capacity for clinical trials and ethical review of research in host countries.

The collaborative research teams addressed each of these concerns *a priori*, anticipating the issues within the protocol that would be impacted by these guidelines. We have detailed below the domains in which these principles were most apparent.

Establishing community partnerships

Lo and Bayer [2] challenged investigators conducting research in host countries to develop partnerships with researchers, government agencies, and community leaders at all stages of trial conduct. This increases the chances that the research meets the needs of host and sponsoring nations and can be carried out successfully. Such partnerships are also essential to ensure that participants' concerns are understood, informed consent is appropriate and understood, and risks are minimized and benefits maximized.

The request for applications (RFA) for this Trial asked teams of US and host country investigators to respond with applications that identified both members of the partnership and described the functions and contributions of both partners. The Trial is governed by a steering committee including both the US and host country principal investigators. All of the Trial working groups (e.g. intervention, assessment, biological outcomes, ethics, ethnography) are composed of US and host country investigators and staff. Serious efforts were made to establish horizontal working relations between US and host country teams, although it was recognized that even a lack of English language proficiency might pose obstacles to equity. It is difficult for anyone to work and write in a second language. Added to that is the fact that scientists in the United States have first-hand knowledge of the NIH and its systems and regulations, and also ways of interacting in scientific settings that individuals elsewhere might consider abrupt, abrasive, or impolite. Therefore, the Trial team worked hard to ensure that all steering committee members had opportunities to speak and to question, to participate in all deliberations, and to have their voices heard as the study procedures were articulated.

All Trial sites developed ongoing relationships with in-country health officials and established community advisory boards to comment on all aspects of study design and implementation. Ethnographic studies conducted in advance of the Trial revealed major community stakeholders and leaders and important constituencies, which have been consulted for advice on all aspects of the study.

To ensure that we addressed the needs of the host country, each team led by the in-country and US leaders engaged in an active search for the risk population most likely to benefit from the Trial. In several countries, identification of appropriate populations and venues took many attempts. In China, the team conducted brief surveys and qualitative studies with sex workers, truck drivers, factory workers, and construction workers in many provinces in order to identify a suitable in-country population. Two sites, India and Peru, had to modify their risk populations from the initial choices in order to identify an appropriate study population. Similarly, Zimbabwe chose village populations in economic transition sites, increasing the team's work to maintain the cohort, but ensuring that a population at high risk would be addressed.

Establishing an acceptable standard of care

This is perhaps the most difficult of all issues, given that the standards of care are evolving and changing because of advocacy and programmes such as the Global Fund to Fight AIDS, Tuberculosis and Malaria [42] and the President's Emergency Program for AIDS Relief [43]. We agreed that all participants should receive counseling equal to Project RESPECT, which found that even brief counseling reduced incident STD [44]. This was also the standard adopted in Project EXPLORE, which tested the efficacy of an individualized intensive intervention in reducing HIV acquisition [45].

Demonstration of disease prevention and reductions in behavioral risk are the primary goals of this phase III prevention trial [46,47]. Therefore, STD diagnostic tests established baselines and were used as the Trial endpoint, despite concerns that this might constrain the Trial. All sites agreed that bacterial STDs should be treated with regimens adopted by the host country and confirmed to be efficacious. We agreed, for ethical and Trial protocol purposes, that individuals would be treated initially according to syndromic management protocols, and treated again if they received positive laboratory results that had not been treated through the syndromic approach.

Difficulties arose with regard to the treatment of HIV, because none of the countries in which the Trial was conducted had easy access to antiretroviral treatment at the beginning of the Trial. After consultation, we decided that individuals diagnosed with HIV during the course of the Trial would be referred to the nearest treatment centers, and that study personnel would work hard to ensure that these participants had access to those centers.

The issue of research sponsors providing treatment for HIV during or after the Trial has been a contentious one, but the generally agreed upon principle is the following: 'The issue of whether Trial sponsors should guarantee lifetime antiretroviral therapy led contentious debates in vaccine research. The present outcome of this debate is that trials rely on publicly funded programs in the host countries to provide antiretroviral treatment to infected Trial participants. This outcome reflects both financial and ethical considerations: a lifelong guarantee of treatment could exhaust limited research resources and does nothing for those who elect not to participate in research' [9].

Although it is important to work with host countries to provide access for research participants, it would not be ethical to provide antiretroviral drugs in a way that produces undue inducement or incentive to participate in the Trial. We thus had to seek a balance between inducement and reasonable access to care. We could not guarantee access to antiretroviral drugs after the end of the Trial. It would not be ethical to start individuals on antiretroviral drugs, and then stop treatment once the Trial was completed. This Trial was supported by the National Institute of Mental Health of the US NIH. The resources were allocated for prevention research, not treatment. Although some have argued that prevention research may carry the requirement for providing treatment for those diagnosed with HIV, the NIH and other groups such as the Bill and Melinda Gates Foundation have argued that such a requirement would place an undue burden on prevention trials, and even deplete already sparse funds further, and perhaps limit the number and quality of trials that might be conducted.

The question arises, then, is it ethical to test for HIV when antiretroviral treatments are not available? Because the vast majority of individuals who need HAART in the areas where we were working lacked access to the treatment at the beginning of our work, this and other HIV prevention trials involving HIV testing raised ethical questions related to diagnosing HIV without providing treatment. Although providing HAART is not required under the Joint United Nations Program on AIDS Guidance on Ethical Considerations in HIV Preventive AIDS Vaccine Research [48], treatment advocates in the United States and other countries are concerned about these issues. Therefore, we engaged in vigorous discussion and consulted ethical experts about the responsibility of the Trial to provide HIV treatment to individuals identified as HIV infected during assessment procedures.

Even without treatment, the benefits of knowing one's serostatus accrue to both the individual and the community. Individuals can take better care of their health, even without access to antiretroviral drugs, and can help stop the epidemic by reducing their transmission behaviors. Evidence indicates that globally approximately half to two-thirds of HIV-positive individuals reduce their transmission acts on learning their serostatus. This is a huge prevention benefit for local communities coping with the virus.

As leaders in the research community, the steering committee agreed on the social responsibility to advocate for better healthcare infrastructure and HIV specialty care in each of the five countries where the Trial was implemented. Investigators were optimistic that considerable progress would be made in terms of access to treatment, hopefully at the level of international standards being developed by multilateral agencies. Several steps have been taken towards this goal since the Trial started (e.g. the United Nations General Assembly Special Session on HIV/AIDS 'Declaration of Commitment on HIV/AIDS', in which prevention and care are linked [49], 'The framework document of the Global Fund to Fight AIDS, Tuberculosis and Malaria' [42], the 3 by 5 initiative of the World Health Organization [50], and the President's Emergency Program for AIDS Relief [43]). Several of the countries participating in the Trial were planning to initiate an HIV treatment programme, but these programmes were initially limited to certain areas and to specific populations. The prevailing view of the group was that the researchers have the responsibility to conduct this prevention study and report their findings as soon as possible to both the government and the local community. Recognizing that many countries have significant competing social priorities, each government is ultimately responsible for facilitating access to treatment for HIV when it is diagnosed. The hope is that the results of this research will assist communities and countries in making the case to their governments for increased access to treatment as part of a broad prevention plan.

The difficult ethical question at this point, in this and similar prevention trials that involve screening for HIV and STDs in host countries, is: do the risks outweigh the benefits of voluntary HIV counseling and testing (VCT) and STD screening in resource-poor settings without current access to antiretroviral therapies and with high levels of stigma within local communities? In other words, are the ethical principles of not doing harm (non-malfeasance) and doing good (beneficence) being properly respected?

This study involved counseling and testing for several bacterial and viral STDs in blood and urine and, in women, vaginal swabs. Although the collection of urine does not pose risks, and the risks of venipuncture are minimal, obtaining self-collected vaginal swabs from women may pose challenges to women unaccustomed to touching their genitals, or, particularly, to women with no previous sexual experience.

When a non-viral STD was identified on the basis of laboratory results, treatment meeting acceptable international standards (such as those developed by the Centers for Disease Control and Prevention) was provided at the study's expense [51]. Participants were informed at the time of biological specimen collection that their STD results would be available within an estimated time period. Information was provided on specified times and locations for receiving test results. Results were provided in-person and privately to each participant, and every effort was made to ensure that participants received their results whether they were positive or negative. Although multiple opportunities to receive results were arranged, along with strong motivational messages to return for results, sites did not directly contact individuals. Free treatment for non-viral STDs was made available either at the study site or through referral at the expense of the study for participants and their regular sexual partners. One ethical dilemma did arise in one of the study countries because the treatment recommended by the investigators for an STD was in conflict with the health policy of a country that wanted to reserve that drug for more serious ailments; consequently, in that situation, the Trial offered treatment that would have been considered less than optimal in the United States, but was locally appropriate. Another ethical dilemma arose when HSV-2 proved highly prevalent, but was treated episodically if at all, even though this infection is observationally associated with HIV acquisition [52–55]. The benefits of treatment to suppress HSV-2 to reduce HIV transmission have not yet been demonstrated [13,53]; if such a benefit is demonstrated in the future, studies may need to consider adding treatment to suppress HSV-2 to the standard HIV prevention protocol. A similar argument might be made for male circumcision, now that the Kenya and Uganda clinical trials have replicated the findings of the South African Orange Farm study [56].

As an HIV/STD prevention trial, the Trial was responsible for trying to prevent infections through known methods. Therefore, sites offered condoms at the time of interview and when laboratory results were reported to the participant. Sites also offered health education (discussion, pamphlets, etc.) at time of interview and when the HIV/STD results were provided. Study counseling included referral to existing testing, counseling, and treatment resources in the area, and encouraged participants to bring in their partners for syndromic treatment in several of the study sites.

One of the most effective methods for preventing HIV transmission involves administering antiretroviral medications to HIV-positive pregnant women to reduce transmission to infants. Before the Trial, this had been demonstrated in studies in the United States, Europe, and the developing world [57]. We had debates within the Trial with regard to providing this care in this study context, especially in Zimbabwe where HIV prevalence is high, the epidemic is a generalized one, and mother-to-child transmission is frequent. After considerable consultation and discussion, investigators decided to counsel pregnant women about the options for preventing transmission during the birthing process, and to provide referral to Ministry of Health-identified local district, provincial or mission hospitals that offer nevirapine for the prevention of mother-to-child transmission. Women were provided with transportation vouchers to reach these hospitals during labor. Therefore, although we decided that providing antiretroviral treatment was not its obligation, the cost-effective feasibility of being able to prevent mother-to-child transmission led the research team to provide access to nevarapine as an antiretroviral prophylactic regime to pregnant women. This decision was not without controversy: is it better to provide nevirapine to the pregnant mother, knowing that the child is likely to be orphaned? Despite the controversy, we provided access to mother-to-child transmission prophylaxis at the birth of the child. We also provided access to prophylactic antibiotics for participants living with HIV. Given the current scale-up of prevention and treatment activities in the developing world, these interventions appeared likely to be sustainable before the Trial ended in the local communities. Furthermore, it was highly likely that the capacity existed or could be built to sustain these interventions. Finally, these decisions were consistent with in-country policies.

Regarding the benefits of VCT in a situation without general access to treatment, our experience has been that most individuals enrolled in the study wanted to know their HIV status so that they could plan for the future, particularly in terms of family responsibilities [58,59]. Individuals also mentioned the opportunity to live more positive lives in terms of taking better care of themselves and adopting behaviors that could prevent further

transmission [60,61]. In many countries, individuals who wish to know their HIV status face barriers that are often logistical or cost related, and this study design removed many of these barriers. Offering VCT as part of the study to individuals eligible to participate in the Trial provided a significant potential benefit to these individuals.

The other issue to consider regarding the potential risk or benefit to individuals is their alternatives. VCT outside of this study may be difficult to access at some sites because of logistical issues (location and expense), but testing may be available in private clinics or government-sponsored programmes. Pre and post test counseling is rarely offered in private doctor's offices, and the quality of the counseling at public VCT sites is frequently inadequate compared with protocol standards. Post test support services are also limited outside the study protocol, suggesting that the potential for social harm from the research study may be lower than for testing conducted outside of the Trial.

Finally, it should be noted that the most affected countries would receive the most direct benefit of this research. This intervention has already proved efficacious in the United States, and the purpose of this Trial is to prove such efficacy in less resourced countries, with the advantage of its low cost and its being based on a simple concept: social communication. This Trial also responds to the ethical principle of justice, the group experiencing the research risk can potentially receive the greatest benefit from the research.

Ensuring that prevention can be achieved in the international context

One major advantage of the Trial is that the intervention, if it proves to be efficacious, can be implemented at low cost in a variety of settings. Furthermore, developing the intervention for the study resulted in treatment and training manuals in host country languages, adapted to local cultures as a result of extensive ethnography and pilot testing, and these manuals can be adapted for wider dissemination once the study is over.

Providing the experimental intervention to comparison communities and participants

For many reasons, the steering committee decided to offer the experimental intervention to the comparison communities and participants after data collection concluded in a particular area but before unblinding occurred at the end of the Trial. First, the steering committee decided that comparison participants should have access to the experimental intervention if they chose to participate in it. Second, waiting until the Trial was unblinded to offer the intervention to comparison communities would not have been feasible because the study will not have funding after unblinding in 2008. Finally, implementing the intervention in the comparison communities provided the opportunity for a variety of experiments to determine ways to adapt and implement the intervention in real-world settings. In a very real sense, it allowed the investigative teams to take the first step in adapting the intervention and training manuals for use by non-governmental organizations, ministries of health, local health authorities, and others.

Additional Trial responsibilities

The investigators in this Trial also adopted, consistent with Lo and Bayer [2], two additional principles of operation as they designed and implemented the Trial. The investigators in this study felt strongly that it was important to leave behind the capacity and ability to conduct further prevention trials. This translated into specific strategies for building local capacity and translating the findings into policy and practice.

Building capacity

Capacity was built in several important ways. In the first years of the Trial, the Fogarty International Center of the NIH provided US$50 000 to each US and international country pair for training purposes. Each of the sites used these funds in different ways, but all provided training in research skills for international staff. Because the study was powered partially on STD and HIV endpoints, laboratories in each country had to be developed or enhanced so that they could reliably and validly conduct the necessary assays. This required training laboratory personnel, providing or upgrading equipment, and certifying staff and laboratories through the core laboratory at the Johns Hopkins University School of Medicine. Information technology capacity was developed for data storage, management, and transfer to the data coordinating center at RTI International in North Carolina. Investments were made in equipment, laptops, secure broadband data lines, and the personnel necessary to meet this requirement. Capacity was also built among staff participating in all of the Trial workgroups. Each workgroup was composed of US and international scientists and staff, working together to understand theory and translate theory into operations. Training manuals and programmes were developed in each of the host country languages, and staffs were taught how to train and supervise others in programme implementation and evaluation. Staffs in all sites were trained in research ethics, and quality assurance checks and monitoring provided further opportunities for ethics training.

The US institutions participating in the Trial expanded their repertoire of skills and capacities for conducting research in the developing world. Important working relationships between host country and US scientists were deepened, and all sites worked to develop additional projects for the benefit of the host country. The US

researchers had the opportunity to learn about the cultural adaptation of interventions in general, and site-specific needs for intervention adaptation and adoption through their improved knowledge of diverse realities. Successful strategies for ensuring timely and accurate accounting and money transfers were developed, as were the requirements for specimen transfer and validation checks.

Moving research into policy and practice

The final ethical requirement laid out by Lo and Bayer [2] stipulated that trial investigators should attempt to find ways to ensure that trial strategies are available to affected communities once the trial is over. This implies more than making materials and manuals available, and more than providing training to non-governmental organizations and Ministry of Health personnel. The steering committee for the Trial interpreted this requirement to mean that it was essential to advocate for prevention, especially for cost-effective strategies, and keep host country governmental personnel abreast of Trial implementation, feasibility, and outcomes. Each site is developing materials that can be used in-country for the diffusion of the intervention throughout the host countries.

In conclusion, using a rigorous clinical trials design, this study developed, adapted, and evaluated the efficacy of a behavioral intervention for reducing HIV and STD transmission in resource-limited settings. The challenges in conducting such a study were enormous, but the need is even more enormous. An HIV vaccine is still years away, and biomedical preventive strategies, although promising, will always need to be provided together with behavioral strategies [13,62]. We have outlined here the ethical challenges we faced and the strategies we used to resolve them. We presented them in this paper to document the issues encountered, our decisions regarding their resolution, and to contribute to the overall development of ethical standards for HIV prevention trials in the developing world. We hope that others benefit from our thinking, take our deliberations forward, and continue these important discussions.

References

1. MacQueen KM, Shapiro K, Karim QA, Sugarman J. **Ethical challenges in international HIV prevention research.** *Account Res* 2004; **11**:49–61.
2. Lo B, Bayer R. **Establishing ethical trials for treatment and prevention of AIDS in developing countries.** *BMJ* 2003; **327**:337–339.
3. Fischer BA IV. **A summary of important documents in the field of research ethics.** *Schizophr Bull* 2006; **32**:69–80.
4. Gray RH, Quinn TC, Serwadda D, Sewankambo NK, Wabwire-Mangen F, Wawer MJ. **The ethics of research in developing countries.** *N Engl J Med* 2000; **343**:361–362; author reply 363.
5. Hyder AA, Wali SA, Khan AN, Teoh NB, Kass NE, Dawson L. **Ethical review of health research: a perspective from developing country researchers.** *J Med Ethics* 2004; **30**:68–72.
6. Benatar SR. **Towards progress in resolving dilemmas in international research ethics.** *J Law Med Ethics* 2004; **32**:574–582.
7. Benatar SR. **Moral imagination: the missing component in global health.** *PLoS Med* 2005; **2**:e400.
8. Benatar D. **Bioethics and health and human rights: a critical view.** *J Med Ethics* 2006; **32**:17–20.
9. Grant RM, Buchbinder S, Cates W Jr, Clarke E, Coates T, Cohen MS, *et al*. **AIDS. Promote HIV chemoprophylaxis research, don't prevent it.** *Science* 2005; **309**:2170–2171.
10. Page-Shafer K, Saphonn V, Sun LP, Vun MC, Cooper DA, Kaldor JM. **HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia.** *Lancet* 2005; **366**:1499–1503.
11. Cáceres C, Salazar X, Rosasco A, Mendoza W, Leon S, Sandoval C, *et al*. **Where the needs are: identifying those at higher risk for HIV to implement a prevention trial in lower-income communities in Peru: implications for public health programming**. Poster presentation at the *XVth International AIDS Conference*. MedGenMed, Bangkok, Thailand, 11-16 July 2004 [Abstract MoPeC3595].
12. Caceres CF, Mendoza W. **Monitoring trends in sexual behaviour and HIV/STIs in Peru: are available data sufficient?** *Sex Transm Infect* 2004; **80 (Suppl. 2)**:ii80–ii84.
13. Cohen J. **HIV/AIDS. Prevention cocktails: combining tools to Stop HIV's spread.** *Science* 2005; **309**:1002–1005.
14. National Bioethics Advisory Commission (NBAC). *Ethical and policy issues in international research: clinical trials in developing countries*. Vol. I: Report and recommendations of the National Bioethics Advisory Commission. Bethesda, MD: NBAC; April 2001. Available at: http://www.bioethics.gov/reports/past_commissions/nbac_international.pdf. Accessed: 24 May 2006.
15. NIMH Collaborative HIV/STD Prevention Trial Group. **Role of the data safety and monitoring board in an international trial.** *AIDS* 2007; **21 (Suppl. 2)**: S99–S102.
16. World Medical Association. **Revising the declaration of Helsinki**. *Bull Med Ethics* 2000; **158**:9–11.
17. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. **Ethical principles and guidelines for the protection of human subjects of research; Belmont Report: notice of report for public comment**. *Fed Regist* 1979; **44**:23191–23197.
18. Holden C. **APA adopts detailed code on human experimentation.** *Science* 1973; **179**:662.
19. Ostrom RA, Serovich JM, Lim JY, Mason TL. **The role of stigma in reasons for HIV disclosure and non-disclosure to children.** *AIDS Care* 2006; **18**:60–65.
20. Ding Y, Detels R, Zhao Z, Zhu Y, Zhu G, Zhang B, *et al*. **HIV infection and sexually transmitted diseases in female commercial sex workers in China.** *J Acquir Immune Defic Syndr* 2005; **38**:314–319.
21. Beyrer C, Sripaipan T, Tovanbutra S, Jittiwutikarn J, Suriyanon V, Vongchak T, *et al*. **High HIV, hepatitis C and sexual risks among drug-using men who have sex with men in northern Thailand.** *AIDS* 2005; **19**:1535–1540.
22. Wu Z, Liu Z, Detels R. **HIV-1 infection in commercial plasma donors in China.** *Lancet* 1995; **346**:61–62.
23. Wu Z, Rou K, Detels R. **Prevalence of HIV infection among former commercial plasma donors in rural eastern China.** *Health Policy Plan* 2001; **16**:41–46.
24. Punpanich W, Ungchusak K, Detels R. **Thailand's response to the HIV epidemic: yesterday, today, and tomorrow.** *AIDS Educ Prev* 2004; **16 (3 Suppl. A)**:119–136.
25. Keller HE, Lee S. **Ethical issues surrounding human participants research using the Internet.** *Ethics Behav* 2003; **13**:211–219.
26. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al*. **Viral load and heterosexual transmission of human immunodeficiency virus type 1: Rakai Project Study Group.** *N Engl J Med* 2000; **342**:921–929.
27. Cowan FM, French R, Johnson AM. **The role and effectiveness of partner notification in STD control: a review.** *Genitourin Med* 1996; **72**:247–252.
28. Peterman T, Toomey KE, Dicker LW, Zaidi AA, Wroten JE, Carolina J. **Partner notification for syphilis: a randomized, controlled trial of three approaches.** *Sex Transm Dis* 1997; **24**:511–518.

29. Joint United Nations Program on AIDS (UNAIDS). *Opening up the HIV/AIDS epidemic: guidance on encouraging beneficial disclosure, ethical partner counseling and appropriate use of HIV case reporting*. Geneva: UNAIDS; 2000.
30. Long CM, Klausner JD, Leon S, Jones FR, Giron M, Cuadros J, *et al*., the NIMH Collaborative HIV/STD Prevention Trial Group. **Syphilis treatment and HIV infection in a population-based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru.** *Sex Transm Dis* 2006; **33**:151–155.
31. Auerbach JD. **Principles of positive prevention.** *J Acquir Immune Defic Syndr* 2004; **37 (Suppl 2)**:S122–S125.
32. Centers for Disease Control and Prevention (CDC). **Using the Internet for partner notification of sexually transmitted diseases – Los Angeles County, California, 2003**. *MMWR Morb Mortal Wkly Rep* 2004; **53**:129–131.
33. Constant P. **Internet use and partner notification in a cluster of HIV and other STD among men who have sex with men. Paper presented at the STD/HIV Prevention and the Internet conference**. Washington DC; 2003.
34. Golden MR. **Expedited partner therapy for sexually transmitted diseases.** *Clin Infect Dis* 2005; **41**:630–633.
35. Golden MR, Whittington WL, Handsfield HH, Hughes JP, Stamm WE, Hogben M, *et al*. **Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection.** *N Engl J Med* 2005; **352**:676–685.
36. Gordon CM, Stall R, Cheever LW. **Prevention interventions with persons living with HIV/AIDS: challenges, progress, and research priorities.** *J Acquir Immune Defic Syndr* 2004; **37 (Suppl. 2)**:S53–S57.
37. Hogben M, McCree DH, Golden MR. **Patient-delivered partner therapy for sexually transmitted diseases as practiced by U.S. physicians.** *Sex Transm Dis* 2005; **32**:101–105.
38. Hogben M, Paffel J, Broussard D, Wolf W, Kenney K, Rubin S, *et al*. **Syphilis partner notification with men who have sex with men: a review and commentary.** *Sex Transm Dis* 2005; **32 (10 Suppl.)**:S43–S47.
39. Hughes G, Brady AR, Catchpole MA, Fenton KA, Rogers PA, Kinghorn GR, *et al*. **Characteristics of those who repeatedly acquire sexually transmitted infections: a retrospective cohort study of attendees at three urban sexually transmitted disease clinics in England.** *Sex Transm Dis* 2001; **28**:379–386.
40. Sugarman J, Lavori PW, Boeger M, Cain C, Edsond R, Morrison V, *et al*. **Evaluating the quality of informed consent.** *Clin Trials* 2005; **2**:34–41.
41. Gray RH, Sewankambo NK, Wawer MJ, Serwadda D, Kiwanuka N, Lutalo T. **Disclosure of HIV status on informed consent forms presents an ethical dilemma for protection of human subjects.** *J Acquir Immune Defic Syndr* 2006; **41**:246–248.
42. Global Fund to Fight AIDS, Tuberculosis and Malaria. *The framework document of the Global Fund to Fight AIDS, Tuberculosis and Malaria*. Geneva, Switzerland. Available at: http://www.theglobalfund.org/en/about/how/. Accessed: 24 February 2006.
43. US Department of Health and Human Services. *Progress on the President's emergency plan for AIDS relief*. 23 February 2004. Available at: http://www.globalhealth.gov/PEPFAR_Progress_022304.shtml. Accessed: 24 February 2006.
44. Kamb ML, Fishbein M, Douglas JM Jr, Rhodes F, Rogers J, Bolan G, *et al*. **Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group.** *JAMA* 1998; **280**:1161–1167.
45. Koblin B, Chesney M, Coates T. **Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study.** *Lancet* 2004; **364**:41–50.
46. Fishbein M, Pequegnat W. **Evaluating AIDS prevention interventions using behavioral and biological outcome measures.** *Sex Transm Dis* 2000; **27**:101–110.
47. Pequegnat W, Fishbein M, Celentano D, Ehrhardt A, Garnett G, Holtgrave D, *et al*. **NIMH/APPC workgroup on behavioral and biological outcomes in HIV/STD prevention studies: a position statement.** *Sex Transm Dis* 2000; **27**:127–132.
48. Joint United Nations Program on AIDS (UNAIDS). *Ethical considerations in HIV preventive AIDS vaccine research: UNAIDS guidance document* (prepublication version). 2000 February. Available at: http://www.iaen.org/vaccine/library.php. Accessed: 24 February 2006.
49. United Nations General Assembly Special Session (UNGASS) on HIV/AIDS. *Declaration of commitment on HIV/AIDS*. 2001 June. Available at: http://www.ohchr.org/english/issues/hiv/ungass.htm. Accessed: 24 February 2006.
50. World Health Organization. *The 3 by 5 initiative*. 2006. Available at: http://www.who.int/3by5/en/. Accessed: 24 February 2006.
51. Centers for Disease Control and Prevention (CDC). **1998 Guidelines for treatment of sexually transmitted diseases.** *MMWR Morb Mortal Wkly Rep* 1998; **47**:1–116.
52. Corey L, Wald A, Celum CL, Quinn TC. **The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics.** *J Acquir Immune Defic Syndr* 2004; **35**:435–445.
53. Celum C, Levine R, Weaver M, Wald A. **Genital herpes and human immunodeficiency virus: double trouble.** *Bull WHO* 2004; **82**:447–453.
54. Konda KA, Klausner JD, Lescano AG, Leon S, Castillo R, Gadea N, *et al*. **The risk of HIV and HSV-2 acquisition among men who have sex only with men in urban, coastal Peru.** Poster presentation at the *54th Annual Meeting of the American Society of Tropical Medicine and Hygiene*. Washington, DC, 2005 [Presentation number 776].
55. Konda KA, Klausner JD, Lescano AG, Leon S, Jones FR, Pajuelo J, *et al*., the NIMH Collaborative HIV/STI Prevention Trial Group. **The epidemiology of herpes simplex virus type 2 infection in low-income urban populations in coastal Peru.** *Sex Transm Dis* 2005; **32**:534–541.
56. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. **Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial.** *PLoS Med* 2005; **2**:e298.
57. Dabis F, Leroy V, Castetbon K, Spira R, Newell ML, Salamon R. **Preventing mother-to-child transmission of HIV-1 in Africa in the year 2000.** *AIDS* 2000; **14**:1017–1026.
58. The Voluntary HIV-1 Counseling and Testing Efficacy Study Group. **Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomised trial**. *Lancet* 2000; **356**:103–112.
59. Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, *et al*. **Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania.** *Lancet* 2000; **356**:113–121.
60. Allen S, Tice J, Van de Perre P, Serufilira A, Hudes E, Nsengumuremyi F, *et al*. **Effect of serotesting with counseling on condom use and seroconversion among HIV discordant couples in Africa.** *BMJ* 1992; **304**:1605–1609.
61. Allen SA, Serufilira A, Bogaerts J, Van de Perre P, Nsengumuremyi F, Lindan C, *et al*. **Confidential HIV testing and condom promotion in Africa. Impact on HIV and gonorrhea rates.** *JAMA* 1992; **268**:3338–3343.
62. Pequegnat W, Stover E. **Behavioral prevention is today's AIDS vaccine!.** *AIDS* 2000; **14 (Suppl. 2)**:S1–S7.