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Developing ethics guidance for HIV prevention research: the HPTN approach

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Introduction

More than 25 years into the human immunodeficiency virus (HIV) epidemic, in excess of two million new infections continue to occur each year, and approximately two million people died of AIDS-related causes in 2007 alone (UNAIDS 2008). From a scientific and public health perspective, primary HIV prevention research, as well as research with those acutely infected and with established infections, should focus predominately on communities and groups with high HIV incidence. But while research is crucially important for groups at heightened risk for HIV, the design and conduct of HIV prevention research with these populations continues to raise considerable ethical challenges, particularly in social contexts marked by poverty, weak health care infrastructures, inequity, discrimination and stigma.

The HIV Prevention Trials Network (HPTN) is a global collaborative network that conducts clinical and behavioral studies on non-vaccine interventions to reduce the transmission of HIV. In keeping with its mission to carry out HIV prevention research at the highest ethical standards, the HPTN Ethics Working Group (EWG) issued its Ethics Guidance for Research in 2003[1]. A number of important developments over the ensuing years prompted the HPTN to revise its ethics document in 2009. In what follows, we describe the developments that motivated the drafting of a revised ethics document, the process by which that revision took place, and some of the key differences between the HPTN ethics document and other relevant guidance in the field.

1. Relevant scientific, policy and ethical developments in HIV prevention since 2003

In the past few years, the global struggle against HIV/AIDS has been a tumultuous affair, marked by striking progress and significant setbacks. On the positive side, global initiatives have increased patient access to antiretroviral treatment, including treatment to prevent mother-to-child HIV transmission, particularly in developing countries with high HIV incidence. ‘Provider-initiated’ HIV testing policies have become more commonplace, increasing the number of persons who know their HIV status. In HIV prevention research,

the greatest success story over this time period was male circumcision, as three randomized controlled trials in Uganda, Kenya and South Africa indicated that circumcision produced a 60% reduction in HIV transmission risk from women to men. On a less positive note, a number of promising HIV prevention trials of vaccines, microbicides, sexually transmitted disease (STI) reduction and diaphragms have shown no statistically significant protective effect. Trials on pre-exposure prophylaxis (PREP) in Cambodia and Cameroon were halted prematurely after complaints from community groups, accusations from activist organizations and unfavorable media coverage.

Since 2003, there has also been greater attention in the scientific literature to ethical issues related to HIV prevention research, such as ethical obligations towards study participants who become HIV-positive during a trial; involvement of vulnerable groups, particularly adolescents, intravenous drug users (IDUs) and pregnant women; ethical obligations towards non-research participants, such as male partners in microbicide trials; ancillary care responsibilities of researchers towards research participants; responsiveness of research to local health priorities; and the use of novel approaches to develop, monitor and evaluate informed consent processes. A number of new or revised ethics and policy documents relevant to HIV prevention research were also published between 2003 and 2009. These include the Global Campaign for Microbicides' Rethinking the Ethical Roadmap for Clinical Testing of Microbicides (2005); UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials (2007); UNAIDS Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials (2007); revisions of the Declaration of Helsinki (2008); the Institute of Medicine's Methodological Challenges in HIV Prevention Trials (2008). Finally, the ethical challenges with the pre-exposure prophylaxis trials in Cameroon and Cambodia were the subject of two detailed reports[2, 3].

The revised HPTN ethics guidance document also partly emerged from empirical activities conducted by HPTN. Between 2003 and 2009, members of HPTN's Ethics Working Group (EWG) conducted research on the ancillary care obligations of research, the collection of biological specimens[4], standards of care within HIV prevention trials[5, 6], perceptions of ethical challenges within the HPTN[7], and informed consent[8].

2. Developing the ethics guidance

The revision process began with a review of preliminary data from a study of actual ethical issues encountered within HPTN research. Research by Borasky et. al.[7] used phone interviews to explore ethical challenges and concerns (regarding responsiveness of research to local needs, post-trial access, standards of care and ancillary care) experienced by those involved in HPTN research, including investigators, study coordinators, IRB members and community advisory board (CAB)/community working group (CWG) members at HPTN research sites in Asia, Africa, South America and the United States. Using these preliminary data and an extensive literature review in order to generate preliminary ethics guidance points and issues, a first draft of a revised ethics guidance document was developed. In November 2008, this draft was circulated to members of the HPTN EWG and other participants in advance of an intensive 2-day meeting to discuss and revise the document. Participants in the meeting included members of working groups (CWG and EWG) within HPTN, representatives of different divisions within NIH (NIHM, NIAID, OAR and NIDA), representatives from other NIH funded networks working on HIV prevention [HIV Vaccine Trials Network (HVTN) and Microbicides Trial Network (MTN)], and Family Health International (FHI) which supports the work of the HPTN. The participants discussed the selection and content of ethics guidance points, attempting to reach consensus among participants on their specific formulations. These discussions were themselves framed and guided by HPTN's commitment to the fundamental ethical principles of research including

respect for persons, beneficence and social justice. After formulating each ethics guidance point, participants attempted to reach consensus on the ethical status of the guidance point (obligatory or aspirational, described in more detail below) and identify who among the stakeholders was primarily responsible for its fulfillment. The initial designation of the ethical status of guidance points proved particularly challenging, as it involves a delicate balance between making the ethical responsibilities of researchers overly demanding (and possibly inhibiting valuable research) or not demanding enough (and failing to adequately meet fundamental ethical principles). A second draft version of the ethics guidance, emerging from this meeting, was then circulated within the HPTN, including CWG members at study sites around the world, to gain further feedback, criticism and advice. The ethics guidance document subsequently underwent three substantial revisions as it was critically examined by the HPTN; the revision process added new guidance points and issues, altered the ethical status of some guidance points, and changed some of the stakeholders responsible for them. A sixth version of the ethics guidance was then distributed for external review and feedback (via email correspondence or listserves) to a number of important stakeholders and experts in the ethics of global health research, such as those involved in Fogarty/NIH research ethics capacity-building initiatives, bioethics centers worldwide, the Wellcome Trust, and the European and Clinical Trials Partnership (EDCTP). Comments and criticisms were incorporated into a final version of the new ethics guidance which was approved by the Executive Committee of the HPTN in May 2009 and posted on its website[9].

3. Approach and goals

The HPTN ethics guidance aims to serve as a useful, practical guide for addressing ethical challenges in all HPTN research, including behavioral studies and non-clinical, community based trials. In keeping with this practical orientation, the points in the ethics guidance are to be integrated into the design, implementation and dissemination of HPTN research. The primary audience of the ethics guidance, therefore, are those involved within the HPTN or those directly affected by its activities. However, given that the 2003 HPTN ethics guidance was regarded as an important contribution to ethical discussions surrounding HIV prevention research[10, 11], the updated guidance aims to be useful for other groups and agencies conducting similar research, and to a general audience interested in issues related to HIV prevention and ethics.

4. Key differences with other related guidance

Unlike related guidance documents, which are organized thematically, the HPTN ethics guidance is structured according to the continuum of research: ethical issues before research begins, ethical issues during the conduct of research, and ethical issues after data collection is completed. Within this structure, the document presents and develops 15 ethics guidance points in detail (see Box 1).

The 15 ethics guidance points overlap to some extent with existing guidance relevant to HIV prevention research, particularly the UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials (2007). Unlike that document, however, the 2009 HPTN ethics guidance specifies the ethical status of each guidance point, because it emerged during discussions about the prior HPTN ethics guidance that researchers wanted to know if specific guidance points constituted ethical requirements or recommendations. In the updated guidance, some guidance points are regarded as ethical obligations, i.e. the actions prescribed by the guidance point normally ought to be followed, and exceptions require a strong ethical justification. Other guidance points are regarded as ethical aspirations, i.e. it would be praiseworthy or commendable to follow the course of action prescribed by the guidance

point, though it is not ethically required. Each guidance point also states who among the stakeholders -- sponsors, principal investigators, protocol teams, Community Working Group, etc. -- is responsible and accountable for ensuring that each guidance point is taken into account. The aim of stipulating the ethical status of each guidance point, as well as identifying those responsible for their fulfillment, is to render the HPTN ethics guidance more directive and user-friendly. In addition, short case studies or vignettes based on actual HPTN research experiences are used throughout the ethics guidance document to illuminate selected guidance points.

In what follows, we specify some of the more substantive differences between the HPTN ethics guidance and other regulations or guidance relevant to HIV prevention research. The positions of other relevant guidance documents on some key ethical issues are also displayed in Table 1.

Standard of prevention

In the HPTN ethics guidance, ‘standard of prevention’ is explicitly distinguished from the more commonly-used notion of ‘standard of care’. Standard of prevention refers to the package of HIV prevention products or services that will be offered to those that participate in HPTN research. While it is important, on scientific grounds, for research participants to be at risk of exposure to HIV, there is a wide ethical consensus that they must be provided with effective means to protect themselves from acquiring the virus. Ethical discussions therefore revolve around the precise content of the ‘prevention package,’ beyond a minimum of HIV voluntary testing and counseling, HIV and STI risk reduction, and provision of male and female condoms.

On this point, the UNAIDS Ethical considerations in biomedical HIV prevention trials (2007) is unambiguous: “Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counseling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial” (Guidance Point 13). This echoes the Declaration of Helsinki (2008), which states: “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current proven intervention” (Paragraph 32). The new HPTN ethics guidance takes a less categorical and more pragmatic position. It defines the necessary conditions for an acceptable prevention package within HIV prevention research as those services (a) known to be effective in preventing HIV transmission, (b) practically achievable as a standard in the local setting and (c) reasonably accessible by those screened or enrolled in HIV prevention. These conditions are partly motivated by concerns about research studies creating inequities by providing participants with comprehensive prevention services unavailable to local communities and unfeasible to integrate into local health systems. In addition, the HPTN guidance acknowledges that some prevention services (like male circumcision) may be culturally inappropriate for some communities, and the provision of others (such as needle exchange) may be illegal and place participants at added risk. Finally, insisting on ‘state of the art’ prevention in every context may compromise the real-world significance of the data, and the production of irrelevant research is both a scientific and ethical concern. Experiences of HPTN researchers working in the field, as well as members of IRBs/research ethics committees, representatives of CABs and Community Working Groups reveal a tension between the ideal to improve local standards of care and treatment and practical obstacles researchers face when pursuing this ideal. In general, the HPTN ethics guidance is grounded in pragmatism which recognizes that HIV prevention research must be conducted according to the highest ethical standards, but at the same time, lofty ethical aspirations will not have a meaningful social impact if they cannot be applied in the concrete research settings and the political, social, economic, cultural and regulatory contexts in which they are embedded.

Provision of successful research interventions

The Declaration of Helsinki (2008) states that at the conclusion of a research study, research participants are entitled to share any benefits resulting from the research, including interventions identified as beneficial (Paragraph 33). The HPTN ethics guidance reflects concerns (also expressed by CIOMS and Nuffield Council on Bioethics) that immediate provision of successful research interventions is not a straightforward matter. Successful drug interventions may need to undergo lengthy regulatory and production scale-up before they reach individual research participants; the overall benefits of a new effective intervention may not be clearly superior to established methods. The HPTN ethics guidance therefore identifies some key questions to be answered regarding 'post-trial access': who will be financially and logistically responsible for providing the intervention, who will gain access to the intervention (participants, communities or others) and for how long access will be provided. Unlike the Nuffield Council of Bioethics (2002), the HPTN ethics guidance stops short of requiring researchers to develop a 'post-study access plan' and integrate it in their study protocols before their research begins. Instead, it requires researchers to start planning for access to successful interventions as early as possible, to modify plans as research unfolds, and to develop an explicit post-study access plan if a beneficial intervention is identified. The guidance emphasizes that participants should be regularly informed about developments in regard to post-study access, and ongoing stakeholder and community consultation is crucial to appropriate sharing of benefits after research is over. As the research by Borasky et. al. reveals, however, developing post-access plans have often not been experienced as a major concern for HIV prevention researchers, for the unfortunate reason that very few studies have yielded effective interventions[7].

Continuing care for research participants

What obligations do HIV prevention researchers have when a research participant, despite being provided with the 'prevention package', becomes HIV positive during the course of the study? According to UNAIDS (2007a), "Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognized as optimal" (Guidance point 14). Some involved in HIV research and ethics argue that with the increase in access to antiretroviral treatment and care services around the world, there is a 'consensus' that those who seroconvert during a trial should be guaranteed access to care and treatment.[12] Others claim that, on closer inspection, this obligation has no rational or ethical basis, because the provision of treatment cannot be justified by a principle of reciprocity or claims of research-related injury.[13]

The HPTN ethics guidance takes a moderate position within this debate. While access to antiretroviral treatment on the part of seroconverters should be the goal, care must be taken not to create or worsen inequities in access to treatment. In addition, those who become HIV positive may not require antiretroviral treatment for a number of years, by which time antiretroviral drugs may (and should) already form part of local HIV care and treatment services. While investigators should ensure that study participants do not suffer discontinuity of care and treatment, research projects cannot reasonably be expected to act as substitutes for local health systems. If, in the worst case scenario, it is highly unlikely that local health services will be able (or willing) to assume care and treatment for those who seroconvert during a HIV prevention study in the foreseeable future, researchers may wish to consider alternative study sites. On the other hand, the HPTN ethics guidance acknowledges that moving HIV prevention studies to better resourced settings may itself perpetuate or exacerbate existing inequities, and therefore takes the position that research may be permissible in locations where treatment and care for those who seroconvert is not yet guaranteed, as long as host governments and communities are committed to the research

and if the study's capacity-building plan includes improvement of local HIV/AIDS services and care.

Standards of care and treatment

Standards of prevention refer to what research participants may or may not receive to lower their risk of HIV infection. Standards of care and treatment refer to the package of medical and health-related services research participants can expect to receive during the course of a study. The HPTN ethics guidance differs from other guidelines in clearly differentiating domains of care to be considered and by its attention to the impact that provision of care and treatment to research participants may have on local health systems. The different domains of care and treatment include: care and treatment for those screened but failing to meet study inclusion criteria due to a pre-existing medical condition; care and treatment provided for research-related reasons; care and treatment provided to participants for medically significant findings occurring during study participation ('ancillary care'), and care, treatment or monetary compensation for research-related injuries. The guidance stresses that research teams must initially make a thorough investigation of standards of care and treatment at study sites, provide at the very least equivalent services if the standards are adequate, and seek to enhance local standards if they are unacceptably low.

The HPTN ethics guidance is one of the few to include discussion of the ancillary care responsibilities of researchers, and to confront the thorny question of compensation for research-related harm. In regard to the former, the guidance stresses the need to know the prevailing health conditions at research sites to at least anticipate some of the ancillary care needs research participants are likely to experience. This knowledge, together with the results of ongoing dialogue with local communities, should be incorporated into research protocols and periodically reviewed in the light of new data. In regard to compensation for harm, the guidance points out that while the National Institutes of Health (NIH) does not provide medical care or financial compensation, compensation for injury can be handled at the site level by arrangements with institutions collaborating in the research, and in some cases NIH funds can be used to purchase insurance coverage to cover research-related injuries. The ethics guidance stresses the need for clear communication in what can be a highly sensitive area: if compensation will not be offered, this should be stated unambiguously in the consent process. If compensation will be offered, the nature of the compensation should be explicitly described incorporating considerations from relevant legal codes and spelling out clearly what constitutes negligent and non-negligent harm, whether medical treatment or financial compensation will be involved, and the process by which harms will be determined to be research-related and compensated.

Engaging communities

Community engagement is a motif running through virtually all guidance points of the HPTN ethics document. The importance of community engagement is regarded as both intrinsic and instrumental, i.e. the involvement of communities in research expresses respect for local communities and enhances the ability to conduct and complete HIV prevention research. The HPTN ethics guidance differs from other related documents, as some have noted[14], by providing a working definition of 'community', as the group of people who will participate in, or are likely to be affected by or have an influence on the conduct of research. While community engagement is a feature in other ethics documents, the HPTN guidance goes into greater detail on its processes and challenges on the basis of HPTN's long experience with participatory community research. The guidance stresses the need to meaningfully involve communities at the earliest stages of the research process, acknowledges that both community members and researchers need to explore each other's perspectives and concerns through 'joint literacy', describes the importance of identifying

appropriate community representatives, explains how the boundaries of community may be expanded by the addition of new stakeholders, and suggests ways of improving communication between researchers, community representatives and members of community advisory boards.

4. Future challenges

The most immediate challenge is to fully operationalize the guidance points of the updated ethics guidance within the day-to-day research practices of the HPTN. Interviews with HPTN stakeholders suggest that the guidance points from the previous ethics document were not always routinely and explicitly taken into account when designing, conducting and disseminating HPTN research[7]. To improve implementation in the future, mechanisms that engage relevant guidance points -- such as ethics checklists researchers must complete in their protocols -- will be developed for each phase along the research continuum.

Ethics guidance such as this are faced with two major challenges: remaining relevant over time and adding significant value to the ethics guidance that already exists. Remaining relevant for the rapidly evolving field of HIV prevention research is especially challenging. Even during the period that the updated HPTN ethics guidance was being developed, HIV prevention research trends appeared which may pose novel ethical questions. For example, current HIV prevention research is being conducted into the effectiveness of a ‘test and treat’ approach, i.e. aggressively testing for HIV and providing anti-retroviral treatment to HIV-positive persons regardless of their viral load or CD4 count. This type of research raises ethical issues around behavioral disinhibition, individual patient benefit and drug resistance[15]. While the 2009 HPTN ethics guidance does not directly address this particular approach, it does provide some analytic and conceptual tools which may be useful for this and other emerging ethical problems. In regard to the need for (yet another) ethics guidance, it should be noted that existing ethics guidance have some serious shortcomings for those engaged in HIV prevention research. The usefulness of some current guidance may be limited, either because they are pitched at too high a level of generality or because they are not sufficiently grounded in the realities of collaborative research involving vulnerable populations. In addition, research ethics guidance tends to focus on ethical issues arising from clinical research with patient populations, rather than the testing of prevention methods (both biomedical and behavioral) with non-patient, at-risk groups. The updated HPTN ethics guidance aims to guide HPTN’s mission of conducting HIV prevention research at the highest ethical standards while helping to fill a gap in this important area of research ethics.

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Box 1

HPTN ethics guidance points

Before research

- Ensuring high-quality scientific and ethical research
- Setting research objectives and priorities
- Engaging communities
- Building local capacity and partnerships
- Ethical issues in study design
- Consent, assent, permission and re-consent
- Addressing vulnerabilities
- Ethical review of research

During research

- Standard of prevention
- Standards of care and treatment
- Independent data safety and monitoring

After research

- Disseminating research results
- Sustaining capacity-building and infrastructure into the future
- Continuing care for research participants
- Provision of successful research interventions

Box 2

Example vignette

Challenges to protecting vulnerable populations in research

Injection drug users (IDUs) are stigmatized to such a great extent that it is very difficult to provide traditional research protections for IDUs who enroll in HIV prevention research. IDUs are often regarded by local governments, local police authorities and many community members as common criminals, and research involving them tends to be discouraged. When research does occur, the government closely monitors who the IDUs are and the local police, who have all the names of participants, may watch them coming in and out of the clinic. In this political and social context, the idea of providing true confidentiality protections for these research participants does not apply, so researchers are forced to look to other risk-reduction approaches for this population. This can involve educating police about proposed research in order to minimize risk to participants.

Table 1

Guidance document	Key ethical issues			
	Responsiveness of research to local needs	**Standards of prevention**	**Provision of treatment to participants who become HIV positive**	**Provision of successful research interventions**
***HIV Prevention Trials Network (HPTN)* Ethics Guidance for Research (2009)**	Early community involvement in protocol development should enhance relevance. Research clearly inappropriate or not feasible for local adoption should not be conducted (Guidance Point 2)	Minimum established prevention methods are obligatory, additions to prevention package depend on sustainability, legal, cultural, scientific and other factors (Guidance Point 9)	Access to HIV treatment should be the goal, and provision of treatment may (partly) be the responsibility of the research funder. Access should not worsen local health inequities(Guidance Point 14)	Researchers should develop plans for post-study access as the research unfolds, in close consultation with community and research participants (Guidance Point 15)
***UNAIDS* (2007) Ethical considerations in biomedical HIV prevention trials**	Conduct of HIV prevention research in vulnerable communities requires that the resulting products are necessary for and responsive to local health needs and priorities (Guidance Point 5)	All participants must receive appropriate counseling and access to state of the art HIV risk reduction methods (Guidance Point 13)	Participants who acquire HIV in a biomedical HIV prevention trial should be provided with international recognized optimal treatment (Guidance Point 14)	Participants should be informed of trial results; responsibilities and plans for access to beneficial preventive interventions (and other benefits) should be developed early (Guidance Point 19)
***World Medical Association* (2008) Declaration of Helsinki**	Research among vulnerable populations is only justified if the research is responsive to the health needs and priorities of this population; there must a reasonable likelihood that this population will benefit from the research results (Paragraph 17)	The benefits, risks and burdens of a new intervention should be tested against the best current method (Paragraph 32)	No specific guidance.	Participants are entitled to be informed and share any benefits resulting from the research (Paragraph 33)
***National Bioethics Advisory Commission* (2001) Ethical and policy issues in international research: clinical trials in developing countries**	Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country (Recommendation 1.3)	No specific guidance regarding prevention research. In general, research designs which do not provide established standards to control groups must justify this decision to ethics committees (Recommendation 2.2)	No specific guidance.	Whenever possible, agreements should be negotiated by the relevant parties before research begins to make the effective intervention or other research benefits available to the host country after the study is completed(Recommendation 4.3.)
***Nuffield Council on Bioethics* (2002) Ethics of research related to healthcare in developing countries**	Externally funded research may fall outside national health priorities, if research builds local capacity or provides other significant benefits, as determined by host and sponsor country ethics committees (Paragraph 10.10)	No specific guidance regarding prevention research. In general, deviations from providing the highest standard of care to research participants can be justified on a case by case basis in consultation with community and ethics review boards (Paragraphs 7.17–7.30)	Participants who develop the disease being investigated in a prevention study should be offered a universal standard of care, when appropriate. If not appropriate, the best available local care should be provided. (Paragraph 7.33)	Ethically unacceptable to start a study without a decision about post-study access of participants to beneficial interventions, communicated in consent process. Lack of access must be justified to ethics committee (Paragraphs 9.21–9.31)
***CIOMS* (2002) International ethical guidelines for biomedical research involving human subjects**	Sponsors and investigators conducting research in vulnerable communities must ensure that research is responsive to local health needs and priorities. True responsiveness requires reasonable availability of beneficial research results (Guideline 10)	Research subjects in control group of a preventive intervention trial should generally receive an established effective intervention; alternative comparators may be ethically acceptable (Guideline 11)	No specific guidance.	Beneficial knowledge and/or research products should be reasonably available to local population. Reasonable availability must be determined by key stakeholders on a case by case basis (Guideline 10)