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Ethical Issues in HIV Prevention Research with People Who Inject Drugs

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Abstract

Background—Injection drug use continues to significantly contribute to new infections with HIV. Moreover, conducting HIV prevention research with people who inject drugs (PWIDs) can be complicated for an array of practical, social, legal and ethical reasons. It is critical that these research efforts are sensitive to the particular vulnerabilities associated with injection drug use as well as those related to being at risk for acquiring HIV so as to minimize harm to participants in research.

Purpose—To describe how we addressed some of these ethical challenges during the course of a large-scale multinational randomized HIV prevention trial involving PWIDs, which was successfully completed.

Methods—The ethical issues encountered during the life-cycle of the trial were catalogued by the principal investigator, study coordinator and ethicist working on the trial. Relevant study documents were then reviewed to provide pertinent details. The ethical issues unique to the trial were then described.

Results—Before implementation, the trial faced particularly complex challenges related to the vulnerability of PWIDs where HIV seroincidence rates in the population were high and legal policies and stigma regarding injection drug use was severe. Accordingly, a rapid policy assessment was commissioned and a series of community engagement activities were conducted. During the trial, in addition to using careful standard operating procedures regarding all aspects of trial conduct and extensive staff training, the trial standardized informed consent procedures and assessed them. Further, social harms were monitored along with physical harms and adverse events. Following the decision to close the study, it was critical to develop an orderly and safe process for closing it. The issue of post-trial access to the study medication and a complex intervention also surfaced for consideration.

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Limitations—The issues described in this paper are necessarily limited to how they manifested themselves within the context of a particular trial that was conducted in two countries. In addition, other stakeholders may have divergent views on the ethical issues described and may also have identified additional ethical issues that would warrant examination.

Conclusions—Adopting similar approaches to addressing ethical issues in future research promises to facilitate this work so that needed strategies to prevent HIV infection among PWIDs can be safely and appropriately tested. Future trials enrolling PWID who are at risk of detainment should identify ways of mapping closely their experiences and perceptions in order to better apprehend some of the ethical issues at stake. In addition, scholarly and policy work needs to address the ethical issues related to post-trial access to multi-modal interventions that may be desired by participants, but are not shown to be effective in achieving the primary outcomes of the study.

Keywords

Research Ethics; Injection Drug Use; HIV Prevention; International

BACKGROUND

Injection drug use continues to significantly contribute to new infections with HIV. Moreover, conducting HIV prevention research with people who inject drugs (PWIDs) can be complicated for an array of practical, social, legal and ethical reasons[1]. These issues are often more sharply focused in international settings, yet given the enormous burden of HIV-infection among PWIDs there is a strong public health and moral urgency to develop and test methods of HIV-prevention for this population[2]. It is critical, however, that these research efforts recognize and address the legal, social, and other vulnerabilities associated with injection drug use so as to minimize harm to study participants. In this paper, we describe how we addressed some of these challenges during the course of a large-scale multinational randomized trial examining a combination HIV prevention strategy for PWIDs. We hope that the general success of these approaches as well as future scholarly and policy work directed at some issues that surfaced over the course of the trial will ultimately help to facilitate further research among this population so that safe and effective HIV prevention strategies can be identified.

HPTN 058, “Drug Treatment Combined With Drug and Risk Reduction Counseling in the Prevention of HIV Infection among Injection Drug Users” (NCT00270257) was a phase III randomized controlled trial that assessed the safety and efficacy of treatment for injection drug use in decreasing HIV transmission and death. HPTN 058 compared two novel approaches to drug treatment as HIV prevention. Active drug users were recruited from the community and assigned to either: 1) short-term medication assisted treatment that consisted of two opportunities for detoxification with buprenorphine/naloxone (BUP/NX) combined with twelve months of behavioral and drug risk counseling (BDRC), or; 2) long-term medication assisted treatment in which BUP/NX was provided three times or more per week for one year plus 12 months of BDRC[3]. The intervention period in both arms lasted one year, with at least one-year of follow-up. The trial was funded by the US National Institutes of Health and conducted at four sites in Thailand (Chiang Mai) and China (Nanning and

Heng County in Guangxi Region; and Urumqi in Xianjiang region). A China HPTN 058 study Joint Working Group was established to coordinate the implementation of the HPTN 058 study. The Joint Working Group consisted of leaders of the China Centers for Disease Control (CDC) and the National Center for STD/AIDS Control and Prevention (NCAIDS), officials from the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Drug Abuse (NIDA), the protocol chair of the HPTN 058 study, the HPTN 058 study Principal Investigators of China CDC and Johns Hopkins University, leaders of the Xinjiang and Guangxi study sites, and experts from the Chinese National Methadone Treatment Program. The director of the NCAIDS and the Director of the NIAID Division of AIDS jointly chaired the Joint Working Group. In addition to other required regulatory reviews for importation of the study drug, prior to implementation the research was approved by Institutional Review Boards (IRBs) at each site. Further, the trial was overseen by the NIAID, Division of AIDS Asia Data and Safety Monitoring Board. Concerns regarding participant risk, both medical and social, were carefully considered with the study team.

In all, 1,250 PWIDs were enrolled over a four and one half year period. Ethical challenges (both anticipated and unexpected) were faced at each stage of the trial: pre-implementation, trial conduct, and trial closure. These will be described in turn.

PRE-IMPLEMENTATION

While research planning commonly involves the need to address ethical and practical issues, HPTN 058 faced particularly complex challenges related to the vulnerability of PWIDs where HIV seroincidence rates in the population were high, legal policies were stringent, and stigma regarding injection drug use was severe.

PWIDs that would be recruited to be enrolled in HPTN 058 faced the possibility of detention and imprisonment, including being placed in “detoxification centers” (E.g., “Compulsory Residential Detoxification/Rehabilitation Centers” in China), “labor camps”, and traditional prisons. Available reports regarding conditions in many of these settings raised some human rights concerns[4]. For example, detention in detoxification centers and ‘involuntary re-education through labor’ typically involve the abrupt cessation of opiates, with or without medical supervision. Moreover, in some settings, established methods of due process did not appear to be available.

To ensure that HPTN 058 would not increase the risk of harm for those recruited and enrolled, a rapid policy assessment was commissioned and a series of community engagement activities were conducted.

Rapid Policy Assessment (RPA). The RPA included a review of national and local laws and implementation policies as well as gathering information from relevant stakeholders[5]. In accordance with the study protocol, the RPA was specifically directed at ensuring that “participants in the research [were not] at significantly elevated risk of arrest, incarceration, physical harm, unwanted disclosure of drug use, or loss of access to health care relative to injection drug users not participating in the 058 study.”[5, p.ix] While the overall RPA for HPTN 058 was coordinated in the United States, data were gathered in China and Thailand

by local experts. This independent review found that participation in HPTN 058 would be unlikely to expose participants to any *incremental* risk. For example, as stated in the report: "We conclude that while drug users in China, as elsewhere, are subject to a variety of socioeconomic and dignitary harms due to stigma and criminalization, these harms are not more likely to occur because of participation in this research as long as local law enforcement is involved in and approves of the process. In fact, enrollment may even have a protective effect if researchers successfully interface with local police"[5, p. xv]. Nevertheless, the RPA made clear that the research team would need to anticipate the possibility of changes to the legal and political landscapes at the study sites and to maintain communications with the local criminal justice systems. Accordingly, as described below, participants were regularly queried about both social risks of participation as well as detention.

Community Engagement. The initial community engagement activities for HPTN 058 consisted of community consultations, site visits, open community forums, and meetings with local IRBs. The community consultations were coordinated by the site staff and their community advisory boards (CABs) and involved both national and local stakeholders, such as government officials, activists, advocates and community members. CABs at each site were expected to include representatives from local health departments, public security and criminal justice authorities, drug users and local advocates. The initial community consultations focused on delivering information about the trial and learning about the local environment and potential barriers to participation. As the protocol was refined, finalized, and implemented, community engagement continued, which facilitated mutual implementation of the project.

These community engagement activities made clear that a major threat to recruitment to HPTN 058 would be concern among PWIDs about elevated risk of being arrested or detained by local authorities as a result of participating in the research. While the need to use standard measures to protect confidentiality were anticipated, special attention was placed on developing agreements with local authorities so that HPTN 058 participants were not at increased risk of arrest or detention. Local authorities tended to share with the HPTN 058 team the desire to minimize harmful drug use practices. This shared desire contributed to the ability of local investigators to negotiate and secure assurances from authorities that they would not target research sites and participants for surveillance. At the same time, authorities maintained discretion over what constituted a violation of local laws.

TRIAL CONDUCT

To ensure that all appropriate participant safeguards were in place, it was necessary to carefully develop standard operating procedures for each aspect of the trial. This included staff training, especially in regard to risk-reduction counseling and prescribing and monitoring of BUP/NX use; the informed consent procedures; and procedures to identify and monitor adverse events, including social harms.

The potential risks associated with HPTN 058 underscored the need for a robust informed consent process. To ensure that prospective participants had an adequate understanding of the trial procedures and risks prior to screening and enrollment, they were required to pass

an informed consent quiz that examined whether study aims, objectives, and requirements were understood. Typically, the content of these quizzes are specified by the local IRB. The HPTN 058 quiz, however, was standardized at all the sites. Potential participants were permitted three attempts to pass the quiz with a score of 80% or higher.

Although such quizzing has become commonplace in some research settings, whether it is acceptable to participants is unclear. Based on community engagement activities, the HPTN 058 research team was concerned that quizzing might be problematic given that many of those recruited had limited formal schooling. A study to assess participant attitudes to quizzing was therefore nested into HPTN 058[6]. It was found that while there were some differences across sites, the majority of participants clearly understood the rationale for quizzing and was not bothered by the quizzing process.

In addition to standard assessments of safety, HPTN 058 included a Social Impact Assessment to determine whether there were negative or positive consequences related to participation in the study. At each regularly scheduled follow-up visit (approximately every 6 months for 2 years) all participants were asked if they had problems related to: 1) police/legal problems; 2) housing; 3) employment; 4) health care/insurance; 5) friends/family; and 6) other. For each problem reported, a Social Impact Log was completed. The Social Impact Log included a description of the event. Participants were also asked whether in their view these events caused a minimal, moderate or major disturbance. Over the course of the study, only four negative social impacts were logged among the 1025 participants in the trial; three involved problems with friends and family and one involved scheduling conflicts between work and medication administration; none were rated as major and all were resolved. However, these reports markedly underestimate negative social impacts due to known incarcerations (as described below), which precluded completion of this assessment at a regular study visit. It is important to note that we have no evidence of any incarceration occurring as a direct result of participation in the study. Nevertheless, for those participants who attended follow-up visits, the vast majority reported a positive social impact related to trial participation (e.g., overall 80% of participants reported such an impact at the scheduled 26 week follow-up visit). Positive social impacts included reduction in use, better relationships, and economic improvement[7].

Although participation in HPTN 058 was not associated with a large number of reported social harms, there were some marked fluctuations in enrollment and participation as a result of both ethnic riots in Xinjiang and periodic changes in law enforcement policies over time at all sites. These political actions obviously had a profound impact on the ability to recruit new participants and to complete follow-up visits. First, the sheer turmoil associated with civil unrest made daily operations difficult, including communications within and outside the region. Nevertheless, a deeply committed research staff was able to implement creative approaches to maintaining trial procedures and transmitting data to the data coordinating center. However, the number of arrests and detention of participants obviously precluded regular follow-up. While the overall detention rate remained similar to baseline, during the intervention period (as reflected in the first semi-annual follow-up visit) the proportion of detentions decreased below baseline. However, across all sites, incarceration typically accounted for over 50% of those missing semi-annual follow-up visits.

Given the impact of these unexpected events, various options were considered to maintain the integrity of the trial, especially with respect to having adequate data regarding the primary outcomes at the final semi-annual follow-up visit. Therefore, even though the trial was designed to be community-based, one possibility that was considered was conducting follow-up visits in these closed settings. While US federal regulations permit some research in prison settings under limited circumstances[8], conducting research in these sorts of closed settings are associated with additional ethical concerns[9]. Thus, before seeking approvals to extend the study to 'prison' settings, the study team elicited information from the study sites to ensure that continuing research would not pose additional risk to the participants. Specifically, sites were asked to provide information about the relevant facilities (e.g., type, location, type of security), potential benefits and risks to conducting study visits in the facility, and ethical implications to following prisoners (e.g., loss of privacy), permissible study activities in the facility, and whether the local site thought that conducting the research in these settings was permissible. Concerns about confidentiality, the lack of ability to administer study medication and the possibility of stigma were raised in both China and Thailand. After weighing the concerns of the study staff and the amount of data to be gained, the research team chose to not pursue any effort to perform study visits in these closed settings.

The local research teams were in communication with government officials throughout the trial, enabling them to both inform officials regarding the impact of political actions and changes in enforcement on the trial, and to inquire about the rights of individuals incarcerated for non-criminal activities. These communications facilitated the implementation of existing policies that allow family members to request review of such cases, resulting in the release of most of the study participants. While this was unquestionably a welcome moment, it paradoxically raised questions regarding the voluntariness of enrollment and retention in the trial. Recall that at the outset of the trial, agreements with authorities were seen to provide a necessary protection for those enrolled. Did enrollment therefore confer an unintended 'benefit', namely, the possibility of release from closed settings for non-criminal activities? At this stage of the trial, however, enrollment was nearly complete, and it was not felt that this actually had a significant impact on the decision to enroll. Whether this influenced continued participation in follow-up visits is unclear.

TRIAL CLOSURE

The DSMB met seven times during the course of the study. Ultimately, the trial was stopped due to a much lower than expected incidence of HIV infection and death, which meant that there was insufficient power to assess the study's primary objective. Nevertheless, it was possible to address a number of other key research questions, including whether the intervention reduced the frequency of drug use and drug-related risk behaviors[3]. To design the close-out plan, an in-person meeting was held. Participants included the protocol team and representatives from the National Institutes of Health, the HIV Prevention Trials Network, each of the local IRBs and CABs, and the site leadership. There was extensive discussion about the rationale for the DSMB's recommendation to stop the trial and the most appropriate method for allowing the largest number of participants possible to complete

their assigned study interventions. Ultimately, all but a few participants were able to complete the full duration of treatment as outlined in the protocol. The guiding principles for developing the close-out plan were transparency; adherence to agreements with participants; protection of the participants well-being, including facilitating the transfer to local drug treatment programs; and maximizing scientific value.

Post-trial access to BUP/NX was also discussed as part of the close-out plan. At the outset of the trial, the manufacturer of BUP/NX had agreed to provide the medication at no cost for participants following the trial until BUP/NX received regulatory approval in the respective countries. Despite this agreement, actual implementation proved to be challenging. First, during the course of HPTN 058, BUP/NX was always delivered in combination with risk reduction counseling and close follow-up. Following the trial, there was no obvious infrastructure to provide these services. Second, there were no immediate plans to make BUP/NX part of national policies, a difficult context for obtaining the necessary import permits.

CONCLUSION

Like much clinical research, HPTN 058 encountered an array of ethical challenges, which needed to be addressed throughout the course of the trial. As a result, the study demonstrates that it is possible to perform rigorous HIV prevention research among PWIDs, one of the populations most affected by the HIV epidemic. At the same time, some of these experiences highlight the need for additional attention.

One required feature of trials conducted by the HIV Prevention Trials Network is that ethical issues are addressed as soon as protocols are approved for development[10]. Each trial has an ethics representative assigned to the protocol to help the research team and sponsor to anticipate and address ethical issues as they arise. The input provided by these ethics specialists is distinct from, and complementary to, other mechanisms of ethics and regulatory oversight and approval such the IRBs and DSMB. In this trial, the study team and funder engaged the ethics representative to help address the ethics issues encountered throughout the life-cycle of the trial, bringing to bear relevant ethics literature and analyses to supplement scientific, practical and regulatory issues as described above.

Despite what seems to be success in negotiating the majority of ethical issues encountered during the trial, most prominently that trial overall did not seem to adversely affect the rights and welfare of participants, some of the issues that surfaced warrant additional attention in the future. For instance, in research with PWIDs it is critical that research does not pose substantial additional risk or social harms. In HPTN 058 negotiations with authorities prior to the trial resulted in agreements to avoid targeting participants for enforcement of policies. Although it is impossible to know with absolute certainty that these agreements were adhered to given the number of participants who were detained by authorities over the course of the trial, there did not seem to be any indication that participants were specifically targeted. Based on the RPA conducted before the trial started, it was clear that some participants would be detained but the crucial issue was that the research did not increase this risk. Future analyses of the data will explore the relationship of detentions to relevant

variables. Regardless, what was not anticipated at the time the RPA was conducted was the ethnic unrest at one site that led to a number of detentions, but again, this was not associated with participation in the research.

As a related matter, because of the agreements of the researchers with officials, on numerous occasions as described above, study staff were in communication with government officials or facilitated the process whereby family members could request a review of the reasons for detention, which sometimes led to the release of the research participants. While we neither formally tracked such interventions nor can assume that the releases would not have occurred without intervention of the research team, if participation in anyway facilitated release from detention, there is potential reason for concern about the truly voluntary nature of participation, particularly with regard to retention. For example, did participants unwillingly feel that they needed to return for study visits in gratitude for help being released? Or did they continue to participate because they perceived participation to be a form of protection should they be detained in the future? Although we don't have evidence of such an effect on voluntariness this issue needs to be considered in future research in such settings. A crucial step would be providing data to assess the reality of these concerns. Accordingly, consideration should be given to formally tracking such interventions as well as attempting to query participants about voluntariness.

Should such perceptions exist, as an ethical matter it will be important to assess whether this poses an undue inducement? In considering this question, it is important to determine if there is a threat to participants' rights and welfare[11]. Fortunately, at least in this study, follow-up posed minimal burden and risks, mitigating such concerns.

In addition, although there has been considerable scholarship dedicated to the issue of post-trial access to interventions tested in research settings, there is clearly a need for additional work. Consistent with current scholarship and guidelines, the HPTN 058 research team had secured a pre-trial agreement for the provision of BUP/NX before the study started with the manufacturer. However, providing the medication following the trial proved to be difficult for unanticipated reasons: the lack of an infrastructure for delivering it or governmental approval for importing it. While others have reported challenges in providing post-trial access and reasons why it need not be provided in certain situations[12–14], the HPTN 058 experience should be included as deliberations about post-trial access continue. In this case, while research participants tended to like the intervention (counseling and BUP/NX), neither combined approach was found to be effective in regard to the primary study outcomes. As such, post-trial access would arguably not be required due to its lack of efficacy. Nevertheless, the manufacturer continued to be willing to provide BUP/NX to participants, but absent data regarding efficacy, local authorities were not inclined to make the necessary arrangements to implement its provision

Providing descriptions of the ethical issues encountered, whether solved or unresolved is intended to not only trigger additional conceptual and policy work, but also to provide a model for future research. In the case of HPTN 058, the RPA and community engagement activities indicated that conducting this novel trial within communities was not likely to cause incremental harm to the rights and welfare of the participants. In addition, participants

were regularly asked to report whether they experienced any adverse social impacts including detention as well as any positive social impacts that resulted from participation. Such approaches were helpful in systematically assessing the non-medical risks and benefits of research participation, which are essential ethical considerations that must be addressed in research in similar settings and with similar populations. Accordingly, those planning similar research should adopt such approaches in order to help ensure that the research is ethically sound at the outset to help determine if the rights and welfare of the participants are able to be protected. While it would be premature to offer clear guidelines regarding the range of necessary and sufficient conditions for determining whether and when such proposed research is ethically appropriate, going forward, having descriptions such as this may help in providing a solid framework upon which to develop them. In order to inform this work, future trials enrolling PWID who are at risk of detainment should identify ways of mapping closely their experiences and perceptions in order to better apprehend the ethical issues at stake. In addition, scholarly and policy work needs to address the ethical issues related to post-trial access to multi-modal interventions that are desired by participants but are not shown to be effective in terms of the primary outcome of the trial.

Such work should help to enhance the next generation of HIV prevention trials with PWIDs so that desperately needed approaches to HIV prevention among PWIDs can be safely and appropriately tested.

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References

1. Joint United Nations Programme on HIV / AIDS (UNAIDS), World Health Organization (WHO). UNAIDS / WHO Guidance Document. Geneva: UNAIDS and World Health Organization; 2007. UNAIDS / 07.28E / JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. Available at: http://data.unaids.org/pub/Report/2007/JC1399_ethical_considerations_en.pdf
2. Beyrer C, Malinowska-Sempruch K, Kamarulzaman A, Kazatchkine M, Sidibe M, Strathdee SA. Time to act: a call for comprehensive responses to HIV in people who use drugs. Lancet. 2010 Aug 14; 376(9740):551–63. [PubMed: 20650515]
3. Metzger, D.; Donnell, D., et al. One year of counseling supported buprenorphine-naloxone treatment for HIV prevention in opiate dependent injecting drug users showed efficacy in reducing opiate use and injection frequency: HPTN 058 in Thailand and China. Poster abstract presented at the 19th International AIDS Conference; Abstract no. THPE191. Available at: http://www.iasociety.org/Abstracts/A200747265.aspx
4. Jürgens R, Csete J, Amon JJ, Baral S, Beyrer C. People who use drugs, HIV, and human rights. Lancet. 2010 Aug 7; 376(9739):475–85. [PubMed: 20650514]
5. Family Health International. HPTN 058: Rapid policy assessment for China and Thailand. Research Triangle Park, NC: Family Health International; 2007.

6. Sugarman J, Corneli A, Donnell D, Liu TY, Rose SM, Celentano DD, Jackson JB, Aramrattana A, Lui W, Shao Y, Fu L, Rui B, Dye B, Metzger D. Are there adverse consequences of quizzing during informed consent for HIV research? J Med Ethics. 2011; 11:693–697. [PubMed: 21653649]
7. Sugarman, J.; Bokoch, K.; Stalter, R.; Liu, T-Y.; Donnell, D. for the HPTN 058 Study Team. Positive social impacts related to participation in a multinational HIV prevention trial involving medication assisted treatment of people who inject drugs. (Poster TUPE387) International AIDS Society Meeting; Kuala Lumpur. 2 July 2013; Available at: http://pag.ias2013.org/EPosterHandler.axd?aid=494
8. US Code of Federal Regulations, Title 45, Part 46, Subpart C, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.
9. Saucier R, Berlinger N, Thomson N, Gusmano M, Wolfe D. The limits of equivalence: ethical dilemmas in providing care in drug detention centers. Int J Prisoner Health. 2010; 6(2):81–87.
10. Rennie, S.; Sugarman, J. HPTN Ethics Working Group. Ethics guidance document for research, HIV Prevention Trials Network. Available at: http://www.hptn.org/web%20documents/EWG/HPTNEthicsGuidanceV10Jun2009.pdf
11. Emanuel EJ, Currie XE, Herman A. Project Phidisa. Undue inducement in clinical research in developing countries: is it a worry? Lancet. 2005; 366:336–40. [PubMed: 16039339]
12. Grady C. The challenge of assuring continued post-trial access to beneficial treatment. Yale J Health Policy, Law, and Ethics. 2005; 5(1):Article 15. Available at: http://digitalcommons.law.yale.edu/yjhple/vol5/iss1/15.
13. Shah S, Elmer S, Grady C. Planning for posttrial access to antiretroviral treatment for research participants in developing countries. Am J Public Health. 2009; 99(9):1556–62. [PubMed: 19608940]
14. Sofaer N, Strech D. Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: a systematic review. Public Health Ethics. 2011; 4(2):160–184. [PubMed: 21754950]