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Planning for Posttrial Access to Antiretroviral Treatment for Research Participants in Developing Countries

Seema Shah, JD, Stacey Elmer, BA, and Christine Grady, RN, PhD

Despite recognition of the importance of posttrial access to antiretroviral therapy (ART), the implementation process has not been studied. We examined whether the National Institutes of Health (NIH) guidance document was being implemented in NIH-funded ART trials conducted in developing countries between July 2005 and June 2007.

All of the 18 studies we identified had posttrial access plans for trial participants. More than 70% had specific mechanisms for posttrial access, but none guaranteed long-term sponsor funding after the trials. The plans reflected variation in local contexts and the uncertainty of predicting local conditions in the long term.

The strength of the NIH guidance document may be that it encourages investigators to formulate plans in advance and to work with other stakeholders to provide access to ART. (*Am J Public Health.* 2009;99:1556–1562. doi:10.2105/AJPH.2008.157982)

INTERNATIONAL COLLABORA-tive research, especially when conducted in communities or countries with limited health care infrastructure, is beset with ethical challenges. One particularly controversial issue is whether and how to ensure continued access to study interventions for research participants after a trial. Until recently, the issue of posttrial access was absent from ethical codes or guidelines for clinical research. Ethics guidance documents,[1] reports,[2,3] and national guidelines[4–7] only began to address participant posttrial access to study interventions in 1997.

The World Medical Association's Declaration of Helsinki added a controversial new paragraph in the 2000 revision:

> At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.[1]

In the 2008 revision, the association backed away from this strong language. It now states only that researchers should describe posttrial access arrangements in the protocol and that participants are entitled to be informed about the study outcome and to share in any benefits.[1] Reports on the ethics of international research by the US National Bioethics Advisory Commission and the United Kingdom's Nuffield Council each devote an entire chapter to what should happen after a research study.[2,3] They concluded that it was essential—although complicated—for research stakeholders to negotiate and plan for posttrial access.

In the United States, the National Institutes of Health (NIH) is the primary government agency responsible for conducting and supporting medical research and the largest funder of research on HIV/AIDS in the world. The overall NIH budget for fiscal year 2007 was US $29.5 billion, of which $2.9 billion was spent on HIV/AIDS.[8] Increasingly, NIH-supported HIV/AIDS research is conducted in collaboration with researchers and communities in developing countries. According to the NIH, an explicit goal of this research is "improv[ing] the health of people living with HIV/AIDS, particularly people in countries most affected by the epidemic."[9] One pivotal part of this research is testing antiretroviral drugs and regimens.

Recognizing an ethical responsibility to address what happens to participants at the end of a trial and the importance of continued effective antiretroviral therapy (ART) for participants enrolled in HIV trials, the NIH Office of AIDS Research convened a group of scientists from across the NIH to address this issue. The result was a guidance document published in March 2005 regarding posttrial availability of ART.[9] This document explained the NIH's expectations for individuals seeking NIH funding through a grant or contract, stating that:

> [f]or antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial.[9(pl)]

However, the guidance noted expressly that "NIH's authority to 'encourage and support research' does not extend to providing treatment following the completion of that research." The guidance further recommended that investigators and contractors work with host countries' authorities and other stakeholders to identify available sources of ART.

Plans for posttrial access to ART are reviewed by NIH program staff and considered in decisions about site selection and study implementation. In July 2005, the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases issued template consent language indicating that, for studies of drugs or agents, posttrial access is to be discussed with participants who are benefiting from the study intervention.

We encountered anecdotal evidence of an investigator who planned to raise funds by selling artwork from the host country in the United States to help pay for posttrial ART for research participants, prompting us to explore this issue further (T. Campbell, MD, oral communication, October 25, 2006). Despite considerable recognition of the importance of posttrial access, implementation of the guidelines has not been studied. To better systematically understand how posttrial access has been implemented in light of the NIH guidance, we reviewed posttrial access plans in HIV/AIDS research funded by the NIH. Our examination of the data reveals both lessons learned and issues that remain unresolved in the design of posttrial access policy.

METHODS

To identify protocols subject to the NIH guidance on posttrial access, we searched the DAIDS Enterprise Information System, a centralized database for clinical trial protocols managed or supported by DAIDS, on June 19, 2007. This search identified all protocols from DAIDS clinical trials networks and investigator-initiated grant mechanisms that (1) included ART as a study agent; (2) were in the protocol status of pending, open to accrual, enrolling, or closed to accrual (i.e., trials that were proposed, in development, or had been withdrawn at the time of the search were excluded from the sample); and (3) were open to foreign sites (whether conducted in a foreign site only or in both US and foreign sites). We then narrowed the list to the protocols that were subject to the March 2005 ART guidance and the July 28, 2005, informed consent template language issued by DAIDS.[10]

We examined protocol documents and sample informed consent forms, obtained from the Enterprise Information System, for language addressing the guidance. Relevant keywords or phrases included *after the study*, *upon completion of the study*, and *posttrial*. We coded protocols according to whether they included (1) no statements about posttrial access, (2) a statement that ART would not be provided by the study after its completion but that study staff would discuss posttrial access with participants if it would be of benefit to them, (3) a description of at least 1 mechanism for posttrial access to which study participants would be referred, or (4) a referral to another source for posttrial access plus additional efforts to secure access.

In addition to the protocol or sample informed consent form, some study materials included letters sent to DAIDS that addressed posttrial access; we obtained and analyzed all of these letters. Most of the letters were written by principal investigators at the site, doctors from clinics near the site, members of the ministry of health in the host country, or US investigators. We also obtained site-specific consent forms for a subset of the sample and coded them by the same system we used for the protocols.

RESULTS

We identified 18 HIV studies involving ART that were subject to the March 2005 NIH guidance and to the DAIDS July 28, 2005, informed consent template language regarding posttrial access to ART. The studies were conducted in the United States and 14 other countries, including more than 96 sites in developing countries. The majority of these studies were conducted solely in developing countries and targeted participants who had never received ART before enrolling in research. Nine studies involved adults only, 5 involved adults and children, and 4 involved children only. Participants received ART as part of the study for periods ranging from 12 weeks to 5 years; two thirds of the studies treated and followed participants on ART for more than 1 year (Table 1).

All 18 studies addressed the issue of posttrial access for trial participants. All but one of the studies discussed posttrial access in the protocol or the included sample informed consent form. For the one study that did not address posttrial access in the protocol, site-specific plans for access were addressed in letters sent to DAIDS.

More than 70% of the studies (13 of 18) identified mechanisms through which posttrial access could be obtained. Protocols, consent forms, and letters for 9 studies included language assuring participants that they would have posttrial access to ART. For example, one stated that participants who completed clinical trials at the site "would be eligible for access

TABLE 1—Antiretroviral Studies Subject to NIH Guidance on Posttrial Access to ART in Developing Countries, 2005–2007

	No. of Studies
Study population	
Children	4
Children and adults	5
Adults	9
Treatment history of participants	
ART naïve	14
ART experienced	2
Either allowed	2
Duration of study	
<6 mo	2
≥6 mo to 1 y	4
>1 y to 3 y	7
>3 y	5
Countries involved	
Botswana	1
Brazil	4
Cambodia	2
Haiti	2
India	4
Kenya	1
Malawi	4
Peru	2
Senegal	1
South Africa	10
Thailand	4
Uganda	2
United States	4
Zambia	2
Zimbabwe	3
Country-specific study	
Single nation	10
Multinational	8

Note. NIH = National Institutes of Health; ART = antiretroviral therapy.

to antiretroviral medications under the Ministry's ART Access Programme." One study simply indicated that participants could purchase their drugs at a clinic for the equivalent of US$30 to US$150 per month. Five studies incorporated the template language provided by DAIDS, which states that the study will not be able to provide ART after trial participation is complete, but "[i]f continuing to take these or similar [insert drug(s), agent(s), and so on.] would be of benefit to you, the study staff will discuss how you may be able to obtain them" (Table 2). Template consent language was also contained in site-specific informed consent forms for one of these studies. Although no study guaranteed long-term funding of posttrial access to ART by the study sponsor, one study indicated that the sponsor would provide a 2-month supply of ART to ensure that participants would continue therapy in the time between ending study participation and enrolling in an ART access program. Another study indicated that unused and unopened study drugs would be provided to participants after the study.

Half of the studies contained descriptions of posttrial access plans that included coordination with external funding sources such as the President's Emergency Plan for AIDS Relief, the Global Fund, or nationwide access programs created by the governments of the host countries. No study indicated that former research participants would receive priority access over any other individuals in these programs (Table 2). Three studies identified other external funding mechanisms. For example, several letters for one study listed more than one avenue for obtaining posttrial access, including public sector hospitals, nongovernmental organizations supported by the Global Fund, employer-based health insurance, and enrollment in other research studies. A few studies addressed how drugs available through external funding mechanisms would complement drugs provided in the study. For example, one study listed the drugs offered through the government program and noted, "The use of the . . . study drugs is not likely to compromise response to subsequent treatment with the ARVs that are available within the government ART program."

A few studies went beyond the requirements of the guidance and addressed other issues relevant to posttrial access. For instance, one study created an immediate catchment system to provide access to ART for participants who withdrew from the study prematurely. One multisite study indicated that at 4 of its 12 sites, participants would be provided with long-term posttrial supplemental care through local public clinics or a national health program—care such as monitoring of immune function and providing prophylaxis against or treatment of opportunistic infections. The provision of care ranged from 3 to 5 years. Of note, one of these sites planned to explore the feasibility of raising money from local philanthropists and large companies to provide ART to participants. We also identified 3 prevention trials that explicitly identified avenues for posttrial access; these were not incorporated in our analysis because they were not subject to the guidance provided by NIH.

DISCUSSION

Our review demonstrates that NIH-funded HIV investigators studying ART drugs in developing countries are addressing the issue

TABLE 2—Sample Language Concerning Post-trial Access to ART in NIH-Funded Antiretroviral Studies in Developing Countries, 2005–2007

Category[a]	Sample Language
2. No provision of ART by the study, but posttrial access to be discussed with participants if it would be beneficial to them	"After your child has completed study participation, the study will not be able to continue to provide your child with the study medicines that he/she took during the study. If continuing to take these or similar medicines would be of benefit to your child, the study staff will discuss how you may be able to obtain them."
	"Once the study is over, the study will no longer provide you with anti-HIV drugs. At that time, you may have to stop a drug combination that has worked well for you, either because you cannot afford the treatment or because those drugs are not available in your country. Efforts will be made by your doctor to find a way to continue ART drugs after the study is over. Continued treatment cannot be guaranteed."
3. Referral to other programs that offered ART	"After completion of the study, the study team will arrange for your child to receive treatment as he/she is entitled to as part of the treatment program by the Ministry of Public Health. Your child may take part in other studies that he/she is eligible for. The study doctors and the nurses will suggest these options for you to decide."
	"Widespread use of HAART in South Africa is a rapidly evolving issue. At [1] site, HAART is now available to employees of [a mining company] through the mine health services, based on clinical criteria and at no cost to the patient. This program is a long-term commitment of the mining industry, and will be available after the study is completed. The Western Cape Province has put a HAART access plan into effect that is allowing implementation of wide coverage for prevention of mother to child transmission of HIV with nevirapine, HAART post-exposure prophylaxis for individual victims of rape, and affordable HAART regimens for individuals with WHO clinical stage 3 or 4. The provincial government will provide all drugs after the study if the current donation program is unable to do so."
	"We recognize that as a research institution there is a large number of clients who will be identified as HIV positive through the implementation of their research studies. Just as we would accept any HIV positive client referral, we welcome all HIV positive clients that are referred from their studies and provide the same quality care to these individuals."[b]
4. Referral for provision of ART with additional efforts to secure access	"At the end of the trial, patients will be integrated into the regular HIV/AIDS program. . . . Measures and insurance . . . have been taken to ensure that ARV medications are still available for all study participants after the study ends."
	"At the end of the study, each HIV infected participant will have an access to posttrial care. This care will include primary HIV/AIDS clinical care, prophylactic treatment to prevent opportunistic infections, referral for treatment of opportunistic infections to appropriate Government hospitals and the monitoring of immune function. We are making efforts to provide an access to ART if clinically indicated. We shall seek the help in this regard by the [local authorities]. . . . We are also planning to explore networking with various organizations to procure financial support to patients for ART. Lastly we are hoping to raise a corpus of funds with the help of local philanthropists and industrial houses that can be used to provide ART."

Note. NIH = National Institutes of Health; ART = antiretroviral therapy; HAART = highly active antiretroviral therapy.
[a]Category 1 was not included because it designated study protocols that did not have language about posttrial access. None of the studies in our sample fell into this category.
[b]From a letter sent by a health care institution.

of posttrial access and thereby complying with the NIH guidance. The guidance states that the NIH expects investigators and contractors to address the provision of ART to trial participants after trial completion. Compliance with the guidance ranged from incorporating the DAIDS template language into study protocols to identifying explicit funding mechanisms and guaranteeing transitional posttrial access. Consistent with this guidance, no studies guaranteed NIH funding for posttrial access to ART. The majority of the studies identified external funding mechanisms available in developing countries, rather than funding from sponsors or the NIH. Although one study guaranteed 2-month transitional access, no study guaranteed long-term posttrial access.

Our data suggest 4 conclusions that may help inform the development of future posttrial access policies: (1) plans for posttrial access in part reflected variation in local contexts and resources, (2) most studies partnered with external funding sources and institutions, (3) some investigators went beyond what the guidance required, and (4) plans for posttrial access were affected by the uncertainty of predicting long-term local conditions. These conclusions further lead us to raise critical, unresolved questions

about the nature of the obligation for posttrial access.

First, to some degree, our findings reflected variation in local contexts and available resources, particularly in whether the host countries had established national ART or health care programs. For instance, studies conducted in Brazil could rely on the Brazilian government's provision of national health care and ART to ensure posttrial access for participants. By contrast, researchers conducting studies in countries without a system of access to ART must work harder to develop plans for posttrial provision of care. The study that informed participants they could purchase their drugs at a clinic for the equivalent of US $30 to US $150 per month, for example, was conducted in a country without a national plan to provide ART.

Rather than limiting research to countries in which posttrial access can be guaranteed, the guidance states that plans for posttrial access will be taken into account in awarding research grants and contracts. It is important to note that, if the guidance had made posttrial access an absolute requirement for conducting research, research might only be conducted in countries where posttrial access is feasible. This could prevent researchers from interacting with those who may be most in need and who have the fewest resources, thus denying these potential participants and communities a chance to benefit from research.

Second, requiring provisions for posttrial access encourages partnership with local governments and other organizations. The NIH guidance specifically suggests partnering with existing programs and local officials to anticipate the needs of trial participants together. The majority of investigators in our sample appeared to have engaged in this form of collaborative partnership. This approach may help local officials prepare for trial participants' needs at the conclusion of a trial and appropriately incorporate research results into their health care system. Furthermore, by permitting some flexibility in how access will be achieved, the NIH guidance may enable the development of access plans that are likely to be sustainable long after the research is completed. The Declaration of Helsinki's revised position on posttrial access similarly allows increased flexibility by encouraging researchers to describe posttrial arrangements in the protocol and by stating that participants are entitled to share in the benefits of the study, without requiring more specific details. However, it does not address the importance of collaboration and partnership in creating long-term and enduring mechanisms for posttrial care.

Third, a few investigators in our sample creatively considered issues beyond those the guidance addressed. Some of their initiatives, such as creating systems for participants who withdraw from research prematurely, continuing to provide supplemental or ancillary care for up to 5 years, and providing treatment to participants while they transition to other sources for ART, suggest possibilities for future policy directions. It is important to note, however, that some mechanisms, such as providing unused study drugs to participants, may not be permitted by some funding organizations. We also found 3 trials that had plans for posttrial access even though they were not subject to the NIH guidance, which could indicate that the guidance has had spillover effects or that there is increasing emphasis in the field on the importance of posttrial access.

Finally, some study protocols were careful to point out that planning for access requires some prediction of the local context and funding mechanisms available years from the time the study begins, which are unpredictable in many developing countries. One protocol stated,

> It should be noted that it is impossible to predict exactly how posttrial care will be provided once the study ends (up to five years from now) especially in the rapidly progressing political environment.

Negotiating posttrial access in advance may help stabilize existing programs by allowing them to anticipate needs and reduce (but not eliminate) future uncertainty. Treatment of HIV and AIDS is a moving target characterized by significant change, hurdles, and progress and one that involves a large and diverse network of players. The uncertainty involved in addressing posttrial access makes the task difficult, but how such uncertainty affects the nature of posttrial obligations is unclear.

These observations lead to a fundamental, important, and unresolved question: What is the nature and extent of the obligation to provide posttrial treatment access? To date, there is no satisfactory account in the literature of what justifies posttrial obligations and who bears them, although several possibilities have been suggested. Some claim that obligations for posttrial access arise because researchers or sponsors working in developing countries interact with research participants with great need.[11] Others argue that people from developed countries may have obligations to rectify past (historical) injustices imposed on people from developing countries or ongoing injustice in the current world order.[12] Alternatively, research sponsors and researchers may have duties of reciprocity if participants have taken on risks to generate research findings.[13] Researcher obligations may also stem from the thus far indeterminate risk of causing harm if participants develop resistance to ART.[2,14,15] If trial participants do not have access to nationwide programs when their study participation is concluded, they will likely experience an interruption in their treatment and may have resulting complications. Does the harm from treatment interruption at the end of the research outweigh the benefit of obtaining early treatment through the research? Without an answer, it is unclear whether conducting such research creates an obligation to rectify harm.

Although there is no consensus regarding who bears what responsibility, it is likely that several different parties bear some measure of obligation toward research participants after a study is over. The extent to which these

obligations are affected by other considerations, such as scarcity of resources in the host country, the risk–benefit ratio of the study, and the depth and length of the investigator–participant relationship, remain undetermined.

Limitations

We examined only trials of antiretroviral drugs sponsored by DAIDS and therefore did not consider research on other conditions, treatments, and types of interventions or studies with other funding sources. The data were derived from paper submissions to DAIDS and therefore may not have included creative strategies for addressing posttrial access that investigators did not describe in their protocols, consent documents, or letters sent to DAIDS. We did not capture all site-specific plans developed by investigators because we did not have access to site-specific informed consent forms for the entire sample. We also did not have data to assess what effect the guidance might have had on site selection.

Our purpose was not to collect information about whether the plans that the investigators developed were likely to be effective or were carried out, and many of the studies in our sample were multiyear studies that are still ongoing. For these reasons, our data do not address whether the reported compliance with the guidance satisfied its stated goal—that participants in treatment trials continue to receive effective ART after the study. Investigating the actual effect of the NIH guidance on individual participants and surveying review committees to better understand their involvement in the development and follow-through of plans for posttrial access may be promising avenues of future research.

Conclusions

All DAIDS protocols we studied fell under the NIH guidance addressed the provision of posttrial access to ART. The strength of the NIH guidance is that it encourages investigators to think in advance about posttrial access for the participants of ART trials and collaborate with existing entities to facilitate access to needed therapy. The flexibility of the NIH guidance facilitates learning about unintended consequences and practical difficulties, a more effective strategy than imposing requirements with which investigators may or may not be able to comply. The guidance encourages investigators to contact ministries of health or other ART access programs well in advance of the need for posttrial access, which could prompt local officials to anticipate trial participants' needs and increase the chances that the plans for posttrial access will endure. Communication with local officials is likely to have the more general effect of fostering collaborative partnerships that support and sustain the ethical conduct of international research. Although many questions about posttrial obligations remain unanswered, responding to the HIV/AIDS epidemic has required groundbreaking solutions to many difficult problems, and addressing posttrial access appears to be no exception. ■

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Contributors

S. Shah and C. Grady originated the study, analyzed data, and drafted the article. S. Shah and S. Elmer collected the data. S. Elmer helped with data entry.

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Human Participant Protection

No human participants were involved in this study, and therefore no protocol approval was required.

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Ethical Considerations in HIV/AIDS Biobehavioral Surveys That Use Respondent-Driven Sampling: Illustrations From Lebanon

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Respondent-driven sampling is especially useful for reaching hidden populations and is increasingly used internationally in public health research, particularly on HIV. Respondent-driven sampling involves peer recruitment and has a dual-incentive structure: both recruiters and their peer recruits are paid.

Recent literature focusing on the ethical dimensions of this method in the US context has identified integral safeguards that protect against ethical violations. We analyzed a study of 3 groups in Lebanon who are at risk for HIV (injection drug users, men who have sex with men, female sex workers) and the ethical issues that arose.

More explicit attention should be given to ethical issues involved in research implementing respondent-driven sampling of at-risk populations in developing countries, where ethical review mechanisms may be weak. (*Am J Public Health.* 2009;99:1562–1567. doi:10.2105/AJPH.2008.144832)

RESPONDENT-DRIVEN SAM-pling is a relatively new technique that has been effective in sampling difficult-to-reach or invisible populations for which there is no sampling frame.[1–3] This chain-referral method—led by network peers—was developed to avoid many of the problems and biases of other such methods (e.g., snowball sampling). Respondent-driven sampling begins with nonrandomly selected seeds and proceeds in waves: the first wave of participants is referred by seeds from their social networks, the second wave by the first-wave participants, and so on. Critically, for ethical considerations, respondent-driven sampling operates with a dual-incentive structure in which a modest financial incentive is given to all who complete the survey (primary incentive) as well as to recruiters (secondary incentive).

Developed initially in the United States as a method for reaching injection drug users (IDUs),[4] respondent-driven sampling is being widely adopted in developing countries for HIV prevention research among a range of vulnerable groups and for other areas of public health research. This method has been used in more than 30 countries.[5] The literature includes papers about both the method itself[6,7] and findings from respondent-driven sampling studies,[8–12] but discussions of the ethical aspects of such studies have appeared only recently and only in relation to US contexts and studies of IDUs.[5,13] As Semaan et al. acknowledged, social and cultural factors may affect the ethical considerations of respondent-driven sampling studies in other countries.[5] Addressing these concerns is especially important when research is conducted in places where national ethical boards are weak or nonexistent.

We examined ethical concerns arising from an HIV biobehavioral study that used respondent-driven sampling with 3 population groups at high risk of HIV exposure in Lebanon: IDUs, female sex workers, and men who have sex with men (MSM). During the course of this study, which was approved by a university institutional review board, ethical dilemmas emerged. Here we review the recent international literature on ethical dimensions of respondent-driven sampling, describe the methodology of the Lebanese study, and discuss ethical issues we confronted that may be relevant to other respondent-driven sampling studies, particularly in developing countries.

ETHICAL IMPLICATIONS OF RESPONDENT-DRIVEN SAMPLING

In a review of ethical and regulatory considerations in HIV prevention studies that use respondent-driven sampling, coauthored by Douglas Heckathorn, originator of the method, Semaan et al. described 4 integral safeguards that help to prevent ethical