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Investigators' Responsibilities for Human Subjects in Developing Countries

Most people agree that investigators assume some responsibility for their human subjects, but how much? And does it matter where the research is carried out? These issues are raised by the report by Quinn et al. elsewhere in this issue of the *Journal* [1] and by an earlier paper in the *Lancet* [2] concerning another phase of the same project.

The project was carried out in 10 clusters of rural villages in Uganda to delineate the risk factors associated with heterosexual transmission of the human immunodeficiency virus type 1 (HIV-1). Villagers (including pregnant women) were surveyed on five occasions at 10-month intervals. The first goal of the project was to determine whether sexually transmitted diseases such as syphilis and gonorrhea increase the risk of HIV infection. To study that question, the investigators gave residents of 5 of the 10 clusters intermittent antibiotic treatment to reduce the prevalence of sexually transmitted diseases. At each survey, villagers were asked about their sexual practices and medical histories, and blood and other body fluids were taken for testing for HIV-1 and sexually transmitted diseases. As reported in the *Lancet* paper,[2] antibiotic treatment reduced the prevalence of other sexually transmitted diseases, but not the incidence of HIV-1. The current report focuses on the relation between viral load and heterosexual transmission of HIV-1 in couples discordant for HIV-1 status at base line. Not surprisingly, an increasing viral load in the initially HIV-1–positive partner was associated with a greater risk of transmission. In addition, circumcision was found to be protective in male partners. The scientific and clinical implications of these findings are discussed elsewhere in this issue of the *Journal*.[3]

It is important to be clear about what this study meant for the participants. It meant that for up to 30 months, several hundred people with HIV infection were observed but not treated. It was also left up to the seropositive partner in couples discordant for HIV-1 to decide whether the seronegative partner

would be informed, even though both were regularly seen by the investigators. In addition, many people who were found to have other sexually transmitted diseases were left to seek their own treatment. For example, those who lived in the five village clusters given mass antibiotics also received immediate intramuscular penicillin G benzathine if they had a positive serologic test for syphilis, but in the other five clusters, such people were simply referred to free government clinics. Such a study could not have been performed in the United States, where it would be expected that patients with HIV and other sexually transmitted diseases would be treated. In addition, in most states it would be expected that caregivers would see that seronegative partners were informed of their special risk.[4]

Whether research conducted in developing countries should be held to different standards from those applied in the developed countries is a subject of intense debate.[5,6,7,8,9,10,11] Many believe that investigators do not need to provide better care for human subjects than is generally available in the community from which the subjects are drawn. Thus, it is argued, since Ugandans in rural villages generally cannot obtain antiretroviral treatment, they need not be treated for HIV within research studies, even though the investigators could easily provide the drugs. As Quinn et al. say, "Antiretroviral drugs are not available in rural Uganda. Consequently, the HIV-1 RNA levels were not influenced by the use of antiretroviral drugs."[1] As for informing seronegative partners of their risk, Quinn et al. make it clear that they advised seropositive partners to inform their partners (they also provided free condoms), but they did not ascertain whether the seropositive partners actually did so. They cite the policy of the Ugandan government to explain why they themselves did not inform the seronegative partners.

The ethical standards, then, were indeed different from those that would govern research in developed countries. In this regard, the study of Quinn et al. is hardly unique. Many studies in developing countries now use a similar rationale for observing subjects for outcomes that could be prevented. That was true, for example, of the well-publicized trials comparing zidovudine with placebo for the prevention of the transmission of HIV from pregnant women to their infants.[5,7] Despite the fact that such studies would not be permitted in developed countries, they have generally been approved by the relevant ethics-review bodies, in both the host country and the sponsoring country, and efforts are under way to revise international codes of ethics to bring them into line with this practice.[9,10]

Many people believe that the different standards are justified not only by the local economic conditions, but by the special relevance of the studies to the regions in which they are conducted. Thus, the research on HIV in sub-Saharan Africa can be justified by the extraordinary devastation caused by the epidemic there. I agree that research should be relevant to the population from which the subjects are drawn. Unfortunately, that may seldom be the case in developing countries. For example, Quinn et al. found that the risk of heterosexual transmission correlated with viral load, but how will that information be used in Uganda? The very condition that justified doing the study in Uganda in the first place — the lack of availability of antiretroviral treatment — will greatly limit the relevance of the results there. As is so often the case, the results will probably find their greatest application in the developed world.

Given the inevitable concerns about the study by Quinn et al., why was it accepted for publication in the *Journal?* For me, the decision was admittedly a very difficult one. The study had been approved by the

AIDS Research Subcommittee of the Uganda National Council for Science and Technology, the human-subjects review boards of Columbia University and Johns Hopkins University, and the Office for Protection from Research Risk of the National Institutes of Health. The subjects were said to have given oral informed consent (although interviews with subjects of similar studies have indicated that it is very difficult for them to understand that they may not receive effective treatment within the study[12]). After its submission to the *Journal,* the paper was approved not only by the outside peer reviewers, but also by the relevant editors on the *Journal* 's staff. When the paper crossed my desk for final approval, I asked two prominent ethicists who are familiar with research on HIV in developing countries to review it. One thought the study was not ethical; the other thought it was. In the face of these divergent opinions and the favorable views of the other editors and reviewers, I decided to approve publication.

I hope that publication of this paper will once again focus attention on the vexing ethical issues raised by this sort of study. The questions discussed below, in particular, need much more attention.

Codes of ethics governing research on human subjects require that investigators put the welfare of their subjects above the interests of science and of society,[13] but what does that mean in practical terms? Does it mean only that investigators will not harm their subjects in the course of the research? Or does it mean that investigators undertake a broader responsibility for their subjects' welfare that includes trying to treat illnesses that afflict them, even those under study? If the requirement is simply not to do harm through the research, how can investigators make that limited responsibility clear to their subjects and still ensure their cooperation? Most people, after all, naturally look on doctors primarily as healers, not research scientists.

Does it matter whether the illness studied is difficult or expensive to treat? Treating HIV infection in rural Uganda would indeed be both difficult and expensive, and at best, the treatment would only stave off AIDS for the duration of the study, not prevent it altogether. Treating syphilis, on the other hand, is relatively simple and inexpensive. In the study by Quinn et al., should all the other sexually transmitted diseases have been treated by the investigators, but not HIV-1 infection? If the expense of antiretroviral therapy justifies not offering it to subjects in certain parts of the world, should that expense be accepted as immutable? Or should we look more closely at the pricing decisions of the manufacturers of drugs protected by patents and the possibility of competition from generic drugs in developing countries?[14]

The argument that certain subjects are no worse off than if they were not in the study implies that ethical standards governing research should vary with the political and economic conditions of the region. Should they? The answer will depend to some extent on how one sees the limits of the investigators' responsibility. If investigators are responsible for the subjects they enlist in their studies, and only those subjects, then the conditions of the surrounding community are irrelevant. They must do their best for their subjects, regardless. If, however, it is within the purview of investigators to consider the entire population, then perhaps it is inequitable to give research subjects better treatment than their neighbors would receive outside the study.

I believe, as I have argued elsewhere,[6,15] that our ethical standards should not depend on where the research is performed. I also believe that investigators assume broad responsibility for the welfare of the

subjects they enroll in their studies — a responsibility analogous to that of clinicians. That would mean treating illnesses, even if they are not directly caused by the research. Furthermore, I believe that the nature of investigators' responsibility for the welfare of their subjects should not be influenced by the political and economic conditions of the region. It would follow that those conditions should not be used to justify a lower standard of care for some subjects. In practical terms, any other position could lead to the exploitation of people in developing countries in order to conduct research that could not be performed in the sponsoring countries.

I acknowledge, however, that all of these questions are debatable, and that there may be few answers that apply to every situation. What is important is that the issues be explored honestly, not defensively, and that the answers reflect moral reasoning, rather than simply expediency.

Marcia Angell, M.D.

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