The Ethics of Research in Developing Countries

To the Editor: The editorial by Dr. Angell (March 30 issue) that accompanied our article conflated two Rakai Project studies. We conducted a community-based, randomized trial of sexually transmitted disease (STD) control for the prevention of human immunodeficiency virus (HIV) infection in the Rakai district of Uganda, involving 15,127 persons. We subsequently performed a secondary analysis of HIV viral load in 415 retrospectively identified couples in which one partner was HIV-positive and one was initially HIV-negative.

In her editorial, Dr. Angell suggests that the HIV-positive study participants could have been treated with antiretroviral drugs. This is incorrect. The STD trial conducted surveys at 10-month intervals in 56 dispersed rural communities between 1994 and 1998. Antiretroviral monotherapy is of limited value, combination therapy was not described until 1996, and the results of definitive trials were reported only in 1998. Most important, neither we nor the Ugandan government had, or currently have, the clinical capacity to manage antiretroviral treatment, including side effects and compliance. The study was approved by four institutional review boards (IRBs) in Uganda and in the United States and was monitored by a data safety and monitoring board of the National Institutes of Health, which included Ugandan representatives. None of these boards recommended the use of antiretroviral agents in this rural setting.

Dr. Angell notes that “in most states it would be expected that caregivers would see that seronegative partners were informed of their special risk,” even if the HIV-sero-positive partners had not agreed to the disclosure. Participants in the study in Uganda consented to enrollment as individuals, not as couples, and involuntary disclosure of the results of HIV tests would have breached the confidentiality guaranteed as part of the informed-consent process. Ugandan policy states, “It is the right of the patient to decide who else to inform about their results,” because of concern about stigma, discrimination, and violence resulting from involuntary disclosure. Involuntary disclosure would also have undermined trust in the national program of confidential HIV testing and counseling, a cornerstone of Uganda’s successful HIV-prevention policy. We promoted and provided voluntary, confidential, free HIV testing and counseling; strongly encouraged persons who underwent testing to share the results with their partners; offered counseling for couples on request; and provided free condoms and health education. Dr. Angell cites U.S. guidelines recommending involuntary disclosure, which were published after the trial ended and which are not uniformly accepted in this country.

Dr. Angell implies that we offered substandard care to the members of the control group in the STD trial. This is incorrect. For example, the results of tests for syphilis were made available in both study groups, with home treatment offered to members of the intervention group and referrals to government clinics, which were stocked with free penicillin by the Rakai Project, offered to members of the control group. Syphilis in pregnant women declined by 70 percent in both groups. At the time of each survey, we provided free treatment for symptomatic subjects in both groups. At the end of the trial, members of the control group were offered home-based antibiotic therapy identical to that provided in the intervention group. We agree with Dr. Angell that investigators should “provide better care for human subjects than is generally available in the community.” In both study groups, the care provided far exceeded that available in rural Uganda and in many states in this country.

Dr. Angell questions the relevance of our studies to Uganda. Evaluating the control of STDs for the prevention of HIV infection was directly relevant to Ugandan policy. The secondary finding of reduced rates of HIV transmission with lower viral loads provides an impetus for the development of safe, effective, simple, and affordable strategies.
gies (use of antiretroviral agents or vaccines) to control the spread of HIV by reducing viremia. The relevance and ethics of research performed in developing countries need to be addressed in well-informed international forums.

RONALD H. GRAY, M.D.
Johns Hopkins University
Baltimore, MD 21205-2196

THOMAS C. QUINN, M.D.
National Institute of Allergy and Infectious Diseases
Bethesda, MD 20892

DAVID SERWADDA, M.B., Ch.B.
NELSON K. SEWANKAMBO, M.B., Ch.B.
FRED WABWIRE-Mangen, M.B., Ch.B.
Makerere University
Kampala, Uganda

MARLA J. WAVER, M.D.
Columbia University
New York, NY 10032


To the Editor: In research involving human subjects, ethical principles and standards are for the protection of the subjects. If the intention is to study the subjects for their benefit individually, collectively, and in the community, then the main objective must be to benefit the subjects in their own setting. The intention must be to help the population find a way to cope with the disease burden, not to offer new options that are just as out of reach as those that already exist. Otherwise, it would be difficult to claim that the study was conducted for the benefit of the local population, not for that of other populations.

In the study by Quinn et al., is there any hope that the information gleaned will benefit the population studied? Will members of this population be able to afford viral load testing? Will adult circumcision be of any benefit? Will this information lead to a reduction in the cost of antiretroviral drugs, making them more affordable in developing countries? These and other questions about the ethical nature of such studies must be answered if the study subjects are not to be seen as being exploited.

ANTHONY M.A. MULLINGS, M.B., B.S., D.M.
University of the West Indies, Mona Kingston 7, Jamaica, West Indies

To the Editor: As an AIDS researcher in a "developing" country, I know that new drugs and effective vaccines for HIV infection are urgently needed. However, this urgency is being used to lower the standards established by the Declaration of Helsinki,1,2 which states that the "best proven diagnostic and therapeutic methods" must be provided to all study subjects. A 1999 draft of a document intended as a substitute for the declaration proposes the wording "best proven methods that would otherwise be available to the subject of research." Thus, if nothing were available, the "best proven" method would be to make nothing available. The researchers' rationale is that poor countries do not provide antiretroviral agents anyway and that their high costs would make the trials too expensive to conduct. The lack of availability of antiretroviral agents is used to justify the performance of placebo-controlled trials even though effective drugs exist. The argument is that such trials are more efficient and less expensive to perform than non-placebo-controlled trials.

Clinical trials should be performed when use of the "best proven" methods can be assured. This approach may delay access to trials for some countries but will be safer and ethical. If at the end of the trial the drug, vaccine, or procedure is found to be effective, it should be made available wherever it is needed. The plan for this provision should be discussed at the outset among all parties. The justification for different ethical standards for poor countries is based on economic grounds, not on ethical or scientific grounds. Such trials should not be permitted.3

DIRceu B. Greco, M.D.
Federal University of Minas Gerais
30130-100 Belo Horizonte, Brazil


To the Editor: I am perplexed by the Journal's publication of the article on HIV transmission by Quinn et al. and Dr. Angell's accompanying editorial. She expresses grave doubts about the study. These arguments that "ethical standards should not depend on where the research is performed" and "such a study could not have been performed in the United States" strongly indicate that she considers the study unethical. If so, why did she publish the article?

It seems that the Journal is trying to have it both ways: championing the rights of poor Africans in the editorial while endorsing the study by publishing the report on it.