Research Forum: Ethics and Studies of HIV

Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa

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ABSTRACT

The human rights issues raised by the conduct of maternal-fetal human immunodeficiency virus transmission trials in Africa are not unique to either acquired immunodeficency syndrome or Africa, but public discussion of these trials presents an opportunity for the United States and other wealthy nations to take the rights and welfare of impoverished populations seriously. The central issue at stake when developed countries perform research on subjects in developing countries is exploitation. The only way to prevent exploitation of a research population is to insist not only that informed consent be obtained but also that, should an intervention be proven beneficial, the intervention will be delivered to the impoverished population. Human rights are universal and cannot be compromised solely on the basis of beliefs or practices of any one country or group. The challenge to the developed countries is to implement programs to improve the health of the people in developing countries both by improving public health infrastructure and by delivering effective drugs and vaccines to the people. (*Am J Public Health.* 1998;88:560–563)

Introduction

Since the adoption of the Universal Declaration of Human Rights by the United Nations General Assembly in 1948, the countries of the world have agreed that all humans have dignity and rights. In 1998, the 50th anniversary of the Universal Declaration of Human Rights, the Declaration's aspirations have yet to be realized, and poverty, racism, and sexism continue to conspire to frustrate the worldwide human rights movement. The human rights and public health issues of maternal-fetal human immunodeficiency virus (HIV) transmission prevention trials in Africa, Asia, and the Caribbean are not unique to acquired immunodeficiency syndrome (AIDS) or to those countries. Open discussion of these issues provides an opportunity to move the real human rights agenda forward.[1] This is why Global Lawyers and Physicians (GLP), a transnational organization dedicated to promoting and protecting the health-related provisions of the Universal Declaration of Human Rights, joined with Ralph Nader's Public Citizen organization to challenge the conduct of a series of AIDS clinical trials in these developing countries[2] (S. M. Wolfe et al., written communication to Secretary of Health and Human Services Donna Shalala, April 22, 1997).

The Clinical Trials

In 1994, the first effective intervention to reduce the perinatal transmission of HIV was developed in the United States in AIDS Clinical Trials Group (ACTG) Study 076. In that trial, use of zidovudine administered orally to HIV-positive pregnant women as early as the second trimester of pregnancy, intravenously during labor, and orally to their newborns for 6 weeks reduced the incidence of HIV infection by two thirds (from about 25% to about 8%).[3] Six months after stopping the study, the US Public Health Service recommended the ACTG 076 regimen as the standard of care in the United States.[4] In June 1994, the World Health Organization (WHO) convened a meeting in Geneva at which it was concluded (in an unpublished report) that the 076 regime was not feasible in the developing world. At least 16 randomized clinical trials (15 using placebos as controls) were subsequently approved for conduct in developing countries, primarily in Africa. These trials involve more than 17 000 pregnant women. Nine of the studies, most of them comparing shorter courses of zidovudine, vitamin A, or HIV immunoglobulin with placebo, are funded by the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH).[2]

Most of the public discussion about these trials has centered on the use of placebos.[2,5,6] The question of placebo use is a central one in determining how a study should be conducted. But we believe the more important issue these trials raise is the question of whether they should be done at all. Specifically, when is medical research ethically justified in developing countries that do not have adequate health services (or on US populations that have no access to basic health care)? This question is espe-

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cially pertinent since February 1998 when, on the basis of a Thailand study that demonstrated that a short course of zidovudine reduced HIV transmission by 50%, CDC, NIH, and the United Nations Program on AIDS (UNAIDS) officials announced that they would recommend that the use of placebo be halted in all mother-to-fetus transmission studies.[7]

Research on Impoverished Populations

The central issue involved in doing research with impoverished populations is exploitation. Harold Varmus, speaking for NIH, and David Satcher, speaking for CDC, both seem to realize this. They wrote in the *New England Journal of Medicine* last year that "trials that make use of impoverished populations to test drugs for use solely in developed countries violate our most basic understanding of ethical behavior."[6] However, instead of trying to demonstrate how the study interventions, such as a shorter course of zidovudine (AZT), could actually be delivered to the populations of the countries in the studies, they assert that the studies can be justified because they will provide information that the host country can use to "make a sound judgment about the appropriateness and financial feasibility of providing the intervention."[6] However, what these countries require is not good intentions, but a real plan to deliver the intervention, should it be proven beneficial.

Unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gained from the clinical trials for the developed countries' own benefit. If the research reveals regimens of equal efficacy at less cost, these regimens will surely be implemented in the developed world. If the research reveals the regimens to be less efficacious, these results will be added to the scientific literature, and the developed world will not conduct those studies. Ethics and basic human rights principles require not a thin promise, but a real plan as to how the intervention will actually be delivered. Actual delivery is also, of course, required to support even the utilitarian justification for the trials, which is to find a simple, inexpensive, and feasible intervention in as short a time frame as possible because so many people are dying of AIDS. No justification is supportable unless the intervention is actually made widely available to the relevant populations.

TABLE 1—Health Care Expenditures of African Countries Involved in Mother-to-Child HIV Transmission Prevention Trials

Country (Year)	Per Capita (US dollars)	As % of GDP*
Burkina Faso (1992)	22	5.5
Cote d'Ivoire (1995)	22	3.4
Ethiopia (1990)	5	3.9
Kenya (1992)	13	2.5
Malawi (1990)	11	5.0
Tanzania (1990)	5	5.0
Uganda (1994)	10	3.9
Zimbabwe (1991)	86	6.5

Data from World Bank Sector Strategy, Healthm Nutrition, and Population, 1997.
*GDP = gross domestic product.

Neither NIH nor CDC (nor the host countries) has a plan that would make the interventions they are studying available in Africa, where more than two thirds of the people in the world reside who are infected with HIV.[7] As an example, Varmus and Satcher point out that the wholesale cost of zidovudine in the 076 protocol is estimated to be in excess of $800 per mother and infant and that this amount is far greater than what most developing countries can pay for standard care.[6] The CDC estimates the cost of the "short course" zidovudine regimens being investigated to be roughly $50 per person. The cost of merely screening for HIV disease, a precondition for any course of therapy, is approximately $10, and all pregnant women must be screened to find the cases to treat. These costs must be compared with the total per capita health care expenditures of the countries where this research is being conducted (Table 1). Given this fact, African countries involved in the clinical trials (or some other funder) must make realistic assurances that if a research regimen proves effective in reducing mother-to-fetus transmission of HIV, resources will be made available so that the HIV-positive pregnant women in their countries will receive this regimen.

However, the mere assertion that the interventions will be feasible for use in the developing countries is simply not good enough, given our experience and knowledge of what happens in Africa now. For example, we already know that effectively treating sexually transmitted diseases such as syphilis, gonorrhea, and chancroid with the simple and effective treatments that are now available can drastically lower the incidence of HIV infection. Yet, these inexpensive and effective treatments are not delivered to poor Africans. For example, a recent study showed that improving the treatment of sexually transmitted diseases in rural Tanzania could reduce HIV infections by 40%.[8] Nonetheless, this relatively inexpensive and effective intervention is not delivered. Vaccines against devastating diseases have also been developed with sub-Saharan African populations as test subjects.[9] Nonetheless, even though vaccines such as the group A meningococcal meningitis vaccine are inexpensive and effective, they are not adequately delivered to the relevant sub-Saharan African populations.[9]

Cultural Relativism or Universal Human Rights?

In their article in the *New England Journal of Medicine*, Varmus and Satcher sought to bolster their ethical position by quoting the chair of the AIDS Research Committee of the Uganda Cancer Institute, who wrote in a letter to Dr. Varmus:

> These are Ugandan studies conducted by Ugandan investigators on Ugandans. . . . It is not NIH conducting the studies in Uganda, but Ugandans conducting their study on their people for the good of their people.[6]

Two points are especially striking about Varmus' and Satcher's using this justification. First, their justification is simply not accurate. If NIH and CDC were not involved in these studies, these agencies would not have to justify them; indeed, the studies would not have been undertaken. These US agencies *are* involved—these trials are not just Ugandans doing research on other Ugandans. Second, and more importantly, the use of this quotation implies support for an outdated and dangerous view of cultural relativism.

Even if it were true that the studies in question were done by Ugandans on Ugandans, this would not mean that the United States or the international community could conclude that they should not be criticized. (This rationale did not inhibit criticism of apartheid in South Africa, genocide in Rwanda, or torture and murder in the Congo.) Human Rights Watch, referring to

repression in Central Africa, said in its December 1997 review of the year on the issue of human rights that the slogan "African solutions to African problems" is now used as a "thin cover" for abusing citizens.[10] That observation can be applicable to experimentation on citizens as well.

The other major justification both NIH and CDC use for the trials is the consensus reached at the June 1994 meeting of researchers at WHO. Of the many analogies that have been drawn between the HIV transmission prevention trials and the US Public Health Service's Tuskegee syphilis study, perhaps most striking is their reliance on professional consensus instead of ethical principle to justify research on poor, black populations. As historian James Jones wrote in his book *Bad Blood*, which was written about the Tuskegee experiment: "The consensus was that the experiment was worth doing, and in a profession whose members did not have a well-developed system of normative ethics, consensus formed the functional equivalent of moral sanction."[11]

Neither researcher consensus nor host country agreement is ethically sufficient justification for choosing a research population. As the National Research Council's Committee on Human Genome Diversity properly put it, in the context of international research on human subjects, "[s]ensitivity to the specific practices and beliefs of a community cannot be used as a justification for violating universal human rights."[12] Justice and equity questions are also important to the ability of individual research subjects to give informed consent.

Informed Consent

Research subjects should not be drawn from populations who are especially vulnerable (e.g., the poor, children, or mentally impaired persons) unless the population is the only group in which the research can be conducted and the group itself will derive benefits from the research. Even when these conditions are met, informed consent must also be obtained.[13,14] In most settings in Africa, voluntary, informed consent will be problematic and difficult, and it may even preclude ethical research. This is because, in the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as "better than nothing" and research will almost inevitably be confused with treatment, making informed consent difficult.

Interviews with women subjects of the placebo-controlled trial in the Ivory Coast support this conclusion. For example, one subject, Cecile Guede, a 23-year-old HIV-infected mother participating in a US-financed trial, told the *New York Times*, "They gave me a bunch of pills to take, and told me how to take them. Some were for malaria, some were for fevers, and some were supposed to be for the virus. I knew that there were different kinds, but I figured that if one of them didn't work against AIDS, then one of the others would."[15] The *Times* reporter who wrote the front-page story, Howard W. French, said, "For Ms Guede, the reason to enroll in the study last year was clear: it offered her and her infant free health care and a hope to shield her baby from deadly infection. . . . [T]he prospect of help as she brought her baby into the world made taking part in the experiment all but irresistible."[15]

Persons can make a gift of themselves by volunteering for research. However, it is extremely unlikely that poor African women would knowingly volunteer to participate in research that offered no benefit to their communities (because the intervention would not be made available) and that would only serve to enrich the multinational drug companies and the developed world.[12] Thus, a good ethical working rule is that researchers should presume that valid consent cannot be obtained from impoverished populations in the absence of a realistic plan to deliver the intervention to the population. Informed consent, by itself, can protect many subjects of research in developed countries, but its protective power is much more compromised in impoverished populations who are being offered what looks like medical care that is otherwise unavailable to them.

The International Community and the AIDS Pandemic

If the goal of the clinical trials is to reduce the spread of HIV infection in developing countries, what strategy should public health adopt to achieve this end? It is not obvious that the answer is to conduct clinical trials of short-term zidovudine treatment. In the developed world, for example, HIV-infected women are advised not to breast-feed their infants because 8% to 18% of them will be infected with HIV from breast milk.[16] However, in much of the developing world, including in most African countries, WHO continues to recommend breast-feeding because the lack of clean water still makes formula-feeding more dangerous. As long as this recommendation stays in effect, and is followed, even universal use of the ACTG 076 regimen, which would lower the overall newborn infection rate by about 16%, would only likely serve to reduce the incidence of HIV infection in infants by about the same amount that it is increased by breast-feeding (8% to 18%). A more effective public health intervention to improve the health of women and their children may be to put more efforts into providing clean water and sanitation. This will help not only to deal with HIV, but also to alleviate many other problems, including diarrheal diseases.

President Jacques Chirac of France was on target in his December 1997 speech to the 10th International Conference on Sexually Transmitted Disease and AIDS in Africa, which was held in the Ivory Coast. President Chirac proposed creating an international "therapy support fund" that is primarily funded by European countries (the former colonial powers in Africa).[17] Although he put emphasis on the new drugs available for AIDS treatments, it would be more useful to consider the public health priorities of the countries themselves, for example, prevention, especially in areas such as sanitation, water supply, nutrition, education, and the delivery of simple and effective vaccines and medical treatments for sexually transmitted diseases.

Conclusion

Actual delivery of health care requires more than just paying lip service to the principles of the Universal Declaration of Human Rights; it requires a real commitment to human rights and a willingness on the part of the developed countries to take economic, social, and cultural rights as seriously as political and civil rights. □

References

1. Mann JM. Medicine and public health, ethics and human rights. *Hastings Center Rep.* 1997; 27(3): 6–13.
2. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of human immunodeficiency virus in developing countries. *N Engl J Med.* 1997;337:853–856.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med.* 1994; 331:1173–1180.

4. Recommendations of the US Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep.* 1994;43(RR-11):1–20.
5. Angell M. The ethics of clinical research in the Third World. *N Engl J Med.* 1997;337: 847–849.
6. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med.* 1997;337:1003–1005.
7. Brown D. AZT's success in pregnancy may help expand AIDS treatment for poor. *Washington Post.* February 19, 1998:A10.
8. Grosskurth H, Mosha F, Todd J, Mwijarubi E, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomized controlled trial. *Lancet.* 1995;346:530–536.
9. Robbins JB, Towne DW, Gotschlich EC, Schneerson R. 'Love's labours lost': failure to implement mass vaccination against group A meningococcal meningitis in sub-Saharan Africa. *Lancet.* 1997;350:880–882.
10. Clines FX. Rights group assails US on land mines and ties with China. *New York Times.* December 5, 1997:A13.
11. Jones JH. *Bad Blood: The Tuskegee Syphilis Experiment.* New York, NY: Free Press, 1981.
12. Committee on Human Genome Diversity. Evaluating Human Genetic Diversity. Washington, DC: National Academy Press; 1997:65.
13. Annas GJ, Grodin MA, eds. *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation.* New York, NY: Oxford University Press; 1992.
14. Ijsselmuiden CB, Faden RR. Research and informed consent in Africa—another look. *N Engl J Med.* 1992;326:830–834.
15. French HW. AIDS research in Africa: juggling risks and hopes. *New York Times.* October 9, 1997:Al.
16. Van de Perre P. Postnatal transmission of human immunodeficiency virus type l: the breast-feeding dilemma. *Am J Ob Gyn.* 1995;173:483–487.
17. Bunce M. Chirac seeks worldwide relief for AIDS in Africa. *Boston Globe.* December 8, 1997:A2.