POLICY: BIOMEDICINE

The Highest Attainable Standard: Ethical Issues in AIDS Vaccines

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AIDS has had a devastating impact of almost unimaginable proportions on developing countries. Currently, the United Nations estimates that there are 16,000 individuals newly infected with the human immunodeficiency virus (HIV) each day, or 5.8 million per year. Ninety percent of new infections occur in developing countries, where ultimately almost all infected people succumb to the disease or opportunistic infections. By the end of this decade, it is estimated that 40 million people will have died from AIDS, and more than 9 million children will have been orphaned. Because many developing countries cannot afford to implement the new antiretroviral drug therapies—with a current cost of about $12,000 to $15,000 per patient each year in the United States—the only public health measure available to them is counseling against behaviors that increase the risk of the disease.

The scientific community has increasingly come to believe that the best hope for stemming the global epidemic is the development of preventive HIV vaccines. Even before clinical trials are undertaken, ethical guidelines require that "clinical testing must be preceded by sufficient laboratory experiments including, when appropriate, animal testing, to demonstrate a reasonable probability of success without undue risk." This standard must be considered carefully before initiating trials of vaccines containing live attenuated HIV in human volunteers, for example, which could revert to virulence and themselves cause disease.

Clinical vaccine trials, which are the next step, are carried out for multiple reasons, both scientific and practical: To gauge the safety of the candidate vaccine, to ascertain how well a vaccine protects against infection or disease, to better understand protection, to acquire data required for licensure, and to introduce vaccines into public health practice (*1*). Clinical trials of AIDS vaccines present complex ethical issues. A recent controversy (*2*) erupted over the ethics of including placebos in clinical trials designed to test simplified and less costly drug regimens for prevention of maternal-infant HIV transmission. These trials were conducted by investigators in several developing countries, in collaboration with scientists from the United States and other developed countries. There were charges that the existence of effective antiretroviral drugs made the use of placebos unethical and countercharges of ethical imperialism that ignored the realities of economic conditions in the developing world. These events only emphasize the need for the medical community to consider, in advance, critical ethical issues likely to arise in vaccine trials in developing countries.

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Vaccine Expectations and Endpoints

Most vaccines currently in use—those for polio, tetanus, diphtheria, measles, hepatitis B, and influenza, for example—prevent disease without actually preventing infection. Instead, they reduce the number of invading microorganisms, increase the rate of clearance of the infection, prevent the secondary consequences of infection, or prevent transmission. Similarly, few of the candidate HIV vaccines appear promising for preventing infection, and the expectation that HIV vaccines will in fact prevent infection is yielding, in the scientific community, to the hope that they may prevent disease.

In developed countries, it will be ethically required that individuals in vaccine trials who are found to have acquired HIV infection will be offered antiretroviral therapy, which usually dramatically reduces virus levels. If vaccines cannot achieve protection against infection, however, treatment with antiretrovirals will compromise the ability of the trial to measure the efficacy of the vaccine in preventing disease. It may also obscure possible secondary endpoints of vaccine efficacy, such as reduction in viral loads [a promising correlate of disease progression (*3*)] or immunological correlates of protection. Delaying the drug treatment until viral loads can be determined at several time points may present another ethical problem.

Because of these complications, determination of the protective efficacy of HIV vaccine candidates may only be possible in trials in developing countries where the resources are not available to provide antiretroviral drugs. It is that circumstance, plus the fact that development of successful vaccines will be an incremental process requiring multiple trials, that presents the most challenging ethical issues.

The Ethics of Research on Humans

Codification of ethical precepts for experimentation on human beings derives from the Nuremberg Code of 1947, issued to prevent the kinds of medical abuses perpetrated on non-consenting prisoners by physicians in World War II. Many industrialized countries, including the United States, have established their own ethical guidelines for human experimentation (*4*, *5*), but that is rarely the case for developing countries. Because AIDS vaccine trials are likely to require collaborations between developed and developing countries, two documents on human experimentation in international research are most influential: The Declaration of Helsinki, promulgated in 1964 by the World Medical Association (*6*), and the "International Ethical Guidelines for Biomedical Research Involving Human Subjects," published by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) in 1982 (*7*). The most recent version of the CIOMS guidelines, prepared in 1993, is explicitly intended to indicate how the ethical principles of the declaration can effectively be applied in developing countries. Together these documents are accepted by the international medical community as providing for the highest standards of medical ethics in human experimentation, although in most countries they lack the force of law.

These and other guidelines rest on three general ethical principles, made explicit in 1988 in the Belmont Report (*4*): Respect for persons (including their autonomy and self-determination), beneficence (maximizing benefits and minimizing harms), and justice. The last principle also includes distributive justice, which demands "the equitable distribution of both the burdens and the benefits of participation in research." When applied to specific circumstances, these ethical guidelines may conflict with one another. Furthermore, they are silent on the issue of the economic and technical capacity of either the trial population or the host country to implement the recommendations.

The Best Proven Therapeutic Method

CIOMS Guideline 14 quotes Article II.3 of the Helsinki Declaration and states that, "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and

therapeutic method" (7). This guideline is not easy to apply. Is combination antiretroviral therapy the best proven therapeutic for individuals in a vaccine trial who become HIV-infected? Indeed, is there a best proven therapeutic, especially when the national treatment guidelines of the United Kingdom, United States, and other developed nations differ (8)? No one has defined the criteria that would allow a judgment to be made on what constitutes the best proven therapeutic. What is the obligation to individuals who, after agreeing to enter a vaccine trial and giving informed consent to be screened for HIV, are found to be HIV-positive and are thus excluded from the trial? According to CIOMS Guideline 15, these individuals should be referred to medical care. Is it appropriate to refer them to a health service in a country where the standard of care does not include antiretroviral therapy?

Many scientists believe that the only short-term way to ascertain the beneficial effect of immunization on HIV transmission—which is the most important public health endpoint—is vaccination of uninfected sexual partners of HIV-infected individuals. If a HIV-positive, previously infected partner is identified, must he or she be offered and provided antiretroviral therapy as well as counseling? If so, can transmission blocking trials ever ethically be undertaken?

Another facet of this guideline relates to placebo-controlled trials, the focal point of the recent controversy in the maternal-infant transmission trials. The guidelines seem to be clear and unambiguous. Helsinki (Article II.3) states that "the best proven therapeutic" requirement "does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists." That is amplified in CIOMS Guideline 14 to say "If there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified." However, the interpretation of this guideline has also evolved (9).

The guideline is silent on preventive methods, but I shall assume they are implicit in the designation of "diagnostic or therapeutic method." Because no HIV vaccine has yet been tested for efficacy in a Phase III trial, there is no best proven preventive. But what if a vaccine existed that was clearly demonstrated to be 20% effective? Does that establish it as the best preventive method? Would all controls, or perhaps all vaccinees in future trials, have to be given the poorly effective vaccine rather than placebo, even though it may compromise evaluating the effectiveness of a vaccine candidate capable of engendering greater protection?

In a related circumstance, recent trials of acellular pertussis vaccines in Sweden and Italy generated a major ethical controversy regarding the use of a placebo. These countries were chosen in part because the use of whole-cell pertussis vaccine was very low (only 30 to 40% of the population), and so a definitive result could be obtained by studying 15,000 children in Italy and 10,000 in Sweden, rather than the hundreds of thousands or more that would have been required in the United States. Groups received a placebo and various acellular vaccines, and one group in each trial received the best proven preventive: whole-cell pertussis vaccine. The inclusion of the placebo group permitted the trial to reveal not only that the efficacy of the new acellular vaccines (76 to 89% protection) was significantly greater than that of the whole-cell vaccine, but that the standard whole-cell vaccine had far poorer protective efficacy (36 to 48%) relative to placebo than was thought to be the case (*10*).

Expectant mothers in a maternity clinic in Kampala, Uganda. [Reprinted with permission from A. W. Kigotho, *Lancet* **350**, 1456 (1997)]

Another question is whether it will be unethical to carry out placebo-controlled trials in countries that have not yet accepted vaccines proven to be effective elsewhere. In some instances, it is only after local testing that the demand for internationally accepted vaccines results in their adoption by national immunization programs.

A Requirement for Reasonable Availability

CIOMS Guideline 15 on Externally Sponsored Research requires that any trial "must be responsive to the health needs of the host country.... Any product developed through such research [should] be made reasonably available to the inhabitants of the host community or country at completion of successful testing" (7).

In the case of HIV vaccine trials, the ethical principles for provision of the best proven therapeutic and for reasonable availability appear to be in conflict.There are several facets of this conflict of principles. One is the cost of the best proven therapeutic. For example, Uganda is a country of 16 million people with a gross national product per capita of $170, one physician per 100,000 people, and an annual per capita expenditure on health of $6 (*11*). Uganda suffers one of the greatest burdens from AIDS, with 11 to 12% of pregnant women estimated to be already infected with HIV and at least 100,000 children orphaned by AIDS (*12*). It is also a country that has made a major commitment to health infrastructure over many years to be able to conduct HIV vaccine trials. When individuals become HIV-infected during the course of vaccine trials, would the $12,000 to $15,000 annual cost for antiretroviral therapy (if considered the best proven therapeutic) be assumed by the companies producing the candidate vaccines, the host country, or the sponsoring country or agency?

Although the problem might be obviated if antiretroviral therapy regimens were not considered the best proven therapeutic, this would be irresponsible circumvention of the issue by semantics. In my view, the question is more general than just the case of AIDS vaccines and relates to any trials of vaccines or drugs for diseases such as tuberculosis and pneumonia, or even for noncommunicable diseases. For example, chronic noncommunicable ailments (including cardiovascular, neoplastic, and psychiatric disorders) form the most rapidly rising category of disease in developing countries (*13*). Few, if any, clinical trials in developing countries have evaluated whether simple, inexpensive interventions, such as aspirin and β-blockers, will reduce mortality from heart attacks and strokes, as they do in the industrialized world; consequently, these treatments are not widely applied. Were the standard of best proven therapeutic method to be literally invoked in such a trial, many study subjects suffering heart attacks would have to be provided with either angioplasty or coronary artery bypass surgery, which are hardly reasonably available in countries where per capita expenditures for health are $10 per year or less. The more general question is that if the best proven therapeutic standard of the industrialized countries were literally applied without qualification, could there ever be efficacy trials of AIDS vac-

cines or of many other interventions? And if not, how would interventions most responsive to the health needs of the host country ever be developed and tested?

Who Controls Controlled Trials?

When ethical norms or standards of care differ among countries, whose ethical rules prevail? For AIDS vaccines, even the guidelines explicitly designed to protect populations of developing countries from exploitation are problematic. CIOMS Guideline 8, which states that "Phase I and II vaccine studies should be conducted only in developed communities of the country of the sponsor" (*7*) is particularly troubling to AIDS researchers and health leaders of countries where AIDS is endemic. Phase I early safety trials require only small numbers of volunteers (typically 20 to 60) and can and should be carried out quickly in the countries where the vaccines are developed. However, the question asked by scientists from developing countries is why, given the urgency of the epidemic, must we delay expanded safety (Phase II) trials until such trials are completed in a developed country, where accrual of patients into trials is often a very time-consuming process, sometimes requiring a year or more? The beneficent intent of avoiding exploitation is clear. The guidelines, however, are seen to be paternalistic or imperialistic and to preempt the sovereign right of developing countries to make decisions that profoundly affect the health of their people.

A Process for Resolving Ethical Issues

UNAIDS was created by the United Nations to lead and coordinate all UN agency activities in combating the AIDS epidemic. A group of bioethicists, human rights lawyers, community leaders, public health officials, physicians, representatives of CIOMS, and AIDS scientists from 13 countries was recently convened by UNAIDS to identify ethical issues in AIDS vaccine trials (*14*). The UNAIDS meeting raised many of the ethical issues discussed here, as well as others that must be considered in moving forward with vaccine trials, including the question of whether all ethical issues must be resolved before efficacy trials may be initiated. It was recognized that thoughtful people of good will can disagree on ethical interpretations of the guidelines and that most of the current guidelines will be applicable in their present form to the ethical questions of AIDS vaccine research.

Nevertheless, there are critical issues that require that the current guidelines be reconsidered, clarified, strengthened, further elaborated, or modified. In this context, UNAIDS has commissioned working papers to provide ethical, legal, and scientific background information. A process of consultation is being initiated with public health, science, ethical, and community leadership in countries and regions around the world that are involved in HIV vaccine research, with the aim of developing a consensus on these issues.

It would be inappropriate in this article to preempt in any way the findings of the UNAIDS process, but some personal thoughts on approaching the issues presented here may be helpful. The Helsinki and CIOMS guidelines have for decades been universally respected and should not lightly be changed. Nevertheless, they are living documents that must evolve to encompass and provide guidance for changing realities in global health. I believe that the guidelines stipulating the best proven therapeutic method and reasonable availability require clarification and perhaps modification. One framework for doing so might be to incorporate the basic concept of the Charter of the World Health Organization (WHO), which states that "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social conditions." Without changing the existing guidelines significantly, I believe it is possible and necessary to clarify what is attainable for their implementation in developing countries whose health care resources are severely constrained. Further, guidelines enjoining developing countries from carrying out Phase II trials until they are completed in developed countries are indeed paternalistic or worse, and ought to be modified. The general qualification I would suggest to ensure that trials are ethically carried out and are not exploitative is that UNAIDS, CIOMS, or WHO should provide independent review of the protocols to ensure that they are ethically and scientifically sound and as safe as possible. It is essential that research of the highest attainable ethical standard be carried out, with due recognition of the global needs and opportunities, burdens and benefits, and resource constraints for individuals and countries.

References and Notes

1. Trials can create a demand by proving to the local community that an effective treatment or vaccine is available. For example, although *Hemophilus influenzae B* and hepatitis B vaccines are highly effective and are recommended by WHO for universal immunization, they are currently used in only a minority of national vaccine programs.
2. M. Angell, *N. Engl. J. Med.* **337**, 847 (1997); P. Lurie and S. M. Wolfe, *ibid.*, p. 853; H. Varmus and D. Satcher, *ibid.*, p. 1003.
3. J. W. Mellors *et al.*, *Ann. Intern. Med.* **126**, 12946 (1997).
4. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* [U.S. Government Printing Office (GPO 887-809), 1988]; Code of Federal Regulations, *Regulations on the Protection of Human Subjects*, Title 45, Part 46 (45CFR46), Title 21, Parts 50 and 56 (21CFR50, 21CFR56); U.S. Public Health Service, *Consultation on International Collaborative Human Immunodeficiency Virus (HIV) Research* (Assistant Secretary for Health, Department of Health and Human Services, Washington, DC, (1990).
5. For Europe, see Council of Europe, *Convention on Human Rights and Biomedicine* (Strasbourg, 1997); M. A. M. deWachter, *Hastings Center Report* **27**, 13 (1997); and F. W. Dommel and D. Alexander, *Kennedy Inst. Ethics J.* **7**, 259 (1997).
6. Declaration of Helsinki [World Medical Association, Ferney-Voltaire, France, 1964 (revised 1974, 1983, 1989, and 1996)].
7. CIOMS, in collaboration with WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [CIOMS, Geneva, Switzerland, 1982 (revised in 1993)].This document contains 15 guidelines that address fundamental ethical principles relating to the need for informed consent and freedom to withdraw from studies; the use of children, prisoners, and vulnerable populations in research; undue inducements to participate in trials; indemnification for injuries suffered as a consequence of the research; and mechanisms for ethical review, among others.
8. C. C. Carpenter *et al.*, *J. Am. Med. Assoc.* **277**, 1962 (1997). A draft set of revised Centers for Disease Control guidelines is currently under review. British HIV Association Guidelines, *Lancet* **349**, 1086 (1997). Early initiation of treatment with combination chemotherapy including protease inhibitors is recommended in the U.S. guidelines prepared by the International AIDS Society–USA Panel. In contrast, the U.K. guidelines recommend treatment initially only with anti–reverse transcriptase drugs and inclusion of protease inhibitors in therapy only at later stages of disease.
9. Povl Riis, chairman of the Central Scientific-Ethical Committee of Denmark, a member of the committee that drafted the Helsinki Declaration in 1974 and a co-author of the "best proven therapeutic method" sentence in the declaration, has indicated that "In the seventies we focused mainly on clinical-pharmacological trials in developed countries. During the last 15 years, the Danish Committee System has interpreted the above sentence" as implicitly qualified by ". . . in accordance with national accessibility," and "with the indispensable condition that the project is of great importance to the developing country and consequently is not intending to test drugs or methods of primary interest to the donating country." (P. Riis, personal communication).
10. D. Greco *et al.*, *N. Engl. J. Med.* **334**, 341 (1996); L. Gustafsson *et al.*, *ibid.*, p. 349 (1996). Another example is the cholera vaccine trials in Bangladesh in the 1960s, in which children in the unvaccinated experimental groups, if not protected by the vaccine, were at risk for rapid death from dehydration. A system was put in place for the trial to allow rapid oral rehydration to any child in the trial contracting cholera. That system remains in place. W. E. Van Heyningen and J. Seale, *Cholera: The American Scientific Experience, 1947–1980* (Westview, Boulder, CO, 1983).
11. The World Bank, World Development Report 1993, *Investing in Health* (Oxford Univ. Press, 1993).
12. UNAIDS Programme, Geneva, Switzerland.
13. C. J. W. Murray and A. Lopez, Eds., *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*, Vol. 1. (Harvard Univ. Press, Cambridge, MA, 1996).
14. UNAIDS, *Ethical Considerations in Clinical Trials of Preventive HIV Vaccines*, proceedings of a meeting held 23 to 24 September 1997 (UNAIDS, Geneva, Switzerland, 1997).

15. Many of the ideas in this article derive from discussions with the participants at the UNAIDS meeting (*12*). I thank R. Macklin for her critical reading of the manuscript; P. Riis for permission to quote from his letter to me; J. Esparza, D. Guenter, and S. Kalibala of UNAIDS for current AIDS statistics; J. Weber for guidelines for care in the United Kingdom; R. Glass for information on the cholera vaccine trials; and J. LaMontagne for information on the acellular pertussis vaccine trials. I thank D. Baltimore, M. L. Clements Mann, M Johnston, P. Fast, A. Fauci, C. Grady, D. Ho, J. Mann, D. Richmond, P. Smith, and H. Varmus for thoughtful comments on the manuscript and R. Levine, M. Sommerville, and E. Mbidde for helpful discussions.