meaning but, in our view, misguided pressure?[9–11] Or has Congress perhaps turned this scientific and ethical issue into a political one? In view of the consequences of the new joint position taken by the 4 agencies, the international community surely incurs a moral obligation to act. The particular and pressing issue is how to make the new intervention, or other alternatives to the standard regimen, affordable in the poorest nations.

Radical reduction in transmission of HIV from mother to child—and, hence, in the number of babies born with HIV infection—is now within reach. In the international community, then, does the political will exist to make good on the obligations entailed by this decision? Will the financial resources and support for providing the requisite treatment and building service structures for delivery be mobilized? That is one way to rescue this judgment by major agencies from charges of ill-considered haste, at best, and much else, at worst.

This new development only enhances the relevance to the current research scene of the papers in this issue of the Journal. In the face of international collaboration on research between rich and poor nations, these papers raise matters that will have to be confronted again and again. It is in that light that the papers should be read. In this instance once more, the past is prologue. □

Mervyn Susser
Editor

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Editorial: HIV Research, Ethics, and the Developing World

Six articles in this issue of the Journal address the conduct of human immunodeficiency virus (HIV) research in the developing world. The issues they raise, however, are neither unique to HIV nor unique to developing countries. In this editorial, we discuss several of these issues, including the failure to provide interventions of known efficacy, ethical relevance of study design, informed consent, and exploitation.

A challenge raised by de Zoysa et al.[1], Karim,[2] Wittkowski et al.,[3] and others,[4,5] is whether, or under what conditions, it is ethical in research to fail to provide an intervention of known efficacy. Perhaps the easiest case is raised by de Zoysa et al., in which they argue that HIV spermicide trials cannot be conducted ethically without also providing all participants with condoms. When the efficacy of spermicides is unknown and a cheap, effective, and available alternative (condoms) exists, no one disagrees that condoms must be provided to all research participants, even though knowledge about spermicide efficacy would come more quickly and with greater certainty if a placebo-controlled spermicide trial or an equivalency trial were conducted.

The further we diverge from this situation, in which an effective, easy-to-implement intervention is available, to situations that resemble the international clinical trials to prevent perinatal transmission of HIV, as discussed by Bayer[4], Karim[2], and Annas and Grodin[5], the less clear the ethical mandate becomes. Here, the debate has focused on whether the standard of care in the United States—an expensive and complex regimen of zidovudine—must be provided to all HIV-infected pregnant women who join a research study in the developing world. Different scientists and scholars in bioethics have drawn the line differently in terms of what interventions routinely available in the developed world must be provided to research participants in the developing world. At an extreme, no one suggests requiring that the most expensive and complex of Western tertiary care, for example, renal dialysis or coronary bypass, must be provided in research conducted in the developing world. Indeed, public debates about the HIV perinatal transmission trials have not even focused on whether the women in the trials should be provided HIV combination therapy as they would be in the West[8] or whether they should even have the zidovudine continued postpartum.

In addition to discussing the recent debate concerning international HIV research, these articles also focus on whether or not randomized, controlled trials must be conducted for researchers to learn about an intervention's efficacy. The choice of a study design is not simply between ethically questionable perfect trials that produce complete knowledge versus imperfect designs that produce no knowledge at all. Moreover, less rigorous designs, such as observational studies, that resolve certain ethical quandaries—as de Zoysa et al. suggest in the context of condom distribution in spermicide trials—are not necessarily free of other ethical problems. One such problem is that these studies may provide only limited guidance for public health policy. This is illustrated by Wittkowski et al., who report on a repeat analysis of an observational study that strongly suggests vaginal spermicides effectively prevent HIV transmission. The authors acknowledge, however, that an observational design cannot match a randomized trial in accounting for potential confounding and that their results should be interpreted with caution.

Clearly, basing public health policy on a single observational study would be premature; however, multiple observational studies with findings comparable to the analysis by Wittkowski et al. could provide ethical justification for designing randomized equivalency trials comparing the effectiveness of condoms with spermicide. The results of these trials, in turn, should be sufficient for developing public health policy. Under many circumstances, this research strategy may appropriately accommodate ethical considerations with public health needs. The lapse of time in establishing an acceptable treatmen in such a series of studies, however, should

Editor's Note. See related articles by de Zoysa et al. (p 571), Karim (p 564), Wittkowski et al. (p 590), Bayer (p 567), Annas and Grodin (p 560), and Karim et al. (p 637) in this issue.

be weighed against the prospect of obtaining quicker results from one or two placebo-controlled trials.

Another issue raised in these articles is that of informed consent, one of the cornerstones of research ethics. Clearly, as Karim et al.[9] suggest, the quality of informed consent is compromised when potential patient-participants believe, even wrongly, that their medical care is contingent on their agreeing to participate in research. In contexts such as the Karim et al. study, it is important to emphasize to potential participants that neither their access to medical care, nor the quality of the care they receive, will be affected in any respect by their decision. Although it is sometimes difficult to clarify this separation of research from medical care, potential participants can be made aware through effective communication that a decision about research has no implications for their medical best interests. A more challenging situation occurs when potential participants *rightly* believe that their medical care is contingent on their agreeing to enroll in research. This issue is raised by de Zoysa et al. and Annas and Grodin. All too often, a research project offers the best medical care or the only medical care available, and it may be impossible for potential subjects who are ill or at risk to refuse research participation.

When such circumstances prevail, informed consent is profoundly compromised. The burden of proof is on the proponents of the research. At minimum, they must provide good, morally relevant reasons why the research should be conducted in a population that ordinarily does not have access to the medical care in question, rather than in a population that does. Additionally, without question, all subjects must be better off for being in the research. The risks and burdens imposed must be no worse than would be permitted were the research conducted in an economically advantaged population.

This last condition is introduced to prevent exploitation. We agree with Annas and Grodin that the risk of exploitation is a central moral concern in research. Exploitation occurs when unfair advantage is taken of the negative circumstances of others. These include poverty, absence of medical care, homelessness, imprisonment, and serious illness. Under conditions horrific enough, people may be better off as research subjects, even if they are thereby exposed to significant risk or painful procedures that in the end have no medical benefit. Although conducting research with disadvantaged people can be morally appropriate, the ethical stakes are much higher.

Problems with exploitation and informed consent often coincide, but they are separable concerns. Annas and Grodin maintain that it is extremely unlikely that poor Africans would knowingly volunteer for research that would accrue benefits solely for the multinational drug companies and the developed world and not for their own communities (because the intervention would not be made available). Thus, 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."

On the contrary, we believe some poor Africans might knowingly participate in research that offers sufficient personal benefit to them at minimal risk but no benefit to their communities. That some or even many Africans might so consent to participation, however, does not make the research ethically acceptable. We agree with Annas and Grodin that such research is exploitive. It is fundamentally wrong to use the bodies of the poor to advance the exclusive interests of the wealthy.

In the specific, recent controversy surrounding HIV vertical transmission trials, no one is claiming otherwise. A foundational premise of the argument by Karim[2] in defense of the trials is that the results are urgently needed in Africa to guide the delivery of affordable and implementable interventions. Annas and Grodin are challenging that premise. They see no real plan for delivering even a short course of zidovudine to pregnant women of African countries (should a short course prove effective), given the extreme resource constraints that those and other developing nations face.

Annas and Grodin's challenge is well taken. Ethics requires more than vague promises. But what would an acceptable plan for implementation look like? Who would have to make what kind of assurances to whom? For example, would it be necessary for drug companies and international organizations to guarantee that, from the end of the trial forward, all affected pregnant women in the country in which the trial is conducted will receive the short course if it is efficacious? What if the guarantee is only for 5 years, or for one? Or only for the women of the township, not the nation? Who is to judge the adequacy and assess the validity of whatever assurance of access is made? These are difficult questions that the international research community must address if we are to have an adequate structure for ensuring the ethics of research in developing countries.

Also central to these difficult questions are deep challenges about who has the standing or authority to resolve them, and by what standards. Procedurally, American regulations and practices require that research set in the developing world and conducted or funded, even in part, by Americans must be approved by an American institutional review board (IRB) and a similar board in the local country, where the research will be conducted. In the current controversy over the placebo-controlled trials, much has been made about approval of the trials by local review boards and of the defense of the trials by investigators from the affected developing countries. Although such support is clearly relevant to the ethics debate, Annas and Grodin rightly point out that approval by local authorities and review groups does not in itself guarantee that research is ethical, nor does it remove the moral ground for criticism by outsiders.

It is less clear, however, whether cultural relativism in research ethics is the basis for the dispute between some African supporters of the clinical trials and some Western critics. If these countries had health care budgets similar to our own, little disagreement might arise between Africans and Americans about what constitutes an ethical trial design. The more relevant question is not whether different cultural values justify different research designs, but rather whether different economic situations do. Surely the ethics of research are affected by relevant background conditions, but in what ways? What are the ethical implications when research studies are designed to address public health crises under extreme resource constraints?

Finally, we concur with Bayer that the use of the Tuskegee analogy when discussing the recent controversy in international perinatal HIV research is wholly inappropriate. The relevant question is whether the trials are *ethical*, not whether the trials resemble Tuskegee (here, in fact, we agree with Bayer that the two cases are significantly different morally). The Tuskegee analogy, as does the Holocaust analogy, guarantees attention to an argument. At very least, however, these analogies distract from a critical and honest dialogue, offend many, and belittle grim history.

The ethics of American researchers or funders conducting research in resource-poor environments is challenging beyond words. In the examples at hand, we face an agonizing choice. On the one hand, by adhering to Western standards of medical care, we could produce great benefit to the persons who participate in trials but slower progress for medical science. On the other hand, by providing less benefit to research participants in developing countries than that which is provided in developed countries, we are more likely to yield quicker and more relevant answers for the larger community. Such a dilemma calls for extensive further public discussion, which must include the voices of all relevant communities, from American researchers, fun-

ders, and IRBs, to local country researchers, governments, review boards, and, most especially, potential research participants and their communities. We can be confident that the ethics of international research will benefit from so much public attention. □

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