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Ethics of Placebo-Controlled Trials of Zidovudine to Prevent the Perinatal Transmission of HIV in the Third World

To the Editor: Lurie and Wolfe (Sept. 18 issue)[1] claim that ongoing placebo-controlled trials of antiretroviral agents to reduce perinatal transmission of the human immunodeficiency virus (HIV) in developing countries are unethical. As executive director of the World Health Organization Global Program on AIDS, I convened the June 1994 meeting that considered how best to apply the impressive results of AIDS Clinical Trials Group (ACTG) study 076 in developing countries, where 90 percent of HIV infections occur. Twenty-eight experts from eight developed and six developing countries participated.

Contrary to the accusations of Lurie and Wolfe, the only relevant information known at that time was that in most cases perinatal transmission occurred during the last few weeks of pregnancy, and this gave us hope that an affordable short-course regimen (two to three weeks) could be effective. Data from the 12-week subgroup analysis of the ACTG 076 study and data on the pharmacokinetics of zidovudine were not available. Even if the subgroup analysis had been available, it would not have helped in a determination of the efficacy of a two-to-three-week regimen.

At the meeting it was unanimously recommended that the shorter regimens be evaluated through a placebo-controlled design. The reasons were multiple: there was no information on efficacy in breast-feeding populations or on

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drug tolerance in women with high rates of anemia, accurate efficacy data were needed to justify drug-related expenditure, and such a design, because of its use of a smaller sample size, would most expeditiously provide the information needed to maximize the saving of the lives of newborns. Because of its cost and logistical constraints, the ACTG 076 regimen could never become the standard of care for developing countries. . . .

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1. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. N Engl J Med 1997;337:853-856.[Full Text]

To the Editor: Lurie and Wolfe charge that trials in developing countries of affordable and implementable interventions against perinatal transmission of HIV that are supported by the Centers for Disease Control and Prevention (CDC) and others are unethical because they compare an experimental short regimen of zidovudine with placebo rather than with the ACTG 076 zidovudine regimen used in developed countries (i.e., an "equivalency" design).[1] We wish to explain why the CDC-sponsored collaborative trials in Thailand and the Ivory Coast used placebo for the comparison group.

The trials first must assess the safety of zidovudine in the local populations. In Ivory Coast, for example, where anemia and perinatal mortality are common, using zidovudine as the control would preclude an evaluation of whether zidovudine contributes to any such serious adverse outcomes observed in the trial. Without a non-zidovudine group, any adverse maternal, delivery-related, or neonatal outcome could be attributed to zidovudine.

More important, comparison with the ACTG 076 regimen does not address the principal public health question for these countries: whether an implementable zidovudine regimen is better than the local practice of no antiretroviral intervention. This requires comparing the proposed intervention with current practice. With an equivalency design, only if the shorter intervention is found to be as effective as the ACTG 076 regimen can its efficacy be inferred. If, however, the shorter regimen is not as effective as the longer one, it would remain unclear whether the shorter version is better than no antiretroviral intervention.

The requirement that the same standard of ethics apply in both host and sponsoring countries was scrupulously observed in these studies, which were reviewed and approved by ethics committees in the three countries. . . .

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1. Recommendations of the U. S. Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1994;43:1-20.

To the Editor: All of us who have worked in the developing world have seen innumerable examples of children dying because of the lack of basic sanitation, penicillin, oral-rehydration fluid, or the like. Providing expensive antiviral agents is often out of the question. Given that there are not the resources to purchase zidovudine, the practice in most countries is to give nothing to infants born to women infected with HIV type 1. Thus, when one is conducting a study to find the least expensive alternative to the very expensive U.S. standard, it is reasonable to use a placebo group to get a solid answer. The first ethical standard in such a case is not to put the volunteers at increased risk. Clearly, doing what is usual in a country does not put the infants at increased risk. The second ethical standard is to undertake a sound scientific study that will accurately estimate the benefits of a variety of, one hopes, affordable treatment regimens. A placebo group is required for this. . . .

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To the Editor: . . . Ugandan studies are responsive to the health needs and the priorities of the nation. Research subjects have been selected in such a way that the burdens and benefits of the research will be equitably distributed, and the appropriate authorities, including the national ethics review committee, have satisfied themselves that the research meets their own ethical requirements. With these requirements met, if Ugandans cannot carry out research on their people for the good of their nation, applying ethical standards in their local circumstances, then who will?
Lurie and Wolfe attempt to provide evidence that the theoretical equipoise between placebo and short-course zidovudine is disturbed. However, they fail to recommend a better treatment. Given that the ACTG 076 regimen has not been used in this country, given that we do not know at what stage of pregnancy most cases of transmission take place in malarial areas or the impact of breast-feeding on transmission rates, and given the absence of preliminary data in support of short-course zidovudine, equipoise with respect to the Ugandan population is not disturbed. And in Chalmers's view,[1] which my colleagues and I share, equipoise is disturbed when the odds that plan A will be more successful than plan B are anything other than 50 percent. Hence, the need for research.

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To the Editor: Even if one does not entirely accept all the arguments proposed by Lurie and Wolfe about the ethical obligation of comparing simplified preventive treatments with zidovudine with complete treatment according to the ACTG 076 protocol rather than with a placebo, the use of randomization in this situation raises various difficulties. However, there is an observational type of alternative that is less traumatic for those involved and that can reasonably be used to assess the efficacy of a prophylactic strategy.

Over the past 10 years, numerous cohorts have been established around the world in both developing and industrialized countries for the analysis of the epidemiology of mother-to-child transmission of HIV. The transmission rates in these cohorts are consistent and dependent on the same obstetrical and maternal immunologic and virologic factors, the contribution of which is now well established (although it explains only part of the variability in the transmission rate). After adjustment for various interpretive biases (particularly those associated with the problem of following uninfected children), the rates are very similar and stable: 20 percent to 30 percent in Africa (with breast-feeding)[1,2,3,4] and 15 to 25 percent in industrialized countries (with bottle feeding).

The massive use of zidovudine in American and European cohorts that followed the release of the results of the ACTG 076 protocol[5] has confirmed the trial results.[5,6,7,8,9,10] Treating all women who are informed and volunteer in any cohort for which the transmission rate is clearly established and has been stable for a period of months should allow the effects of the treatment to be assessed. This is not a so-called historical comparison so disliked by methodologists, but a continuous observation of the transmission rate (a biologic phenomenon) and any variations associated with the therapeutic treatment. Moreover, it would be possible to compare the transmission rate adjusted for biologic and obstetrical parameters between treated mothers and those not receiving the treatment (because of refusal or other reasons) during the same period.

It is true that there could be bias arising from the slight decline in the transmission rate, which is not due to zidovudine, recently observed in various cohorts,[10] but this phenomenon is gradual, very unlike the large and sudden drop associated with the application of effective prophylaxis. Nevertheless, the margin of error of this type of approach is undoubtedly larger than that of a randomized trial. The error could be reduced by comparing the reproducibility in two or three further cohorts. If the effect is not large enough to be unambiguous (a reduction of less than 50 percent in the transmission rate, for example) or not reproducible in different cohorts, it would be unclear whether the strategy was satisfactory. In that case, it may not justify the financial effort that the international community is (I hope) prepared to make to reduce HIV transmission in the poorest countries.

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To the Editor: If we fail to challenge the notion that there can be a lower, local standard of care for people in the developing world, the same arguments could be offered in support of similarly objectionable studies in groups within the United States. This is not implausible, as more explicit forms of market-based health care rationing threaten to force on certain U.S. communities economically determined standards of care.

Exploitation by industrialized countries of the human and natural resources of the developing world has a long and tragic history. It has never been difficult for economically wealthy countries to justify their acts by citing, for example, the supposed genetic or moral inferiority of those exploited. Substituting economic inferiority in these old arguments makes the enterprise no less offensive. Public health interventions necessarily involve attention to costs, but physicians, even those conducting research, must never abandon their principal duties as caretakers and advocates for the individual patient. Human subjects in clinical trials are, first and foremost, patients and thus deserve care that is both medically sound and compassionate.

Roy J. Kim, M.D.

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To the Editor: . . . One of the major problems in the Third World is the weak ethics and scientific committees that review scientific studies. The membership consists of interested parties, such as the investigators, and they may receive incentives, including coauthorship or a ticket to an international conference. This is a serious conflict of interest. . . .

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To the Editor: . . . Subjects in trials such as those referred to by Lurie and Wolfe may misapprehend the benefits and risks at stake. The very desperation of women with no other alternatives to protect their children from HIV infection can be extremely coercive.[1] Illiteracy rates in some of these countries also work against the presumption that people fully understand what is at stake in the trials. For these reasons, it cannot be said that obtaining consent from the subject is adequate to protect the subjects involved from research risks. We conclude, therefore, that these trials are unethical insofar as they make use of a captive population and impose risks that depart from the accepted standard of medical care.

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To the Editor: . . . Varmus and Satcher (Oct 2. issue)[1] quote a Ugandan researcher as saying that "it is not [the National Institutes of Health] conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people." Since the Tuskegee study was conducted by Americans on Americans, this argument obviously does not stand. More important, researchers in developing nations derive substantial individual and institutional benefits from sponsored research, irrespective of their status as initiators of or collaborators in such research. Unethical research will not benefit developing countries in the long run, since it undermines human rights, which are the very foundation on which sustainable development needs to be built. In addition, it violates the principle of justice that a continent impoverished through colonialism, and forced to continue to be unable to provide gold-standard treatment because of debt traps, will continue to provide the human laboratory where placebo-controlled trials can be conducted because locally affordable care is often no more than placebo treatment.

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To the Editor: The real transgression is not in the design of the placebo-controlled trials in HIV-infected African women, but rather in their number. Surely, by pooling intellectual and financial capital, 2 or 3 large trials could have been done rather than the 16 currently under way. A few larger trials would have been better positioned to evaluate efficiently the most promising and practical interventions and the effects of the timing, dose, and duration of therapy. Larger trials could also have employed unbalanced randomization strategies to limit the number of subjects assigned to placebo.

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To the Editor: . . . The real double standard lies not in the way the trials are being conducted, but in the inequity in access to medicines in different countries. Our challenge is how to make the best-proved and most applicable regimens available to women in developing countries. The Joint United Nations Programme on HIV/AIDS is working with the United Nations Children's Fund on implementation plans to prevent mother-to-child transmission of HIV in 10 developing countries, in anticipation of applicable interventions resulting from the trials. The program is also in advanced discussions with a number of pharmaceutical companies to make antiretroviral packages aimed at preventing mother-to-child transmission more affordable.
It is efforts of this kind that require public attention, not those that may jeopardize much-needed research in countries already carrying the burden of the HIV–AIDS epidemic.

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To the Editor: The ethical justification for performing the reduced-dosage trials of zidovudine in impoverished countries is that such research could lead to therapies that will benefit the residents of those countries. Indeed, this is the argument made by Varmus and Satcher.[1] But the only way these studies could be of any benefit to the countries where the research is conducted is for the company that sells the drugs, the entity funding the research, or the government that invites or permits the research to be done on its population to guarantee that if the research hypothesis is proved, the therapy will be made available to those in the country who need it.[2]
Varmus and Satcher point out that the per-capita expenditure for health care in Malawi, for example, is just over $1. Given this fact, Malawi (or some other funder) must make realistic assurances that if research proves that $200 worth of zidovudine is effective in reducing mother-to-infant transmission of HIV, resources will be made

available so that the women of Malawi will receive this regimen. If they will not receive the regimen, then no such research on this population would be ethical, regardless of whether the control subjects receive placebo or the full course of the ACTG 076 regimen. To use a population as research subjects because of its poverty and inability to obtain care, and then not to use that knowledge for the direct benefit of that population, is the very definition of exploitation.

The exploitation is made starker by the fact that richer nations will unquestionably benefit from this research. If it is proved that lower doses of zidovudine provide adequate protection against mother-to-child transmission of HIV, it is certain that the richer countries that currently provide and pay for zidovudine will begin to use these lower doses, thereby receiving economic benefit. If the studies show that the lower doses are ineffective, then the richer countries will not need to put their own populations at risk to discover this fact. Either way, wealthier countries benefit.

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To the Editor: While designing a clinical trial in Thailand in early 1994, we felt that both scientifically and ethically, the only option for a controlled study design was an equivalency study.[1] This was for many months the focus of our discussions with the National Institutes of Health (NIH) Study Section, whose primary criticism was directed at our proposed use of the standard ACTG 076 regimen, rather than a placebo, for the control group. We argued that given the prognosis of perinatally acquired HIV infection, only the proven effective treatment could be used as the reference; that no data supported the reviewers' fear that the shorter regimen might be no more efficacious than no treatment; and that their objection that developing countries could be left stranded if the short treatment turned out to be less efficacious than the ACTG 076 standard was unfounded. Indeed, sound policy making in precisely those countries in which resources are scarce requires such information. It should be noted that during this lengthy process, the NIH staff never put pressure on us to include a placebo group in our design.

We believe that much of the debate in the past few months is the result of an unrecognized confusion about the role of clinical research in a public health crisis. Although clinical research may be justified by such a crisis and is indeed expected to contribute to its solution, it is not in itself the solution. Research in developing countries proved years ago that vitamin A supplementation could decrease infant mortality by 30 percent and that a vaccine could prevent the perinatal transmission of hepatitis B, and yet, these lifesaving, cost-effective, public health interventions are still not available in the countries that need them most.[2] No one can guarantee that the discovery of an effective, easier-to-use, more affordable method to prevent perinatal HIV will lead to its widespread application. This sad reality mandates that human

subjects, particularly the politically and economically vulnerable, as well as those who cannot provide consent — children in this case — should be protected during research. Indeed, as recently as last year, the good clinical-practice guidelines recommended by the International Conference on Harmonisation[3] restated that the researcher's primary ethical responsibility is for the welfare of subjects participating in the research, not for the welfare of future patients who may benefit from it.

At the same time, urgency in terms of public health demands that we implement as quickly as possible and wherever possible the methods of treatment that we already have — in this case, zidovudine prophylaxis and safe, supervised formula feeding. In Thailand, after a 1995 economic analysis by the Ministry of Public Health, the World Bank, and the World Health Organization, which showed that antiretroviral agents for perinatal prevention of HIV were affordable and cost effective,[4] the Thai Food and Drug Administration approved the use of zidovudine for this purpose, and both the Ministry of Public Health and the Thai Red Cross have begun programs to provide it to HIV-infected pregnant women.

Recognizing that clinical trials in developing countries raise complex issues particular to each region, time, and experimental question, we can rely only on the principles fundamental to medical practice and the scientific method to resolve the dilemmas these issues may pose. It is also clear that these decisions affect not only the present, but also the future, since clinical research worldwide would be jeopardized if potential participants feared that, within a trial, they risked being denied the most effective treatments available.

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The above letters and the Occasional Notes article by Dr. Phanuphak that appears elsewhere in this issue of the *Journal* were referred to Drs. Lurie and Wolfe and to Drs. Varmus and Satcher. Drs. Varmus and Satcher declined to reply. Drs. Lurie and Wolfe reply below:

To the Editor: Many defenses of the studies, mentioned above, are either contradicted by data available when the studies were designed or have since been abandoned by the sponsoring agencies themselves.

Merson, for example, claims that the ACTG 076 subanalysis showing the marked superiority of an average of seven weeks of zidovudine over placebo was "not available" at the time of the meeting in June 1994 of the World Health Organization Global Program on AIDS at which the use of placebo-controlled trials was endorsed. Yet these very data were presented at the February 1994 meeting of the ACTG 076 Monitoring Board, and officials from the NIH and CDC (including an NIH-affiliated coauthor of the ACTG 076 report) were present at the June 1994 meeting. The ethics review by the Global Program on AIDS was also slipshod: no ethicists were present at the June meeting, and the program did not even have its own formal ethics committee to review the trial.

Simonds et al., from the CDC, insist that only placebo-controlled trials can establish the safety of zidovudine in this population, and mention exacerbation of anemia as a possible risk of treatment. But the rates of anemia that could outweigh a 15 percent absolute reduction in fatal infant infections seem inconceivably high. Data available from the developing world do not suggest that zidovudine has unacceptable hematologic toxicity.[1,2]

Francis argues that the use of placebo is justified because the standard of care in these developing countries is not to treat with zidovudine. Yet the CDC's placebo-controlled trial in Thailand and the U.S. Army's observational study continued even after Thai researchers terminated their placebo-controlled trial when zidovudine became available

locally.[3] Even Varmus and Satcher, whose agencies sponsor most of the studies, have dismissed Francis's argument as too simplistic.[4]

Mbidde may believe that ethical equipoise has not been disturbed, but the CDC does not. In the CDC's Thailand protocol, the agency states that the study "is proposed in the belief that short-course oral therapy may be as effective or nearly as effective as the full ACTG 076 regimen,"[5] which means they expected it to be better than placebo.

The attempts of the Joint United Nations Programme on HIV/AIDS to make antiretroviral drugs available in developing countries are too little and too late. A decade after the efficacy of zidovudine was first demonstrated, only four countries are currently targeted under the expanded-access program, and the project is short on specifics. Although Dr. Piot continues to defend the placebo-controlled trials, his employer, World Health Organization director-general Hiroshi Nakajima, describes the studies as "unjustifiable . . . even in Asia, even in Africa."[6]

The researchers could have designed their studies to minimize the incidence of the fatal disease they were attempting to prevent and chose not to. As Kim proclaims, "physicians, even those conducting research, must never abandon their principal duties as caretakers and advocates for the individual patient."

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Editor's note: On February 18, 1998, the CDC suspended the placebo arm of its vertical-transmission studies in Thailand and Ivory Coast, citing preliminary data from the Thai study showing that a short-course regimen of zidovudine during pregnancy reduced by half the rate of maternal-to-fetal HIV transmission in non–breast-feeding women. In a joint statement, the Joint United Nations Programme on HIV/AIDS, the National Institutes of Health, and the French National Agency for AIDS Research announced that an international meeting would be held soon to "discuss the far-reaching scientific and policy implications of these findings."

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