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Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries

[Sounding Board]

Lurie, Peter; Wolfe, Sidney M.

Public Citizen's Health Research Group; Washington, DC 20009

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It has been almost three years since the Journal [1] published the results of AIDS Clinical Trials Group (ACTG) Study 076, the first randomized, controlled trial in which an intervention was proved to reduce the incidence of human immunodeficiency virus (HIV) infection. The antiretroviral drug zidovudine, administered orally to HIV-positive pregnant women in the United States and France, administered intravenously during labor, and subsequently administered to the newborn infants, reduced the incidence of HIV infection by two thirds. [2] The regimen can save the life of one of every seven infants born to HIV-infected women.

Because of these findings, the study was terminated at the first interim analysis and within two months after the results had been announced, the Public Health Service had convened a meeting and concluded that the ACTG 076 regimen should be recommended for all HIV-positive pregnant women without substantial prior exposure to zidovudine and should be considered for other HIV-positive pregnant women on a case-by-case basis. [3] The standard of care for HIV-positive pregnant women thus became the ACTG 076 regimen.

In the United States, three recent studies of clinical practice report that the use of the ACTG 076 regimen is associated with decreases of 50 percent or more in perinatal HIV transmission. [4-6] But in developing countries, especially in Asia and sub-Saharan Africa, where it is projected that by the year 2000, 6 million pregnant women will be infected with HIV, [7] the potential of the ACTG 076 regimen

remains unrealized primarily because of the drug's exorbitant cost in most countries.

Clearly, a regimen that is less expensive than ACTG 076 but as effective is desirable, in both developing and industrialized countries. But there has been uncertainty about what research design to use in the search for a less expensive regimen. In June 1994, the World Health Organization (WHO) convened a group in Geneva to assess the agenda for research on perinatal HIV transmission in the wake of ACTG 076. The group, which included no ethicists, concluded, "Placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent [perinatal] transmission of HIV." [8] This unpublished document has been widely cited as justification for subsequent trials in developing countries. In our view, most of these trials are unethical and will lead to hundreds of preventable HIV infections in infants.

Primarily on the basis of documents obtained from the Centers for Disease Control and Prevention (CDC), we have identified 18 randomized, controlled trials of interventions to prevent perinatal HIV transmission that either began to enroll patients after the ACTG 076 study was completed or have not yet begun to enroll patients. The studies are designed to evaluate a variety of interventions: antiretroviral drugs such as zidovudine (usually in regimens that are less expensive or complex than the ACTG 076 regimen), vitamin A and its derivatives, intrapartum vaginal washing, and HIV immune globulin, a form of immunotherapy. These trials involve a total of more than 17,000 women.

In the two studies being performed in the United States, the patients in all the study groups have unrestricted access to zidovudine or other antiretroviral drugs. In 15 of the 16 trials in developing countries, however, some or all of the patients are not provided with antiretroviral drugs. Nine of the 15 studies being conducted outside the United States are funded by the U.S. government through the CDC or the National Institutes of Health (NIH), 5 are funded by other governments, and 1 is funded by the United Nations AIDS Program. The studies are being conducted in Cote d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic. These 15 studies clearly violate recent guidelines designed specifically to address ethical issues pertaining to studies in developing countries. According to these guidelines, "The ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country." [9] In addition, U.S. regulations governing studies performed with federal funds domestically or abroad specify that research procedures must "not unnecessarily expose subjects to risk." [10]

The 16th study is noteworthy both as a model of an ethically conducted study attempting to identify less expensive antiretroviral regimens and as an indication of how strong the placebo-controlled trial orthodoxy is. In 1994, Marc Lallemand, a researcher at the Harvard School of Public Health, applied for NIH funding for an equivalency study in Thailand in which three shorter zidovudine regimens were to be compared with a regimen similar to that used in the ACTG 076 study. An equivalency study is typically conducted when a particular regimen has already been proved effective and one is interested in determining whether a second regimen is about as effective but less toxic or expensive. [11] The NIH study section repeatedly put pressure on Lallemand and the Harvard School of Public Health to conduct a placebo-controlled trial instead, prompting the director of Harvard's human subjects committee to reply, "The conduct of a placebo-controlled trial for [zidovudine] in pregnant women in Thailand would be unethical and unacceptable, since an active-controlled trial is feasible." [12] The NIH eventually relented, and the study is now under way. Since the nine studies of antiretroviral drugs have attracted the most attention, we focus on them in this article.

Asking the Wrong Research Question [↗](#)

There are numerous areas of agreement between those conducting or defending these placebo-controlled studies in developing countries and those opposing such trials. The two sides agree that perinatal HIV transmission is a grave problem meriting concerted international attention; that the ACTG 076 trial was a major breakthrough in perinatal HIV prevention; that there is a role for research on this topic in developing countries; that identifying less expensive, similarly effective interventions would be of enormous benefit, given the limited resources for medical care in most developing countries; and that randomized studies can help identify such interventions.

The sole point of disagreement is the best comparison group to use in assessing the effectiveness of less-expensive interventions once an effective intervention has been identified. The researchers conducting the placebo-controlled trials assert that such trials represent the only appropriate research design, implying that they answer the question, "Is the shorter regimen better than nothing?" We take the more optimistic view that, given the findings of ACTG 076 and other clinical information, researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen. The proposal for the Harvard study in Thailand states the research question clearly: "Can we reduce the duration of prophylactic [zidovudine] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG 076 [zidovudine] regimen?" [\[13\]](#) We believe that such equivalency studies of alternative antiretroviral regimens will provide even more useful results than placebo-controlled trials, without the deaths of hundreds of newborns that are inevitable if placebo groups are used.

At a recent congressional hearing on research ethics, NIH director Harold Varmus was asked how the Department of Health and Human Services could be funding both a placebo-controlled trial (through the CDC) and a non-placebo-controlled equivalency study (through the NIH) in Thailand. Dr. Varmus conceded that placebo-controlled studies are "not the only way to achieve results." [\[14\]](#) If the research can be satisfactorily conducted in more than one way, why not select the approach that minimizes loss of life?

Inadequate Analysis of Data from ACTG 076 and Other Sources [↗](#)

The NIH, CDC, WHO, and the researchers conducting the studies we consider unethical argue that differences in the duration and route of administration of antiretroviral agents in the shorter regimens, as compared with the ACTG 076 regimen, justify the use of a placebo group. [\[15-18\]](#) Given that ACTG 076 was a well-conducted, randomized, controlled trial, it is disturbing that the rich data available from the study were not adequately used by the group assembled by WHO in June 1994, which recommended placebo-controlled trials after ACTG 076, or by the investigators of the 15 studies we consider unethical.

In fact, the ACTG 076 investigators conducted a subgroup analysis to identify an appropriate period for prepartum administration of zidovudine. The approximate median duration of prepartum treatment was 12 weeks. In a comparison of treatment for 12 weeks or less (average, 7) with treatment for more than 12 weeks (average, 17), there was no univariate association between the duration of treatment and its effect in reducing perinatal HIV transmission ($P = 0.99$) (Gelber R: personal communication). This analysis is somewhat limited by the number of infected infants and its post hoc nature. However, when

combined with information such as the fact that in non-breast-feeding populations an estimated 65 percent of cases of perinatal HIV infection are transmitted during delivery and 95 percent of the remaining cases are transmitted within two months of delivery, [19] the analysis suggests that the shorter regimens may be equally effective. This finding should have been explored in later studies by randomly assigning women to longer or shorter treatment regimens.

What about the argument that the use of the oral route for intrapartum administration of zidovudine in the present trials (as opposed to the intravenous route in ACTG 076) justifies the use of a placebo? In its protocols for its two studies in Thailand and Cote d'Ivoire, the CDC acknowledged that previous "pharmacokinetic modelling data suggest that [zidovudine] serum levels obtained with this [oral] dose will be similar to levels obtained with an intravenous infusion." [20]

Thus, on the basis of the ACTG 076 data, knowledge about the timing of perinatal transmission, and pharmacokinetic data, the researchers should have had every reason to believe that well-designed shorter regimens would be more effective than placebo. These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds. [21]

Defining Placebo as the Standard of Care in Developing Countries

Some officials and researchers have defended the use of placebo-controlled studies in developing countries by arguing that the subjects are treated at least according to the standard of care in these countries, which consists of unproven regimens or no treatment at all. This assertion reveals a fundamental misunderstanding of the concept of the standard of care. In developing countries, the standard of care (in this case, not providing zidovudine to HIV-positive pregnant women) is not based on a consideration of alternative treatments or previous clinical data, but is instead an economically determined policy of governments that cannot afford the prices set by drug companies. We agree with the Council for International Organizations of Medical Sciences that researchers working in developing countries have an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring country, when possible. [9] An exception would be a standard of care that required an exorbitant expenditure, such as the cost of building a coronary care unit. Since zidovudine is usually made available free of charge by the manufacturer for use in clinical trials, excessive cost is not a factor in this case. Acceptance of a standard of care that does not conform to the standard in the sponsoring country results in a double standard in research. Such a double standard, which permits research designs that are unacceptable in the sponsoring country, creates an incentive to use as research subjects those with the least access to health care.

What are the potential implications of accepting such a double standard? Researchers might inject live malaria parasites into HIV-positive subjects in China in order to study the effect on the progression of HIV infection, even though the study protocol had been rejected in the United States and Mexico. Or researchers might randomly assign malnourished San (bushmen) to receive vitamin-fortified or standard bread. One might also justify trials of HIV vaccines in which the subjects were not provided with condoms or state-of-the-art counseling about safe sex by arguing that they are not customarily provided in the developing countries in question. These are not simply hypothetical worst-case scenarios; the first two studies have already been performed, [22,23] and the third has been proposed and criticized. [24]

Annas and Grodin recently commented on the characterization and justification of placebos as a

standard of care: "'Nothing' is a description of what happens; 'standard of care' is a normative standard of effective medical treatment, whether or not it is provided to a particular community." [\[25\]](#)

Justifying Placebo-Controlled Trials by Claiming They Are More Rapid [↑](#)

Researchers have also sought to justify placebo-controlled trials by arguing that they require fewer subjects than equivalency studies and can therefore be completed more rapidly. Because equivalency studies are simply concerned with excluding alternative interventions that fall below some preestablished level of efficacy (as opposed to establishing which intervention is superior), it is customary to use one-sided statistical testing in such studies. [\[11\]](#) The numbers of women needed for a placebo-controlled trial and an equivalency study are similar. [\[26\]](#) In a placebo-controlled trial of a short course of zidovudine, with rates of perinatal HIV transmission of 25 percent in the placebo group and 15 percent in the zidovudine group, an alpha level of 0.05 (two-sided), and a beta level of 0.2, 500 subjects would be needed. An equivalency study with a transmission rate of 10 percent in the group receiving the ACTG 076 regimen, a difference in efficacy of 6 percent (above the 10 percent), an alpha level of 0.05 (one-sided), and a beta level of 0.2 would require 620 subjects (McCarthy W: personal communication).

Toward a Single International Standard of Ethical Research [↑](#)

Researchers assume greater ethical responsibilities when they enroll subjects in clinical studies, a precept acknowledged by Varmus recently when he insisted that all subjects in an NIH-sponsored needle-exchange trial be offered hepatitis B vaccine. [\[27\]](#) Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential exploitation in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.

With the increasing globalization of trade, government research dollars becoming scarce, and more attention being paid to the hazards posed by "emerging infections" to the residents of industrialized countries, it is likely that studies in developing countries will increase. It is time to develop standards of research that preclude the kinds of double standards evident in these trials. In an editorial published nine years ago in the *Journal*, Marcia Angell stated, "Human subjects in any part of the world should be protected by an irreducible set of ethical standards." [\[28\]](#) Tragically, for the hundreds of infants who have needlessly contracted HIV infection in the perinatal-transmission studies that have already been completed, any such protection will have come too late.

Peter Lurie, M.D., M.P.H.

Sidney M. Wolfe, M.D.

Public Citizen's Health Research Group; Washington, DC 20009

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