Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

June 11, 1997

President William J. Clinton
1600 Pennsylvania Avenue
Washington, DC

Dear President Clinton:

The United States government is sponsoring biomedical research on mother-to-infant HIV transmission in developing countries that could not be carried out in the U.S. Many people believe it is therefore unethical to conduct these studies in Africa, Asia, and the Caribbean, as is currently planned. This is because thousands of HIV+ pregnant women in these studies are being denied access to AZT, a treatment that has been proven to be dramatically effective in reducing the rate of HIV transmission from pregnant women to their babies. Experts in HIV/AIDS and research methodology attest that these studies could be redesigned to be ethical while still answering the relevant research questions.

On April 22 of this year we wrote to HHS Secretary Shalala strongly urging that nine developing country experiments involving HIV+ pregnant women, funded by the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC) be changed so that all subjects receive an active treatment rather than consigning several thousand women to get a placebo or other unproven treatments. While we support the goal of these studies, namely to find a less expensive, shorter and less-complicated treatment regimen to reduce maternal-infant transmission of HIV than that proven effective in the study known as ACTG 076, we stated that it was highly unethical to achieve that goal by exposing large numbers of women to no treatment (a placebo) or treatments not proven effective. We suggested that all women should get some arguably effective treatment and that, for example, these shorter courses of treatment could be compared to the full 076 regimen. Such a study design could have resulted in the prevention of up to 1,000 unnecessary HIV infections in the U.S-funded studies.

Since April 22, we have obtained government documents and other information which further strengthen the case for immediately redesigning these studies to prevent further loss of life in infants whose mothers do not receive AZT. At the very least, if you are unwilling to order these experiments to be changed to equivalency studies (see below) now, this matter is clearly

urgent and controversial enough to be promptly reviewed by the newly constituted Presidential National Bioethics Advisory Commission (NBAC) when it meets again next month. A recommendation for a referral to NBAC has been endorsed by Dr. Philip Lee, former Assistant Secretary for Health of HHS,[1] Dr. Thomas Murray, a member of the NBAC[2] and Director of the Center for Biomedical Ethics, Case Western Reserve University School of Medicine, Dr. Richard Humphrey,[3] a Johns Hopkins University Medical School and School of Public Health faculty member (despite the fact that his institution is involved in six of the studies) and Dr. Arthur Caplan, Director of the Center for Bioethics, University of Pennsylvania.[4]

The new findings which further undermine the ethical basis for the current studies are:

- Despite American researchers' emphasis on how widely these studies have been endorsed by developing country scientists, Cote d'Ivoire researchers actually involved in the CDC study there raised ethical questions about conducting placebo-controlled trials in that country: An internal CDC memo dated January 27, 1995, in a section on ethical issues stated that **"Despite detailed discussions (both verbal and in the protocol) justifying the use of placebo, it has become evident that some of the Ivoirian physicians working at project RETRO-CI [the CDC research base in Cote d'Ivoire=CI], several of our important Ivoirian collaborators, and a number of international researchers involved in MTCHC [mother to child HIV transmission], do not feel comfortable with the use of placebo."**(emphasis supplied) CDC described the views of these dissenters as: "since all children infected with HIV during the trial would likely die, it is argued that it would not be ethical to subject these families to the risk of placebo within the context of a clinical trial."[5] Their concerns appear to have been overpowered by CDC's and others' arguments supporting the use of placebos.

  Similarly, in an NIH-funded study in Ethiopia which involves Johns Hopkins University, the local ethical review committee voted by a narrow and controversial 6 to 5 vote to approve of that study, the first time the committee had taken a formal vote. In addition, 135 physicians from Brazil have written to Secretary Shalala criticizing the U.S.-funded studies.

- In Thailand, the CDC is also conducting a placebo-controlled study involving AZT, claiming that, since the standard of care in Thailand is not to give AZT to HIV+ pregnant women, it is necessary to have one group of women in the study get a placebo. In sharp contrast, the investigators of a study funded by NIH (also an HHS agency) in the same country does not use a placebo. Instead it compares the shorter, simpler treatments to the full 076 regimen in an equivalency study (see below). Asked about the contradiction between these two kinds of studies in Thailand when he was testifying before Rep. Christopher Shays' Subcommittee on Human Resources on May 8, 1997, NIH Director Harold Varmus conceded that placebo-controlled studies are "not the only way to achieve results." If placebo-controlled trials are not the only acceptable research design, why is NIH funding a placebo-controlled trial?

- The researchers, in the equivalency study from Harvard and Thailand, had to overcome efforts by an NIH study section which tried to force them to change the design of their study to placebo-controlled. Indeed, officials at NIH supported the Harvard researchers in their efforts to conduct the equivalency study instead of a placebo-controlled trial. Responding to the study section's pressure in December 1994, long before CDC's placebo-controlled trial had begun in Thailand, the Director of Harvard's Human Subjects Committee wrote NIH that "Our Committee members believe that once an active therapy for particular diseases is identified, use of placebo-control trials of different agents and different modes of administration may be **unethical. The conduct of a placebo-controlled trial for ZDV [AZT] in pregnant women in Thailand would be unethical and unacceptable since an active-controlled trial is feasible...."**(emphasis supplied)[6]

  (Actually, there was a third maternal-infant HIV transmission study in Thailand at one point, a placebo-controlled study conducted by a Thai university. However, during the trial, AZT became more available in Thailand. It is manufactured locally by the Government Pharmaceutical Organization and costs $0.36 per 100 mg capsule. The Ministry of Public Health provides AZT free to about 2,000 poor patients and others receive the drug free through the Thai Red Cross Society. With this increased availability, the Thai researchers terminated their study so that no one would receive placebo. However, the CDC researchers continue to enroll patients in their placebo-controlled study.)

- In June 1994, a WHO meeting recommended that "placebo-controlled trials offer the best option for rapid and scientifically valid assessment of alternative [to the 076 regimen] antiretroviral drug regimens to prevent MTI [maternal to infant] transmission of HIV," and this dictum has been widely cited as justification for doing placebo-controlled trials. For example, the CDC states in its response to our April 22nd letter that a study comparing short-course AZT treatment with the regimen proved effective in Protocol 076 "would require an extremely large study that would take a long time to complete." In a May 1995 memo reviewing possible maternal-infant transmission study designs, the Division of HIV/AIDS Prevention at CDC considers seven different clinical trial designs and endorses placebo-controlled trials, but fails to even mention the alternative that we suggest and which has been adopted in the NIH-funded study being conducted by Harvard University and local researchers in Thailand: an equivalency study.

  Equivalency studies are typically conducted when a regimen has been proved effective and one is interested in determining whether a second regimen is about as effective, but less toxic or less expensive. (By contrast, a placebo-controlled trial asks whether a given intervention is better than nothing.) The current state of knowledge in maternal-infant transmission studies of antiretrovirals mandates such an approach,

and would prevent the unnecessary loss of life.

Despite WHO/CDC (some NIH) insistence on the superiority of placebo-controlled trials, a recent review by a statistician consultant demonstrates that an equivalency study can be conducted using approximately the same number of subjects as placebo-controlled trial[7] (See attachment) In a placebo-controlled trial, assuming that the HIV transmission rate in the placebo group would be 25% and that in the short-course AZT group it would be 15%, 500 subjects would be needed to reach statistical significance. In an equivalence study, assuming that HIV transmission in the 076-regimen group was 10% and setting a "tolerance" for a 6% difference between the groups (this means that one would be willing to accept up to a 6% difference between the groups; 6% was the tolerance used in the NIH-funded equivalency study in Thailand), 620 subjects would be needed. If the tolerance were further increased to 7%, only 454 subjects would be needed.

Further emphasizing that placebo-controlled trials are not necessarily speedy, the December 12, 1996 minutes of the Data Safety Monitoring Board of the CDC-funded study in Cote d'Ivoire stated that "in [the] first 28 weeks of study only 6% of the total number of women who need to be entered have been recruited" and that "rate of accrual is much slower than the anticipated rate...." The speed of the trial is, therefore, more likely to depend on actual conditions in the field than on minor differences in sample size.

- The studies are duplicative and poorly coordinated as demonstrated by 1/ the conflict between the two studies in Thailand (see above), 2/ the fact that one NIH-funded vitamin A vs placebo study in Tanzania was designed without AZT in either part of the study because the investigators had been told that AZT was not a possibility in that country while the UN AIDS study in the same country uses AZT and two other antiviral drugs vs a placebo in its design and 3/ even among the AZT placebo-controlled trials, there are large differences in experimental design, making ultimate policy judgments difficult.

A recent letter to HHS Secretary Shalala from Dr. Curt Furberg, formerly the Director of Clinical Trials for the National Heart, Lung and Blood Institute of NIH, former President of the Society of Clinical Trials and currently Chairman of the Department of Public Health Sciences at Bowman Gray School of Medicine stated that "My first major concern relates to the coordination of these programs. Based on my review of the design of the 15 international randomized clinical trials that are evaluating treatments for mother-to-infant HIV transmission, it appears that the program coordination for these trials has been less than optimal. There is a real risk that this could lead to 1/ unnecessary delays in getting important scientific answers and 2/ duplication in effort, leading to waste of research resources and possibly to conflicting results from underpowered experiments. Fewer, but larger trials would have the advantage of providing faster and more reliable answers."

Dr. Furberg also criticized the placebo-controlled mantra of the WHO because it "fails to recognize that there are other and better design options." He referred to the Harvard equivalency study in Thailand as such a study. He concluded by stating that "These concerns--inadequate study coordination, suboptimal design, and ethically inappropriate care.....reflect poorly on the scientists and institutions conducting these studies and on the funding agencies and, ultimately, the U.S. government. I urge you to consider immediately convening a meeting that would include the involved parties as well as a number of 'outside' qualified scientists and ethicists. This urgent public health problem needs to be addressed in a balanced fashion, in hopes of reaching reasonable and expeditious solutions."[8]

- Even though they are to be faulted for charging as much as they have for these and other drugs, at least two pharmaceutical companies have raised serious ethical questions about conducting placebo-controlled studies involving AZT after ACTG 076. Hoffmann-La Roche senior medical advisor Peter King, whose company makes DDC, a rival drug to AZT, said " We know AZT works. It cuts transmission by two-thirds. So any trial with a complete placebo arm is completely unethical."[9] Jennifer McMillan, an official with Glaxo-Wellcome (the manufacturer of AZT), has stated that the company has expressed serious reservations about placebo-controlled trials because such a design entails denying patients treatment known to benefit them.[10]

- Finally, Congresswoman Patsy Mink, a victim of unethical human experimentation with diethylstilbestrol (DES) in the 1950s, has written to Secretary Shalala about these experiments: Referring to these studies, she wrote: "There is no justification for our country to fund these experiments in developing countries without the same standard of care and concern for the children. Before another scandal exposes our indefensible disregard for life, I urge you to amend the protocol for these overseas experiments to conform to international, moral and ethical standards. We should be more meticulous in our insistence that in dealing with developing countries we follow the most stringent and highest standards that we insist for ourselves. We should never be the funders of overseas experiments that do not have the same safeguards as we would have if they were being conducted in this country."[11]

In sum, we believe this new information adds significantly to that in our April 22 letter, and further undermines the ethical basis for these US-funded studies. The reputation of the United States as a world leader in ethical medical research is at stake. We hope that you will respond rapidly to this urgent request.

Sincerely,

Sidney M. Wolfe, M.D.
Director

Peter Lurie, M.D., MPH
Research Associate
Public Citizen's Health Research Group

1. Personal communication with Sidney Wolfe, June 8, 1997.

2. Personal communication with Sidney Wolfe, June 6, 1997.

3. Letter from Dr. Richard Humphrey, Associate Professor of Medicine, Pathology and Oncology, Johns Hopkins University School of Medicine and School of Public Health, to HHS Secretary Donna Shalala, June 5, 1997. The letter also said that "Having talked with several of my colleagues here at Hopkins, it is only honest to tell you that there has been a lot of discussion about this issue and that a unanimity of opinion about these issues does not exist."

4. Personal communication with Sidney Wolfe, June 8, 1997

5. CDC memo dated January 27, 1995 from Tim Dondero, Phil Neiberg and Martha Rogers to Alan E. Greenberg and Stefan Z. Wiktor.

6. Letter from Troyan Brennan, M.D., Chairperson of Human Subjects Committee, Harvard School of Public Health, to Dr. Gilbert Meier, Division of Research Ethics, NIH, December 28, 1994.

7. Analysis done by William McCarthy, PhD, a biostatistician, for Public Citizen's Health Research Group.

8. Letter from Curt Furberg, M.D., PhD, to HHS Secretary Shalala, June 5, 1997.

9. Michael Day. *How the West Gets Well*. New Scientist. May 17, 1997.

10. Personal communication with Sidney Wolfe, June 5, 1997.

11. Letter from Congresswoman Patsy Mink, (D-Hawaii), to HHS Secretary Shalala, May 21, 1997.

Attachment

Placebo-controlled trial (Short-course AZT vs. placebo)

Assumptions:
HIV transmission rate in placebo group = 25%
Beta = 0.2
Alpha = 0.05 (two-sided)
Equal numbers of subjects in each study arm

HIV transmission rate in short-course group	13%	15%	16%	19%	20%	21%	24%
Required sample size	334	500	630	1494	2188	3472	58072

Equivalency trial (Protocol 076 vs. short-course AZT)

Assumptions:
HIV transmission rate in Protocol 076 rate: 10%
Beta = 0.2
Alpha = 0.05 (one-sided)
Equal numbers of subjects in each arm

Tolerance	5%	6%	7%	10%
Required sample size	892	620	454	224

HARVARD SCHOOL
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TROYEN A. BRENNAN, M.D., J.D., M.P.H.
Professor of Law and Public Health
Professor of Medicine

June 10, 1997

Donna Shalala, Secretary
Department of Health and Human Services
2003 Independence Ave
Room 6006
Washington, D.C.

Dear Ms Shalala:

I have been following with interest the recent debate over the ethics of placebo/control trials for pregnant women in developing countries who may be at risk of transmitting HIV to their offspring. Our Human Subjects Committee at the Harvard School of Public Health approved two of these studies. As the Chairperson, I was involved in and take responsibility for our decisions.

One study involved treating women prophylactically with AZT to avoid transmission in Thailand. Although some international organizations had advocated use of placebo to evaluate the efficacy of the AZT, given the existing data and the commitment of the Thai government to use of AZT in pregnancy, our investigator successfully advocated with NIH for an active control arm; ethically it seemed to us anything else would have been unacceptable.

The other study concerned use of Vitamin A in pregnancy to prevent transmission in sub-Saharan Africa. The study was designed before information on the efficacy of AZT was known. Once this information came available , we thought that the key issue would be the availability of AZT in the study country. We were assured that during the trial AZT would not be available and so testing this lower cost strategy seemed appropriate. With the possibility that AZT might now be more widely available, this decision will have to be carefully re-considered.

We continue to believe that we made the right decisions. Nonetheless, I think it is necessary to scrutinize and re-scrutinize decisions in this very sensitive area. Therefore,

I personally believe that Public Citizen has discharged an important civic duty in bringing these issues to light. We must continue to be concerned about using double standards when we do research in developing countries. Therefore I am surprised by the academic attacks on Dr. Wolfe and Public Citizen. We should be welcoming this oversight and attention to the issues.

Nor do I believe that Public Citizen's concerns represent cultural imperialism. I think that there are some basic human rights that we must all uphold, and I believe that Public Citizen's penetrating questions serve that purpose.

As contexts change in developing countries, so must our views about what research is acceptable. In my view, and it is my personal view (I am not speaking on behalf of Harvard University), it is unethical to do placebo/control trials of AZT in the perinatal setting in Thailand today; and it may be becoming unethical to do so in some areas of Sub-Saharan Africa. Moreover, as a researcher and human subjects committee member I believe we should encourage others to question our decisions and engender debate.

Sincerely yours,

Troyen A. Brennan