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AIDS TRIALS

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Contacts:
Peter Lurie, Hotel Jean-Jacques Rousseau, Geneva (Phone: (22)731-5570; Fax: (22)738-4105)
Sidney Wolfe, Washington, DC, USA: Phone: (202)588-1000
Brian Dooley, Washington, DC, USA: Phone: (202)588-7703
Booth Gunter, Washington, DC, USA: Phone: (202)588-7741

HEALTH GROUP ATTACKS SECOND GENERATION OF UNETHICAL PERINATAL TRIALS IN AFRICA

Researchers to Deny HIV-positive Pregnant Women Effective, Less Expensive Drug Regimens

HIV-positive pregnant African women involved in HIV experiments continue to be denied effective treatment, resulting in the needless infection of dozens of babies, says Public Citizen's Health Research Group.

Despite the U.S. Centers for Disease Control and Prevention (CDC)'s identification of a less-expensive regimen of AZT capable of reducing HIV transmission from mother to infant by 51%, several studies now being designed still do not plan to provide this potentially life-saving intervention, says the group.

This and further unethical aspects of past and present perinatal HIV trials in developing countries will be explored by Peter Lurie, MD, MPH of Public Citizen's Health Research Group in an oral presentation at 15:00 on Wednesday, July 1, 1998 in Hall I at the 12th World AIDS Conference in Geneva, Switzerland. In a highly unusual scheduling decision by the organizers, Dr. Hoosen Coovadia of the University of Natal in South Africa, who has conducted some of the unethical research, is to provide a "Reply" immediately after Dr. Lurie's presentation.

In April 1997, Public Citizen's Health Research Group criticized 15 studies, most funded by the U.S. government, in which thousands of HIV-positive pregnant women were denied access to AZT, a drug shown in a study in the U.S. and France to dramatically reduce perinatal HIV transmission. The studies were designed to identify more affordable versions of the successful U.S./French regimen that could be utilized in developing countries where the vast majority of

the 500,000 annual perinatal HIV transmission occur. Public Citizen criticized the failure to provide AZT to some of the women in these studies; in some studies women received placebos instead of the known effective medication.

In September 1997, Public Citizen renewed its attack in the *New England Journal of Medicine*; the Journal's Executive Editor, Marcia Angell, supported Public Citizen's criticism. Despite this, most of the studies continued. In February 1998 a CDC-sponsored placebo-controlled study in Thailand confirmed what Public Citizen had predicted all along: short courses of AZT reduced the rate of HIV transmission from mother to infant, by 51%.

In his presentation, Dr. Lurie will focus on three studies now being designed that do not provide even the less expensive regimen proved effective in the Thailand/CDC study to all study participants. For example, in a study Dr. Coovadia is now planning for potential funding from the Wellcome Trust, HIV-positive pregnant women would simply be observed to determine the rate and predictors of HIV transmission to infants, even though two provinces in South Africa are currently developing plans to provide AZT for such women.

"It is simply unbelievable that any researcher would design a study in which no intervention whatsoever is offered to the women, particularly after the Thai/CDC results," said Dr. Lurie. "What was the purpose of the previous round of studies if not to identify drug regimens that could actually be offered to HIV-positive pregnant women?"

Dr. Lurie will also discuss two U.S. government-funded studies: HIVNET 012 (Principal Investigator: Brooks Jackson, Johns Hopkins University) in which the HIV-positive pregnant women will not receive any AZT prior to delivery (this was an important part of the Thai/CDC regimen) and another HIVNET study involving chlorhexidine vaginal washings (Principal Investigator: Sten Vermund, University of Alabama) in which no women receive any AZT.

Dr. Lurie will also examine the ethical implications of the failure to provide treatment for the women once they have delivered their infants; risks include the development of resistant HIV strains due to stopping and starting drug regimens.

"It seems that these researchers have learned little from the initial debate over the ethics of the perinatal studies," said Dr. Lurie. "Rather than embarking upon a second generation of unethical trials, the researchers should immediately redesign these studies to ensure that all women have access to life-saving antiretroviral medications."

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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

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MEDICAL SCHOOL

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

#1415

HIV experiment

Public Citizen

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Joan Claybrook, President

April 22, 1997

Secretary Donna Shalala
Department of Health and Human Services
200 Independence Ave, SW
Washington, D.C. 20201

Dear Secretary Shalala:

Unless you act now, as many as 1,002 newborn infants in Africa, Asia and the Caribbean will die from unnecessary HIV infections they will contract from their HIV-infected mothers in nine unethical research experiments funded by your Department through either the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC). Even though an NIH-funded randomized, controlled trial (so-called Protocol 076) demonstrated in 1994 that the antiviral drug AZT (zidovudine) can reduce transmission from mother-to-infant by approximately two-thirds,[1] a finding so dramatic that the study was stopped prior to its scheduled completion, some or all of the women in these nine developing country experiments are still not being provided with effective prophylaxis, placing their infants at risk for fatal HIV infection. Instead, they are offered either placebos or interventions that have not been proved effective. In addition, 502 infants in six similar experiments funded by foreign governments (France–two studies, Belgium, Denmark, South Africa) and the United Nations AIDS program will contract HIV, making a total of 1,504 infants who can be expected to die unnecessarily in these experiments, some of which are already under way. These preventable deaths can be averted if you simply require all women in these experiments to be offered some regimen of AZT, or any other regimen proved similarly effective. We are not opposed to randomized, controlled trials of different kinds of arguably effective interventions to reduce mother-to-infant HIV transmission *per se*; we do object to such trials if they deny women access to any intervention already proved effective, such as AZT.

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[1] Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 1994;331:1173-1180.

The scientific basis for treating HIV-infected pregnant women with AZT

It is projected that by the year 2000 six million pregnant women will be infected with HIV, primarily in Asia and sub-Saharan Africa.[8] In the absence of prophylaxis, transmission from HIV-infected mother to infant occurs in between 13% and 48% of pregnancies, with rates in developing countries typically being higher than in industrialized countries.[9] In the U.S., 933 AIDS cases involving mother-to-infant transmission were reported in 1994, and, at least in the period prior to Protocol 076, an estimated 1,000 to 2,000 HIV infections via this route were estimated to occur annually.[10]

The single most important advance in the prevention of HIV transmission from mother to infant has been the AZT regimen demonstrated to be effective in Protocol 076. Beginning in April 1991, researchers at a large number of sites in the U.S. and France conducted a randomized, double-blind, placebo-controlled trial in which the treatment group received oral AZT beginning at 14-34 weeks of pregnancy and intravenous AZT during labor. The newborns received oral AZT beginning shortly after birth and continuing for six weeks. In order to reduce the likelihood that subjects in one of the two study arms were benefiting or being harmed compared to those in the other study arm, a Data and Safety Monitoring Board was constituted and was scheduled to review the interim results on three occasions. At the first interim analysis, in December 1993, the findings were so striking that the study was stopped and AZT prophylaxis was offered to all women and infants still in the study.[11] On June 6-7, 1994, the Public Health Service convened a meeting to discuss the ramifications of Protocol 076 and concluded that the full Protocol 076 regimen should be recommended to all HIV-positive pregnant women without significant prior exposure to AZT, and should be considered for other women on a case-by-case basis.[12] Providing AZT thus became the standard of care for HIV-infected pregnant women.

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[8] Scarlatti G. Paediatric HIV infection. *Lancet* 1996;348:863-868.

[9] Dabis F, Mselatti P, Dunn D, et al. Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues, Ghent (Belgium), 17-20 February, 1992. The Working Group on Mother-to-Child Transmission of HIV. *AIDS* 1993;7:1139-1148.

[10] Centers for Disease Control and Prevention. National HIV serosurveillance summary: results through 1992.Vol. 3 Atlanta: U.S. Department of Health and Human Services, Public Health Service, 1994.

[11] Connor, EM, op. cit.

[12] Centers for Disease Control and Prevention. Recommendations of the U.S. Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *Morbidity and Mortality Weekly Report* 1994;43(RR-11):1-20.

The dangerous double standard being practiced here is underscored by the fact that both of the U.S.-funded studies being conducted in this country provide AZT or other known effective anti-HIV drugs to *all* women, while only one of the 16 studies in the developing world provides AZT to all study groups. Providing AZT prophylaxis to pregnant, HIV-infected women in research studies in developing countries is clearly feasible; six developing country studies other than the one mentioned above provide AZT to some (but not all) of the women in the studies. In each of these six studies, one group of women is given a placebo instead of AZT.

In essence, the U.S.-funded researchers are conducting experiments abroad that would never pass ethical muster in the U.S. For your department to maintain a double standard in which it funds studies that on the one hand routinely provide life-saving drugs to Americans, while on the other deny these drugs to thousands of citizens of developing countries, conveys to the international community the impression that the U.S. government places less value on the lives of non-Americans.

Many people will hear in these experiments echoes of the notorious Tuskegee syphilis study, in which poor, rural African-American men were denied effective treatment for syphilis for decades so that researchers could describe how the untreated disease progressed in African-Americans. This time, the people of color affected are babies from Africa, Asia and the Caribbean, many hundreds of whom will die unnecessarily in the course of this unethical, exploitative research.

Thus, even as the administration moves toward offering a belated apology for the atrocity of Tuskegee,[2] it is perpetrating a new African-Asian-Caribbean Tuskegee in which many more people will die.

These experiments are in clear violation of all of the major international, ethical guidelines. The World Medical Association's 1975 Declaration of Helsinki states unequivocally 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." It also makes clear that the guidelines are for "physicians all over the world."[3] In addition, the research violates at least four of the ten principles of the Nuremberg

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[2] Baker P, Fletcher MA. Binding an untreated wound: Clinton to apologize to blacks victimized in Tuskegee Syphilis Study. *Washington Post,* April 9, 1997, p. A1.

[3] World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, 1964 and revised by the 29th World Medical Assembly, Tokyo, 1975, the 35th World Medical Assembiy, Venice, 1983 and the 41st World Medical Assembly, Hong Kong, 1989.

code (see below).[4] It is also wholly inconsistent with the more recent International Ethical Guidelines for Biomedical Research Involving Human Subjects, which were specifically designed to address ethical issues pertaining to studies in developing countries.[5] Guideline 15 is directly applicable to the situation here:

> An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and *the ethical standards applied should be no less exacting than they would be in the case of research carried out in [the sponsoring] country.* [Emphasis added.]

Indeed, we would argue that ethical safeguards in developing countries should be at least as stringent as in the industrialized world, as people in developing countries are likely to be more vulnerable. Instead, in their zeal to conduct this research, the researchers, using federal government funds, have chosen to ignore these standards of ethical conduct accepted the world over and have sunk to standards below those acceptable in their home countries.

In our view, the research is not only blatantly unethical, but also violates U.S. federal regulations that require that Institutional Review Boards ensure that:

> Risks to subjects are minimized...by using procedures which are consistent with sound research design and *which do not unnecessarily expose subjects to risk.*"[6] [Emphasis added.]

The regulation is also clear that it also applies to "research conducted, supported or otherwise subject to regulation by the Federal Government outside the United States."[7] We request that you immediately initiate an investigation by the HHS Office of the Inspector General into possible violations of federal law.

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[4] Trials of war criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2 Washington, D.C.: U.S. Government Printing Office, 1949.

[5] Council for International Organizations of Medical Sciences, World Health Organization. International Ethical Guidelines for Biomedical Research Involving Human Subjects, 1992.

[6] 45 CFR 46.111(a)(1).

[7] 45 CFR 46.101(9).

In November 1996, the Protocol 076 researchers published updated data describing their findings.[13] In the placebo group, 22.6% of the infants of the HIV-infected mothers had become infected with HIV, compared to only 7.6% of those treated with AZT, a reduction of approximately two-thirds. The provision of AZT to HIV-positive pregnant women is still the only intervention for any group at risk for HIV to be proved effective in reducing the number of new HIV infections in a randomized, controlled trial. The impact on actual clinical outcomes in the U.S. has been dramatic. Three recent reports document decreases in HIV transmission from HIV-infected mother to infant of 50% or more.[14,15,16]

While the industrialized world celebrated these landmark findings, it quickly became clear that the vast majority of HIV-infected women would never receive this potentially life-saving intervention due to both the exorbitant cost of the drug and logistical difficulties in administering and assuring adherence with the complex regimen.

We are, therefore, not opposed to research that modifies the regimen provided in Protocol 076 in order to identify a simpler, less expensive, similarly effective or more cost-effective intervention; we do object to studies in which, after the Protocol 076 results were available, some or all women are only given placebos or regimens without support from randomized, placebo-controlled trials, and are not given effective prophylaxis.

However, the researchers involved in these experiments have exploited the inadequacies of the health care systems in developing countries to conduct research they would never even consider in the U.S. We have obtained a table prepared in

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[13] Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *New England Journal of Medicine* 1996;335:1621-1629.

[14] Fiscus SA, Adimora AA, Schoenbach VJ, et al. Perinatal HIV infection and the effect of zidovudine therapy on transmission in rural and urban counties. *Journal of the American Medical Association* 1996;275:1483-1488.

[15] Cooper E, Diaz C, Pitt J, et al. Impact of ACTG 076: use of zidovudine during pregnancy and changes in the rate of HIV vertical transmission. In: Program and Abstracts of the Third Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 28-February 1, 1996. Washington, D.C.: Infectious Diseases Society of America, 1996:57.

[16] Simonds RJ, Nesheim J, Matheson P, et al. Declining mother to child HIV transmission following perinatal ZDV recommendations. Presented at the 11th International Conference on AIDS, Vancouver,Canada,July 7-12, 1996.

approximately January 1997 by Dr. Joseph Saba of the United Nations AIDS program that summarizes studies of mother-to-infant transmission which have either begun since the completion of the historic Protocol 076 trial or are about to begin (see attached). Other information about these studies was obtained from the Pediatric and Family Studies Section, Epidemiology Branch, Division of HIV/AIDS Prevention, CDC. The studies evaluate a variety of potential interventions: AZT (or other similar anti-HIV drugs), usually in regimens less expensive or complex than in Protocol 076; nevirapine, another anti-HIV drug; Vitamin A; vaginal washes; and HIV immune globulin (a form of immune therapy). The studies involving AZT generally explore the optimal dose and timing of AZT administration. A total of 17 studies appear in the table, two of which are in the U.S. The remainder are in developing countries, primarily in Africa: three studies each in Cote d'Ivoire and Uganda, two studies each in Thailand, Tanzania and South Africa, and one study each in Ethiopia, Burkina Faso, Malawi, Zimbabwe, Kenya, and the Dominican Republic. Two studies are occurring at more than one site. We are also aware of an additional study in Malawi that has been completed but is not in the table. This study enrolled 2,094 women in an NIH-funded study of vaginal washing.[17] Of the studies in the table, two have been completed: the NIH-funded study by Johns Hopkins University in Malawi, the data from which are now being analyzed, and the NIH-funded ACTG 185 in the U.S., which was terminated early when the transmission rate from the women, all of whom received AZT, to their infants was about 4.8%, even lower than in the treatment group in Protocol 076.[18]

The two studies in the U.S. both provide anti-HIV drugs to all study subjects,[19] as does one of the studies in the developing countries, that conducted by Harvard University in Thailand using NIH funds. This leaves 15 randomized, controlled trials (including the one study not in the table), all in developing countries in which some or all HIV-infected pregnant women are denied effective prophylaxis. Seven of the 15 studies are funded by the NIH and two are funded by the CDC. A total of 9,055 women are enrolled in the nine U.S.-funded studies, 2,903 of whom will receive placebos and 3,780 of whom will receive regimens not proved effective in randomized, controlled trials. The remaining six studies are funded by the ANRS (the French equivalent of the NIH; two studies), the United Nations AIDS program, the University

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[17] Biggar RJ, Miotti PG, Taha TE, et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. *Lancet* 1996:347:1647-1650.

[18] Brown D. AZT effective in pregnancy with advanced AIDS. *Washington Post*, March 27, 1997, p. A6.

[19] Even though this is listed as a placebo-controlled study, subjects in ACTG 316 receive AZT in a regimen similar to that studied in Protocol 076 or another anti-HIV drug, unless their physician decides it is not indicated. The study examines whether the addition of intrapartum and postpartum nevirapine confers added protection from infection.

of Natal and Department of Health in South Africa, and groups from Denmark and Belgium. In these six studies, in which 5,160 women are enrolled, 1,855 will receive placebos and 1,490 will receive regimens that have not been proved effective.

(In designating whether women in an experimental arm received effective prophylaxis, a placebo or a regimen not proven effective, we made the following assumptions: 1. if AZT was provided in *any* phase of the study, we classified the study as providing effective prophylaxis; 2. IVIG was considered a regimen not proved effective, rather than a placebo even though the table describes it as a placebo; 3. nevirapine was considered a regimen proved as effective as AZT, even though it is from a different pharmaceutical class from AZT and has not been proved effective in a randomized, controlled trial; and 4. for two studies in the table, the designs of which were not self-evident, we made the following assumptions about study design: for the NIH-sponsored study by Harvard University in Tanzania, we assumed that there would be four study arms: retinol/multivitamin; retinol/placebo; placebo/multivitamin; placebo/placebo. We classified the first three groups as receiving a regimen not proved effective and the fourth as a placebo group. In the Belgian cooperation study in Kenya, we also assumed that the study had four arms: chlorhexidine/azithromycin; chlorhexidine/placebo; placebo/azithromycin; placebo/placebo. Again we classified the first three groups as receiving a regimen not proved effective and the fourth as a placebo group. Each of these four assumptions tends to lead either to underestimations of the number of persons denied effective prophylaxis or to assignment to the not proven effective as opposed to the placebo category, making the calculations conservative.)

It is possible to calculate the number of infants who will unnecessarily become infected with HIV in these unethical studies, assuming that the regimens not yet proved effective are indeed not effective. (This assumption seems reasonable. The only published clinical trial of a prophylactic regimen since Protocol 076, chlorhexidine vaginal washing in Malawi, showed no overall effect on mother-to-infant HIV transmission[20] and the recently terminated ACTG 185 showed no effect of HIVIG on such transmission, although the study's statistical power was low.[21]) First, we assumed that in all of the studies the number of subjects in each study arm is equal, even though we understand that in some studies the placebo groups may be larger to increase statistical power. Second, we assumed that the rate of HIV transmission in the absence of any prophylaxis is the same as that in the placebo group in Protocol 076 (22.6%), even though in some studies, particularly in developing countries, the transmission rate is up to twice as high.[22] Third, we assumed that the administration of AZT would decrease the rate of HIV transmission to the rate observed in the treatment group in Protocol 076 (7.6%), even though the transmission rate in the terminated Protocol 185 was only 4.8%. These three assumptions lead to estimations of the number of preventable HIV infections that are probably lower than is actually the case. In the 15 studies, a total of 10,028 women will not receive effective prophylaxis such as AZT. Fifteen percent of them (22.6% - 7.6%) will give birth to infants with HIV

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[20] Biggar RJ, op. cit.

[21] Brown D, op. cit.

[22] Dabis F, op. cit.

infection that could have been prevented by AZT or a similarly effective regimen–a total of 1,504 preventable deaths. Of these, 1,002 will occur in U.S.-funded studies and 502 will occur in those funded by foreign governments or the United Nations AIDS program. Even if only the placebo arms of the studies are considered, a total of 714 preventable HIV infections, 435 of them in U.S.-funded studies, will occur.

It is a violation of basic research ethics to assert that the failure to prevent HIV infection in these studies is somehow justified by the potential for preventing future HIV infections based on data that may be generated in this research. As the World Medical Association has declared: "Concern for the interests of the subject must always prevail over the interests of science and society."[23] In part, this ethical principle was enunciated to prevent the more powerful from using theoretical future gains to place the less powerful at risk in the present. Indeed, the very fact that the subjects of these studies are persons of color from impoverished, mostly post-colonial societies underscores the dangers of such rationalizations.

Clearly, any simpler or less expensive prophylactic regimen that was as effective and safe as that used in Protocol 076 would be rapidly adopted in the industrialized world and while it is true that many of the strategies being tested in these studies are less expensive than that used in Protocol 076, they may still be unaffordable in developing countries. There is, therefore, no guarantee that women and infants in developing countries will even benefit from any knowledge gained from this research. As a recent editorial entitled "Scientific Imperialism" in the *British Medical Journal* proclaimed: "If they won't benefit from the findings, poor people in the developing world shouldn't be used in research."[24]

Defenders of these studies will no doubt argue that the subjects are being provided the "standard of care" practiced in these developing countries, which is to say regimens that have not been proved effective or no treatment at all. (Of course, this coerces potential subjects to enroll, as outside of the study they stand essentially no chance of obtaining proven effective prophylaxis.) Yet the standard of care in the U.S. –Protocol 076–can be delivered in the research setting in developing countries and is essentially being provided as one of the arms of the only developing country study here that is ethical: Harvard University's NIH-funded study of various regimens of AZT prophylaxis in Thailand. Researchers acquire greater ethical responsibilities when they enroll subjects in studies. As NIH Director Harold Varmus stated at a recent meeting regarding the Alaska needle exchange study, clinical trials funded by the NIH should comply with a higher ethical standard. Instead, many of these studies subscribe to a kind of lowest common denominator ethics in which the abominable state of health

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[23] World Medical Association, op. cit.

[24] Wilmhurst P. Scientific imperialism. *British Medical Journal* 1997;314:840-841.

care in developing countries is used to justify withholding life-saving interventions.

Incredibly, most of these studies have, to the best of our knowledge, passed ethical review by committees both in the developing country and in the West, providing further proof of the inadequacy of the current review system. We believe that the CDC-funded studies have passed review at the CDC itself, but do not know whether NIH's Office for Protection from Research Risks reviewed the NIH-funded studies. (The University researchers would also have been required to seek the formal approval of the Institutional Review Boards at their own institutions.) These events also demonstrate that the approval of a developing country ethics committee, while essential, is not sufficient to guarantee an ethical study. Developing country committee members, most of whom are likely to be researchers, are usually from social classes higher than the study subjects and may not be able to adequately reflect the subjects' interests. For developing country researchers, involvement in international studies offers obvious benefits in prestige and, perhaps, in salary.

It is true that providing AZT according to Protocol 076 or other similar regimens to all subjects could lower the number of new HIV infections to the point that it may be more difficult to statistically demonstrate differences between the study groups. Indeed, this is the crux of the researchers' conflict of interest: it is the potential for large numbers of infections among women denied AZT that makes the developing countries "preferable" as study sites to industrialized countries where AZT would have to be provided to all HIV-positive pregnant women. The solution to this conflict of interest is not to create a research double-standard; it is to spend the money for larger studies, perhaps at multiple sites in the industrialized or developing worlds, with appropriate informed consent. For example, one study arm could receive AZT and the other AZT and the experimental prophylactic regimen. With the public scrutiny that will accompany these studies, as well as the HIV vaccine studies that may follow, researchers cannot afford to be unethical.

The failure to provide effective prophylaxis to all women in these research studies can also not be explained by the cost of providing AZT in the research setting; after all, both the U.S. studies offer anti-HIV drugs to all subjects and seven of the studies outside the U.S. provide some form of AZT prophylaxis in some study treatment arms. The wholesale cost of the Protocol 076 regimen has been estimated at $614[25] and $895[26] per person. In the context of the hundreds of thousands, if not

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[25] Gorsky RD, Farnham PG, Straus WL, et al. Preventing perinatal transmission of HIV -- costs and effectiveness of a recommended intervention. *Public Health Reports* 1996;111:335-341.

[26] Mauskopf JA, Paul JE, Wichman DS, White AD, Tilson HH. Economic impact of treatment of HIV-positive pregnant women and their newborns with zidovudine: implications for HIV screening. *Journal of the American Medical Association* 1996;276:132-138.

millions, of dollars being spent on these studies, this is a modest amount of money. In any event, the manufacturer of AZT has in the past customarily provided the medication for these trials free of charge.

Following World War II, the Nuremberg Code of research conduct was adopted.[27] In this 50th year since the commencement of the Nuremberg doctor trials, it is disheartening in the extreme that, at a minimum, four of the ten principles of the Code have been abrogated in this research. (We have not yet obtained the informed consent forms for these studies, and so it is conceivable that additional principles of the code have not been followed and that the studies are therefore even more unethical than we state here. However, no informed consent process can make ethical the withholding of effective prophylaxis.) The violated Nuremberg principles are:

Principle Two: "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature."

Principle Four: "The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury."

Principle Five: "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur except, perhaps, in those experiments where the experimental physicians also serve as subjects."

Principle Seven: "Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death."

Is it really your Department's position that these Principles apply to research conducted in the U.S., but that researchers using U.S. taxpayers' money are free to disregard them the moment they leave our shores?

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[27] Trials of war criminals before the Nuremberg Military Tribunals, op. cit.

We request that you immediately order the researchers in these studies to provide effective prophylaxis to all subjects in these studies and that you pressure the foreign governments who are also funding these studies to do likewise. We also request that you immediately ask the HHS Office of the Inspector General to launch an investigation into how these U.S.-funded studies received ethical approval and into possible violations of federal law. We are confident that you would not wish the reputation of your department to be stained with the blood of foreign infants.

Sincerely,

Peter Lurie, MD, MPH
Research Associate
Public Citizen's Health Research Group

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group

Wilbert Jordan, MD, MPH
Director, Oasis Clinic and Aids Program
King-Drew Medical Center, Los Angeles
Chairman, Black Los Angeles
AIDS Consortium

George J. Annas, JD, MPH
Professor of Health Law
Health Law Department
Boston University
School of Public Health
Co-founder Global Lawyers and
Physicians: Working Together
for Human Rights

Michael A. Grodin, MD, FAAP
Professor of Medical Ethics
Health Law Department
Boston University
School of Public Health
Co-founder Global Lawyers and
Physicians: Working Together
for Human Rights

George Silver, MD
Emeritus Professor of Medicine
Yale University
School of Medicine

These charts were prepared by Public Citizen's Health Research Group.

Vertical transmission clinical trials

Funding Agency, PI	Sites	Study arm	Prepartum	Intrapartum	Postpartum	Number HIV+ women in group	Status, comments
CDC	Cote d'Ivoire	One	ZDV	ZDV	Nothing	750	Ongoing
		Two	Nothing	Nothing	Nothing	750	
CDC	Thailand	One	ZDV	ZDV	Nothing	196	Ongoing
		Two	Nothing	Nothing	Nothing	196	
UNAIDS	Uganda (2) Tanzania (1) South Africa (2)	One	ZDV/3TC	ZDV/3TC	ZDV/3TC (M/C)	475	Ongoing
		Two	Nothing	ZDV/3TC	ZDV/3TC (M/C)	475	
		Three	Nothing	ZDV/3TC	Nothing	475	
		Four	Nothing	Nothing	Nothing	475	
NIH (Harvard) Mark Lallemant	Thailand	One	ZDV week 28	ZDV	ZDV 6 wks (C)	389	Not started yet
		Two	ZDV week 28	ZDV	ZDV 3 days (C)	389	No placebo group
		Three	ZDV week 36	ZDV	ZDV 6 wks (C)	389	Arm one ~ 076
		Four	ZDV week 36	ZDV	ZDV 3 days (C)	389	
NIH (JHU) Andrea Ruff	Ethiopia	One	ZDV	ZDV	ZDV (M/C)	313	Not started yet
		Two	ZDV	ZDV	Nothing	313	
		Three	Nothing	Nothing	Nothing	313	
NIH (JHU) Brooks Jackson	Uganda	One	Nothing	ZDV	ZDV (C)	400	Not sure if started
		Two	Nothing	NVP	NVP (C)	400	
		Three	Nothing	Nothing	Nothing	400	
ANRS	Cote d'Ivoire Burkina Faso	One	ZDV	ZDV	ZDV (M)	390	"Probably begun"
		Two	Nothing	Nothing	Nothing	390	
ACTG 316	USA	One	±ARV	±ARV/NVP	±ARV/NVP (C)	400	±ARV=as rxd by PMD; stratified random. by ARV
		Two	±ARV	±ARV	±ARV	400	

Funding Agency, PI	Sites	Study arm	Prepartum	Intrapartum	Postpartum	Number HIV+ women in group	Status, comments
NIH (JHU)	Malawi	One	Retinol	Nothing	Retinol (M)	350	
		Two	Nothing	Nothing	Retinol (M)	350	Study completed
U. Natal/DOH Coutsidis	South Africa	One	Retinol/Beta-C	Nothing	Retinol (M)	350	Not pure placebo Ongoing
		Two	Nothing	Nothing	Nothing	350	
NIH (Harvard) Fawzi	Tanzania	One	Retinol/MVit	Retinol/MVit	Retinol/MVit (C)	240	Design unclear
		Two	Retinol/Noth.	Retinol/Noth.	Retinol/Noth. (C)	240	Ongoing
		Three	Noth./MVit	Noth./MVit	Noth./MVit (C)	240	
		Four	Noth./Noth.	Noth./Noth.	Noth./Noth.	240	
Danida	Zimbabwe	One	Micronutrients	Micronutrients	Micronutrients (M)	315	Micronutrients =
		Two	Nothing	Nothing	Nothing	315	A/other vitamins Ongoing
Belgium	Kenya	One	Nothing	Chlorhex/Azith	Nothing	250	Design unclear
		Two	Nothing	Chlorhex/Noth.	Nothing	250	Azithro study
		Three	Nothing	Noth./Azith	Nothing	250	unclear
		Four	Nothing	Noth./Noth	Nothing	250	Probably started
ANRS	Cote d'Ivoire	One	Benzalkonium	Benzalkonium	Bath (C)	75	Phase II->III
		Two	Nothing	Nothing	Nothing	75	
NIH (JHU) Brooks Jackson	Uganda	One	HIVIG	Nothing	Nothing	285	About to start
		Two	IVIG	Nothing	Nothing	285	
NIH (JHU) Halsey	Dominican Republic	One	Nothing	Nothing	HIVIG (C)	350	Not started
		Two	Nothing	Nothing	IVIG (C)	350	
ACTG 185	USA	One	ARV/HIVIG	ARV	ARV/HIVIG (C)	400	Terminated by
		Two	ARV/IVIG	ARV	ARV/IVIG (C)	400	DSMB
NIH Biggar	Malawi	One	Nothing	Chlorhexidine	Chlorhexidine (C)	1090	Completed &
		Two	Nothing	Nothing	Nothing	1004	reported (-) Not in UN table

These four charts were obtained by Public Citizen from the CDC. "ZDV" is used in the charts to refer to AZT.

DESIGN & REGIMENS

TRIALS ON ANTIRETROVIRALS IN PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

Funding Agencies	Sites	Prepartum	Intrapartum	Postpartum	Breastfeeding	Sample Size	Design	Status & timing
CDC	Ivory Coast	ZDV 300mg bid (week 34 -36)	ZDV 300mg/3h	—	Yes	750*2	vs placebo	Phase III ongoing
	Thailand	ZDV 300mg bid (week 34 - 36)	ZDV 300mg/3h	—	No	196*2	vs placebo	Phase III ongoing
UNAIDS	(2 sites) Uganda Tanzania S. Africa (2 sites) 2nd site in Uganda to start soon	ZDV 300mg bid + 3TC 150mg bid (week ~~36~~ 36)	ZDV 300-600mg then 300mg/3h + 3TC 150mg/12h	ZDV 300mg bid 3TC 150mg bid 7 days - mother + ZDV 4mg/kg/12h 3TC 2mg/kg/12h 7 days - child	Yes	1900	vs placebo 4 arms (intra+postpartum & intrapartum only)	Phase III ongoing
NIH Harvard	Thailand	ZDV 300mg bid week 28 vs week 36	ZDV 300mg/3h	ZDV 2mg/kg/6h 6weeks - child vs 3 days - child	No	1500 1554 based on detecting >6% diff in short vs. long antenatal	Factorial, ACTG 076 vs short; no placebo	Phase III (1996-...) 1st March troubles w/ packaging costs

DESIGN & REGIMENS

TRIALS ON ANTIRETROVIRALS IN PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV (continued)

Funding Agencies	Sites	Prepartum	Intrapartum	Postpartum	Breastfeeding	Sample Size	Placebo	Status & timing
NIH JHU	Ethiopia	ZDV 300mg bid week 31 - 34	ZDV 300mg/3h	ZDV 300mg bid 2weeks - mother + ZDV 4mg/kg/12h 2weeks - child	Yes	940 powered to placebo vs all 3 times	vs placebo 3 arms (pre+intra+ post-partum & pre+intrapar tum)	Phase III (1996-...)
NIH JHU Bwaka/Zaire	Uganda	—	ZDV 600mg then 300mg/3h vs NVP	ZDV 4mg/kg/12h 1 weeks - child vs NVP single dose	Yes	1200	vs placebo 3arm	Summer Phase III (1997)
ANRS	Ivory Coast Burkina Faso	ZDV 300mg bid (week 36 - 38)	ZDV 600mg Single dose	ZDV 300mg bid 7 days - mother	Yes	2 x 390	Yes	Phase III
ACTG 316	USA	— ± ZDV (076)	NVP 200mg ± ZDV (076)	NVP 2mg/kg x 1 48-72 hours	No	800	Yes	Phase III (1997)

DESIGN & REGIMENS

TRIALS ON VITAMIN A IN PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

Funding Agencies	Sites	Prepartum	Intrapartum	Postpartum	Breastfeeding	Sample Size	Placebo	Status & timing
NIH JHU	Malawi	Retinol palmitate 10 000IU/d (week 18-34)	—	Retinol palmitate 200 000IU (mother) all mothers	Yes	350*2	Yes for antepartum only	Phase III ongoing
University of Natal + Depart. of health	South Africa	Retinol palmitate 5 000IU/d + β Carotene 30mg (week 26-32)	~~Retinol palmitate 200 000IU~~	Retinol palmitate 200 000IU (mother)	Yes	~~375*2~~ 350	Yes	Phase III ongoing
NIH Harvard Fawzi	Tanzania	Retinol palmitate 5 000IU/d + 30mg β Carotene (week 12-28)	Retinol palmitate 200 000IU	Retinol palmitate 100 000IU at 6 months + 200 000 IU at 12 and 18 months (all infants)	Yes	960	Yes Factorial with multi-vitamin	Phase III ongoing
Danida	Zimbabwe	Multimicronutrients: Vit. A 10 000 IU + 11 vitamins & minerals Start at first antenatal visit (week 26-32)	Multi-micronutrients	Multimicronutrients for 3 months (mother)	Yes	1800 All women (35%HIV+)	Yes	Phase III ongoing

ARM: 1 2 3 4

vit A - yes no yes no

micro yes yes no no

[redacted]

DESIGN & REGIMENS

TRIALS ON VAGINAL WASHING IN PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

Funding Agencies	Sites	Prepartum	Intrapartum	Postpartum	Breastfeeding	Sample Size	Placebo	Status & timing
Belgium cooperation	Kenya	—	Chlorhexidine 0.25% washes by catheter	—	Yes	1000	vs no washing. double random. Azithro vs Pb	Phase III May 96
ANRS	IC	36-38 wks benzalkonium 1 day	1 ovule	bath & nemate	yes	75x2	yes	Phase II

TRIALS ON IMMUNETHERAPY IN PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

Funding Agencies	Sites	Prepartum	Intrapartum	Postpartum	Breastfeeding	Sample Size	Placebo	Status & timing
NIH JHU	Uganda	HIVIG 200mg/kg/month (week 37-38)	—	—	Yes	570	Yes (IVIG)	Phase III 1996
NIH JHU	~~Haiti~~ Dominican Republic	—	—	HIVIG 200-400mg/kg (at birth - child)	~~No~~ mixed	~~570~~ 700	Yes (IVIG)	Phase III 1996
ACTG 185	USA	ZDV+ HIVIG 200mg/kg/m	ZDV	ZDV+ HIVIG 200mg/kg (child)	No	800	Yes (IVIG)	Phase III Ongoing

American-funded studies	
Number of American-funded studies	12
Number of ethical American-funded studies	3
Number of unethical American-funded studies	9
Number of women in all American-funded studies	12,211
Number of women in ethical American-funded studies	3156
Number of women in unethical American-funded studies	9055
Number of women in unethical American-funded studies receiving AZT or equivalent	2372
Number of women in unethical American-funded studies receiving unproved regimens	3780
Number of women in unethical American-funded studies receiving placebos	2903
Number of women in unethical American-funded studies receiving unproved regimens or placebos	6683
Number of preventable infections in placebo portions of foreign-funded studies	435
Number of preventable infections in American-funded studies	1002
Foreign-funded studies	
Number of foreign-funded studies	6
Number of ethical foreign-funded studies	0
Number of unethical foreign-funded studies	6
Number of women in all foreign-funded studies	5160
Number of women in ethical foreign-funded studies	0
Number of women in unethical foreign-funded studies	5160
Number of women in unethical foreign-funded studies receiving AZT or equivalent	1815
Number of women in unethical foreign-funded studies receiving unproved regimens	1490
Number of women in unethical foreign-funded studies receiving placebos	1855
Number of women in unethical foreign-funded studies receiving unproved regimens or placebos	3345
Number of preventable infections in placebo portions of foreign-funded studies	278
Number of preventable infections in foreign-funded studies	502
All studies	
Total number of studies	18
Total number of ethical studies	3
Total number of unethical studies	15
Total number of women in all studies	17,371
Total number of women in ethical studies	3156
Total number of women in unethical studies	14,215
Total number of women in unethical studies receiving AZT or equivalent	4187
Total number of women in unethical studies receiving unproved regimens	5270
Total number of women in unethical studies receiving placebos	4758
Total number of women in unethical studies receiving unproved regimens or placebos	10,028
Total number of preventable infections in placebo portions of studies	714
Total number of preventable infections in studies	1504

Public Citizen

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

January 15, 1999

Jose Esparza, MD, PhD
Team Leader, Vaccines
Department of Policy, Strategy and Research
Joint United Nations Programme on HIV/AIDS
20, avenue Appia
CH-1211 Geneva 27
Switzerland

Re: Comments on Guidance Document on Ethical Considerations in International Trials of HIV Preventive Vaccines

Dear Jose:

The elaborate, time-consuming and expensive UNAIDS consultation on the ethics of HIV vaccine trials seems about to come to its pre-ordained conclusion: in areas of little disagreement, existing standards on the ethical conduct of clinical trials are simply reiterated; in areas of controversy, the Guidance Document in effect provides researchers with a blank check to proceed as they would without the consultation, abrogating existing ethical doctrines, as long as they can convince local researchers to go along. This is not what we had hoped would come of this process; for these reasons and others set forth below we do not endorse the document.

We are further dismayed that the final draft Guidance Document has been sent for comment only to those attending the final consultation meeting in Geneva on June 25 and 26, 1998, and not to those attending the regional workshops in Uganda, Thailand and Brazil, or to those attending the meeting in Washington, DC, USA, as was promised at the Geneva consultation meeting. To add insult to injury, many of the recommendations of the regional workshops have been ignored. We request that the Guidance Document not be finalized until those present at the regional meetings, in particular, have the opportunity to comment.

This Guidance Document should be viewed in its proper historical context: as part of a multi-pronged assault on the ethical standards established in such documents as the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) (proposed changes to these documents are the other prongs of the assault). The result, for the most part, will be a weakening of protections for research subjects in developing countries, opening them up to more exploitation as research increasingly becomes international. There could be no worse time for such a retrenchment.

Ralph Nader, Founder
1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000

collaboration with the sponsors. While on the face of it this may seem reasonable (we believe this is why there was no debate over it), when combined with the lack of consensus over options 2 and 3 and the fact that many are likely to quickly interpret option 2 as meaning that antiretroviral therapy cannot be provided in most likely host countries, this is a *de facto* devolution to the rejected option 1. (Indeed, at the Washington meeting, Dr. Jack Killen of NIH asked whether option 2 could in certain circumstances be equated with option 1.) The result will be that as long as sponsors can identify a willing host country, researchers will have the Guidance Document to back them up in their withholding of known effective therapy, in direct defiance of CIOMS and the Declaration of Helsinki. Of course, this is what many researchers had hoped would come of this process. This decision renders the entire consultation process futile, at least inasmuch as it applies to this most-crucial issue. For if all that has been decided is that the host country should decide, what has been accomplished? Was there ever any question that these two parties would be involved in this decision? What this does is effectively remove UNAIDS or other similar body from the process of making this decision. The purpose of guidelines is not to abdicate responsibility for the most difficult decisions.

It is particularly galling that there is not even any attempt in the Guidance Document to justify this significant departure from the current governing ethics documents. Even though this Guidance Document is occasioned by the need for clear guidelines specifically for the ethical conduct of HIV vaccine trials, the Preamble does not even bother to explain why the specific circumstances of the HIV epidemic merit a departure from the existing guidelines. (This further convinces us that the intended reach of the Guidance Document is broader than the context of HIV vaccine trials.) It is not until page 8 of the 15-page Guidance Document that we encounter material that is HIV-specific.

The Guidance Document fails to even consider alternative study designs to the withholding of effective therapy. Why does the Guidance Document depart from the governing ethics documents without even a discussion of whether viral load measured shortly after seroconversion, an accepted predictor of progression of HIV disease,[5] could be used as a proxy measure, facilitating the provision of antiretrovirals? This issue was raised both in our presentation at the Washington meeting and by participants in the Brazil meeting.[6] And why does the Guidance Document simply accept arguments that providing antiretrovirals will make it impossible to detect vaccine efficacy in delaying the progression of disease when it is clear that antiretrovirals reduce rates of progression but do not eliminate progression? Why were no sample size estimates even examined to see the likely impact of antiretrovirals? Again, the purported needs of researchers have taken precedence over the need to protect human subjects.

We now provide specific comments on the draft Guidance Document.

Page 3, Preamble

Astonishingly, the Preamble to this ethics document actually puts the need to develop the vaccine before the need for human subjects protection. In contrast, the Uganda meeting concluded, "No

would rather hide behind such meaningless slogans as protectionism and paternalism.

Page 5, Vaccine Development Program

There is really nothing in this section that is HIV-specific. One item that should be included, since it was widely agreed upon at the Geneva meeting, is the need for vaccines against the local clades (not simply "a virus that is an important public health problem in the host country.") While the extent of cross-reactivity between viral clades may not be completely resolved at the present time, it is inarguable that the subjects cannot be worse off if the vaccine being tested is actually directed against the local clade.

Page 7, Consultation with the Community

Paragraph 2: The Guidance Document now states that consultation with the community should "preferably" occur before the protocols are finalized. There is no reason for the qualifying word "preferably." The process of considering whether to conduct a study and the process of drafting a protocol is one that takes many months and even years. This is more than enough time to consult with the community in a meaningful way.

Paragraph 4: The Guidance Document appears to permit investigators to conduct community meetings at which the study is described and then have the subjects provide informed consent at the same meeting. This practice should not be endorsed, as it creates a coercive environment in which it will be difficult for subjects to decline enrollment. Furthermore, this erosion of human subjects protections seems unnecessary; many (probably most) studies in developing countries have obtained informed consent on an individual basis without doing so in the context of a community meeting. We would have no objection to community meetings (indeed we would encourage them), as long as the subjects do not provide their consent at the meeting.

Page 8, Informed Consent

Paragraph 3: As was clearly agreed at the Geneva meeting, a comprehensive intervention seeking to prevent HIV transmission (including, as appropriate, sexually transmitted disease treatment, condoms, sterile syringes, and education), not simply "counseling," is required.

It has been widely accepted for years and was clearly noted at the Thailand meeting[13] that subjects need to be informed that they will test positive on some HIV antibody tests and may be subject to discrimination in employment, insurance, health care, housing and ability to travel as a result. This is not mentioned in the Informed Consent section of this Guidance Document. In addition, it is critical that the researchers go beyond mere informing to actually seeking ways to minimize the likelihood of such discrimination. Concrete suggestions about how to do this (e.g., meetings with insurance companies prior to the trial, provision of a card that explains that the bearer is a subject in a study and may falsely test HIV-positive as a result, as has already been done with some success,[14] provision by the sponsor of confirmatory testing for those with

Page 10, Researchers' Obligation to Reduce Risk for Trial Participants

This section is missing a discussion of why these risk-reduction efforts are necessary. The standard obligations of researchers to protect subjects are amplified in the context of HIV vaccine trials where it is quite possible that subjects will engage in higher levels of risk behavior once they enroll in the trial. Such a disinhibiting effect has already been demonstrated in a small study in San Francisco, with levels of counseling and informed consent that will likely exceed what can be offered in studies in developing countries with thousands of subjects.[16] This point was made several times in Washington and in Geneva, at the least (we did not attend the regional meetings), but is missing from the Guidance Document.

Final sentence: "Risk reduction efforts should be evaluated in terms of their success in producing informed decision makers rather than simply in lowering the rate of either high-risk behavior or infection among trial participants since the goal of counseling is to enable people to make choices in the light of relevant facts and not to force them to make particular choices." This sentence is unnecessary, is not reflected in the summaries of the regional meetings where it seems not to have even been raised,[2] was not endorsed in Washington or Geneva, and should therefore be omitted. In addition, it is slanted in ways that do not encourage researchers to make a substantial effort to reduce the risks of transmission. The goal of risk reduction is to have as many HIV-negative subjects as possible; this sentence makes it seem as if an informed, but HIV-positive subject, would be equally acceptable.

Although the inclusion of an acknowledgment of the researchers' conflict of interest (it is not "potential," it is obvious) is important, it is not as useful as recommending the approach that would solve the problem: requiring impartial, well-trained individuals without a direct interest in the trials' outcome to conduct the risk-reduction efforts.[17] This idea received significant support in Geneva and should be included in this Guidance Document.

Page 11, Antiretroviral Prophylaxis in Cases of HIV Exposure

Paragraph 1: The strong statement in the final sentence about not using the possible effect of post-exposure prophylaxis upon the number of end-points as a reason to not provide PEP should be repeated in the next section addressing researchers' obligations to provide treatment to subjects who become infected during the trial. This point was made forcefully at the Brazil meeting: "It would not be ethical to deny counseling, post-exposure prophylaxis or antiretroviral or other treatment to participants solely for the purpose of making a vaccine trial more valid or statistically powerful."[6]

Page 11, Treatment of HIV Infection Acquired During the Conduct of a Vaccine Trial

This remains the most problematic part of the Guidance Document as, in most cases, it will consign developing country subjects to no treatment or treatments known to be inadequate. It is only on close perusal of the Glossary that the Guidance Document's true meaning and

The present Guidance Document creates the incentive for investigators to conduct research in the most impoverished areas, a possibility recognized by those attending the Uganda meeting, who concluded: "It is not ethical to conduct a trial in a given population solely for the purpose of avoiding populations where early treatment is used."[7]

Page 11, Control Arm of Phase III Vaccine Trial

Paragraph 1: We presume that this section is supposed to refer to using an HIV vaccine as the control arm. (Non-HIV vaccines in the control arm are discussed in Paragraph 3 of this section.)

Paragraph 2: Once again, the Guidance Document undermines existing ethics guidelines by permitting the use of placebos when known effective regimens exist. In point (c) of this paragraph, the poverty of the subjects is listed as a "compelling reason" to withhold a known effective vaccine from the comparison group. Providing second class medical care to people because they are poor is inconsistent with any modern notion of human rights. (Imagine if this were done to poor people in a developed country.) Our objections here are similar to those regarding the obligation to provide treatment. The Guidance Document is so intent on providing *carte blanche* for researchers that it doesn't even list possible alternative designs, such as equivalency studies, an issue raised at all three regional meetings.[6,7,13] In its haste to lower standards, it removes incentives for researchers to do a better job in protecting their subjects by considering alternative designs. As the attendees at the Thailand meeting concluded, "It was suggested that the scientific community may rely too readily on the power of randomized placebo-control trials, and that there needs to be encouragement to consider other study designs that could provide adequate data without the risks inherent in randomization."[13] This Guidance Document provides no such encouragement.

This betrays the Guidance Document's hidden assumption that conducting an ethically optimal trial is inherently at odds with a scientifically optimal one. With a bit of creativity, very often one can have both. The purpose of the Guidance Document should be to challenge researchers to design the best trial from both a scientific and ethical perspective. Instead, the Guidance Document permits the dismantling of human subjects protections for the supposed greater scientific good, without even bothering to offer an argument that this is necessary.

Furthermore, the three regional meetings are again ignored. As the summary of the regional meetings makes clear, "The use of a substance in the control arm of an HIV vaccine trial that is not active in preventing HIV is ethical as long as an effective vaccine is not known (emphasis added)."[2] (There was some debate over the definition of "effective.") The current language is inconsistent with this consensus. (This issue was not debated in any significant way at either the Washington or Geneva meetings that followed the regional ones.)

Paragraph 3: It seems here that the Guidance Document's authors have actually felt a few pangs of guilt in their denials of known beneficial treatments to people based on their poverty. To compensate, they now put forth offering non-HIV vaccines to subjects in ways that either are not

research where access to the final product has not occurred must not be repeated in HIV vaccine research ... Potentially, the product should also be available to other developing countries."[2] In addition, the helpful suggestions on how to maximize availability offered at the Thailand meeting[13] and by Dr. Natth at the Washington meeting are not reflected in the Guidance Document.

In sum, this is an extremely disappointing product of a lengthy, expensive process that could have provided useful guidance on how to best protect subjects in HIV vaccine trials. The input of the three regional meetings has been de-emphasized and in its stead there is overemphasis on the Geneva meeting, a meeting at which researchers were over-represented and developing country representatives were relatively under-represented, due to the costs of travel and accommodation. In addition, many developing country representatives were at a linguistic disadvantage.

In an area that for a number of specific reasons (vulnerability of the populations to be studied, researcher conflict of interest, false-positive antibody tests, social discrimination, behavioral disinhibition, etc.) cries out for increased human subjects protections, the Guidance Document instead represents a significant erosion of protections included in the current ethics documents. Indeed, as we have noted, the wider purpose of this Guidance Document seems to be to use it as a stalking horse for revisions of the CIOMS document and the Declaration of Helsinki.

We reiterate our commitment toward identifying a safe and effective HIV vaccine available internationally. But we cannot endorse a Guidance Document that is prepared to so unthinkingly roll back existing protections in the effort to do so, particularly because the burden of these reduced protections is likely to fall disproportionately on residents of developing countries. For in so doing, the Guidance Document is a dramatic departure from WHO's mission statement: "The objective of WHO is the attainment by all peoples of the highest possible level of health." If we cannot accomplish this even in the unique environment of multi-million dollar clinical trials for HIV, the future is very bleak.

Yours sincerely,

Peter Lurie, MD, MPH
Medical Researcher

Sidney M. Wolfe, MD
Director

16. Chesney MA, Chamber DB, Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1997;16:266-71.

17. Chesney MA, Lurie P, Coates TJ. Strategies for addressing the social and behavioral challenges of prophylactic HIV vaccine trials. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1995;9:30-5.