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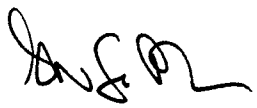
[27] Trials of war criminals before the Nuremberg Military Tribunals, op. cit.

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,



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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	(2sites) Uganda Tanzania S. Africa (2sites) 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-...) ? month troubles w/ packaging costs

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 5 times	vs placebo 3 arms (pre+intra+ post-partum & pre+intrapartum)	Phase III (1996-...)
NIH JHU Bamba/Burkina	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	~~275~~*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 [illegible]	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

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 benzalconium 1 day	1 ovule	both & neonate	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