FOIA Number: 2018-0764-F

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Subgroup/Office of Origin: National AIDS Policy Office

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Subseries:

OA/ID Number: 19403

FolderID:

Folder Title:
Issues - Prevention - Maternal-Infant Transmission

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August 19, 1998, Wednesday
Section: Foreign Desk

Breast-Feeding and H.I.V.: Weighing Health Risks and Treatment Costs

By MICHAEL SPECTER

This village is really just a muddy patch of ground in the tall trees near where the Nile flows out of Lake Victoria. The men work on coffee plantations. The women bear children, fetch water from the well about a mile away and cultivate cassava, potatoes and bananas.

There is no running water, no electricity, no phone. When the long rains come each year they wash out the dirt road for weeks at a time. This is -- and has always been -- a place where people who reach the age of 50 are old, and those who have seen a doctor or swallowed a pill are rare.

The basic rules of public health are clear in Kakulu: Only drink water from the well, not from the polluted Nile, and breast-feeding is the best way to nourish an infant.

At least those were the rules until a few weeks ago, when the United Nations -- struggling to find a way to cope with an AIDS epidemic that threatens the future of Africa, took a giant step toward reversing them. After long deliberation, United Nations AIDS officials announced that women infected with H.I.V. should consider feeding formula instead of breast milk to their babies.

Even discussing such a fundamental shift in public health policy has been agonizing for people who once staged protests in the United States and Western Europe warning that using infant formula in the third world -- where dirty water is often lethal -- would kill thousands of children each year.

Switching to formula would affect the basic behavior of millions of women, and in theory at least, it makes a lot of sense. Three million children have died from AIDS since the epidemic began, and last year alone there were more than 600,000 new cases among babies, many of whom received the virus from the milk in their mothers' breasts. Had they been drinking uncontaminated formula instead -- or had their mothers taken a course of AZT to protect them just before delivery -- more than a third might have been saved.

But here, where theory quickly fades into harsh reality, the math never seems to add up the right way. In African villages there is no debate between breast and bottle and no talk of using a drug like AZT.

Instead, there has been a simple discussion about who will live and who will die. Scarce funds make drug treatments that have become routine in the United States almost impossible to contemplate here. So people infected with the virus die, and usually they die quickly. That makes prevention the only hope for this continent, where 30 million people have already been infected and 10 million have died.

A Young Mother
Infant Formula Is Out of Reach

Feeding formula to babies whose mothers have H.I.V. could save tens of thousands of children each year. So could providing a short course of AZT -- which prevents the AIDS virus from multiplying rapidly in cells -- to a woman in her final stages of pregnancy.

It may sound simple. But nothing about AIDS here ever is.

"I would never be able to feed my baby with formula," said Margaret Birungi Nannyongoi, a slightly overwhelmed 20-year-old who sat on the mud floor of her home, nursing her 3-day-old child, Dorothy Nalule.

Dorothy is her third daughter -- the first died, the next is a listless, underweight 2-year-old with flat, black eyes and a constant cough. Dorothy, frail and pretty in a tiny cotton baby dress, was delivered with the help of friends, on the only mattress in the house.

Like at least 95 percent of Uganda's village women, Mrs. Nannyongoi has no idea whether she is infected with H.I.V. She has never had prenatal care, nor has she ever taken a blood test. She only knows about H.I.V. because it killed two of her brothers. The cost of formula for one child -- when it is available in Uganda and when there is clean water to mix with it -- is on average 1.5 times the sum a village family earns each year. Mrs. Nannyongoi said she has never seen anyone use it.

"It seems so difficult to handle," she said, after hearing what is necessary to keep formula safe for babies. "How would I have the time?" She is currently feeding her baby 10 times a day, and each of those days is filled with essential chores.

Even if the formula were donated and delivered to her home, as United Nations officials hope it would be, she says it would be difficult to find a way to fetch the water, boil it and prepare the meals for her infant while also working in the garden, cook for her husband, herself and her other daughter. But when she was asked if she would use formula if it meant giving her child a better start in life, it took her only two seconds to say yes.

That's because formula holds promise. Unfortunately it's a promise rarely realized in this part of the world.

A Poor Country
Medicine Is Scarce, And Water Unsafe

"Oh sure it could be great," said Dr. Francis Miro, the chief of obstetrics and gynecology at Makerere University Medical School in Kampala, the Ugandan capital.

Makerere is Africa's oldest university, and it was from here nearly 20 years ago that the first vague reports of "slim disease" -- as AIDS was called here before it had a name -- started making their way to America. Since then more than two million people -- nearly 15 percent of the nation -- have become infected and of those, one million have died in this country where many researchers think the AIDS epidemic may have begun.

"Do you know what I would love to be able to do all day?" Dr. Miro asked rhetorically. "I would love to counsel every H.I.V.-positive mother about her choices in life. I would love to tell her about breast milk and about formula. Then I would love to have a conversation with her about what would happen to her in her village if she stopped breast-feeding. What would her mother-in-law say? What would her husband do? And of course I would love to make sure she understood the rules for keeping formula sterile and that she complied with them.

"I would love to do all that," he concluded wearily. "But then I wouldn't be living in Uganda and I wouldn't be talking to my own people. I would be living in America and I would be talking to your people."

Asked if he thought it was always foolish to recommend formula to women living in villages, he closed his eyes and reeled off the numbers. "Twenty-seven percent of babies born to infected mothers become infected from breast-feeding," he said. "In rural areas 85 percent of babies will die from dirty water used in formula. I know what they are trying to do, and I applaud the effort. But you don't need a medical degree to figure out which of those odds to take."

All you have to do is take a walk down the red dust roads near Kakulu. There are no toilets and few outhouses. People live literally from day to day. Water from still pools -- the classic birthplace of malarial mosquitoes -- is often used to

drink because it's so far to walk to the well.

"The temptation is great sometimes," Mrs. Nannyongoi acknowledged. "We try to boil the water but sometimes we don't."

Outside a man is raking about 50 pounds of coffee for bad beans. Nearly a dozen children, most of them naked, play in the yard. In a shack across the way Halimah Namtovu, a 30-year-old woman wrapped in black scarves, sits beneath a picture of Mohammed. Two months ago she gave birth to her ninth child. All of her children are still alive. She said she thought formula would be great, but she has trouble affording soy milk to give her older children. A kilogram costs about a dollar and lasts less than week.

"We all do what our mothers did," she said without rancor. "If there is a better way I have never seen one."

Despite the traditions of millennia, Dr. Miro and countless colleagues agree that something drastic must be done to help protect children from H.I.V. If mothers who are infected with the virus don't breast-feed, their children will have a far better chance of survival.

What is more, AIDS experts now know that if a pregnant woman is treated with a course of AZT during the final stages of her pregnancy, during birth and for a few days after her child is born, transmission of the virus to the child is reduced by half. The cost of such a course of treatment was until recently $200 per person, but with the help of the United Nations AIDS program and the World Health Organization, the price is now $50.

"This is the best life-saving program we have in the developing world," said Dr. Joseph Saba, a clinical research specialist with the United Nations AIDS program who has coordinated the attempt to make drugs more accessible to people in Africa. "You cannot just say to these people you are too poor to live. You have to say we are trying everything on earth to stop this plague. They have to know that we are not condemning them to death."

Dr. Saba comes often to Uganda to mediate between drug companies, health officials and aid agencies in an effort to bring drug prices down so that local governments and at least some people can find a way to buy them. He knows as well as anyone that -- as is the case with the use of formula -- making AZT available to pregnant mothers raises almost as many terrible new questions as it answers. The biggest one is obvious: will AZT encourage women to have children who will all either die or become orphans?

As soon as the mother delivers she will stop taking AZT -- almost no African women can afford to keep on it for long. That means she will die, probably within two or three years, sometimes much sooner. Her child will then almost certainly join the vast army -- in Africa alone the number is now past eight million -- of AIDS orphans.

"What is worse?' asked Dr. Edward Mbidde, the chief of Uganda's Cancer

Institute, and one of the country's medical leaders. "To let a baby die of AIDS when we can save it or to let the baby into the world just to become an orphan in a society that has been overwhelmed with death? I have not yet run into anyone who is qualified to answer that question."

Nobody has. But like everywhere else, people in African villages don't normally choose death when life is even remotely possible.

A Tough Decision
Does Prenatal Care Create Orphans?

Many rural families are large -- the birth rate here is still higher than in most other places in the world -- and the concept of family is defined very broadly.

"Children is what villages in Africa are for," said Eelin Berdall, the Mother Superior of the St. James School, a private Anglican school deep in the bush of western Zimbabwe. "When people start asking questions about whether it is right to have children under certain circumstances they are just thinking Western. Nobody here would ever think that way. Here if somebody is going to die then their mother, father, sister or brother will want children to remember them."

The Mother Superior has been a leader in trying to help get AIDS drugs to pregnant mothers and in trying to help people think of families in unconventional ways.

"Here the child belongs to the family, it is the vehicle of the tribe," she said. "If we can save a child we have to save a child. And with some very strong effort we can save millions."

Dozens of youngsters are playing behind her in the baking midday sun. Some of them walk barefoot distances up to 10 miles a day just to attend the school. Their brown cotton uniforms are donated by a variety of groups. The vaccines they receive are donated by the Government and by the World Health Organization. Their food is brought by concerned friends and neighbors.

"This woman's sister just died of AIDS," the Mother Superior said, summoning a teacher to join her. "She left five children."

Sulfina Dube nods slowly. She is 39. Her sister was one of the few women in this part of the world who could afford formula, and who lived in circumstances where it could be prepared properly and regularly. "My sister understood that it was her only chance to save her baby," said Miss Dube, who now looks after Celie, the youngest of the five children that were left as orphans when her sister died of AIDS this year.

"There was never a minute when any of us wondered whether it was right for Celie to be born, or to survive. How could you even ask something like that?"

Others wonder how you cannot.

"What we are really asking many women is do you want your baby to die of a horrible disease or do you want him to starve to death?" said Sophia Mukasa Monico, the head of TAOS, Uganda's unique AIDS support organization. Taos has 27,000 clients and not one of them receives drugs that are considered routine in the West.

"Is it ethical to bring a baby into this world in that way? Nobody will ever answer that question. We certainly are not going to stop people from having babies. And it's wonderful that there are ways to treat those children and protect them. But let's not look at formula or a few AZT pills as an answer. It's really just a question. Do women who don't breast-feed want to bring orphans into this world? Or do they want to risk killing their children by caring for them? We're used to death around here. But this is a choice only Idi Amin could have made."

Dead Zones

Later articles will report on other aspects of the AIDS crisis in Africa, and then on other continents.

Correction: August 20, 1998, Thursday

Maps yesterday with an article about fears of breast-feeding in Africa because of the AIDS epidemic carried erroneous shading in some copies, overstating or understating the incidence of H.I.V. or AIDS among pregnant women in several countries. Corrected maps appear today on page A10.

The scale for figures referring to children with H.I.V. or AIDS was also misstated. The figures were per 100,000 children, not per 10,000.

Organizations mentioned in this article:

Related Terms:

Hidden HIV / The search is on for people who don't know they carry the virus that causes AIDS

By Laurie Garrett. STAFF WRITER

TENS OF thousands of New Yorkers - and hundreds of thousands of Americans - have never been diagnosed, but they constitute the unknowing "engine of the AIDS epidemic," according to representatives of a leading AIDS advocacy organization.

About 69,000 residents of New York State, including 2,700 Long Islanders and 50,000 people in New York City, may be infected with HIV and not know it, according to a new analysis by the Gay Men's Health Crisis, an AIDS service organization in Manhattan. GMHC's Derek Link made that estimate based on a new set of calculations, which local and state experts praised in recent interviews.

Now that effective treatments are available for HIV infection, public-health advocates in all tiers of government are concentrating on finding undiagnosed HIV carriers.

The goal is to get the undiagnosed tested and into treatment with a combination of anti-HIV drugs. Treatment may decrease an individual's level of infectiousness, and education usually increases his or her concern about spreading HIV. If those carrying the virus are found, counseled and treated, it may be possible to slow, perhaps even stop, New York's epidemic.

Currently, only AIDS cases are reported to local and state officials, as well as to the U.S. Centers for Disease Control and Prevention. Thus, experts are forced to guess how many Americans are HIV-infected but haven't yet developed AIDS. It's a difficult calculation to make, because AIDS is the final stage of a disease process spanning 10 to 15 years.

This means that a glance at even the most recent AIDS data constitutes a look a decade back to when those patients first got infected. It tells experts little about who is getting infected in 1998, how the virus entered their bodies and, of course, how many remain undiagnosed.

No one has previously tried to figure out how large New York's - or any other state's - total undiagnosed HIV population may be. The CDC has for years assumed that known HIV and AIDS cases constitute just 70 percent of the epidemic. Adding a theoretical 30 percent more gives federal officials a "guesstimate" of about 600,000 to 900,000 current HIV cases nationwide.

But a mid-'90s study using a sample pool of infections in Denver, where HIV cases, by law, have been reported by name for more than a decade, found that only 15 percent of all infections are undiagnosed. That statistic was arrived at by comparing the number of HIV cases from a decade ago to its AIDS cases now.

So, using both the 15 and 30 percent figures, Link created high and low estimates of the size of New York's undiagnosed epidemic. He started with the numbers of New Yorkers, county by county, who receive HIV treatment through Medicaid.

"We know in New York, Medicaid is the major source of care - for about 65 to 75 percent of the HIV population," Link said.

Seated in his cubicle in GMHC's policy nerve center, looking out on the Empire State Building, Link explained that he started with those published Medicaid numbers of HIV-positive cases, then expanded upon them by 15 percent and by 30 percent.

"That's very conservative," Link said. "I mean, the CDC says in some areas it could be there is a 70 percent undiagnosed - in those areas where the epidemic is new."

Link's analysis reveals, for example, that assuming a 15 percent rate, there are 2,341 people in Queens who unknowingly carry the virus. Using the CDC's 30 percent figure, Queens has 6,046 undiagnosed cases. The overall spread for New York City is 20,178 undiagnosed (based on the 15 percent figure) to 53,095. Statewide, Link obtained a low-ball estimate of 27,000 undiagnosed HIV cases; the high estimate: 69,000.

"It sounds reasonable," Dr. Perry Smith, director of the New York State Division of Epidemiology, said in an interview. "We don't really have estimates of the total numbers of HIV-infected New Yorkers. We have reached a stage in the epidemic where we're getting down to those persons that are hardest to reach."

Everyone who follows New York's epidemic in an official capacity believes the HIV population is growing. And the fastest expansion is among the state's most disenfranchised: the poor, intravenous-drug users, people of color, gay teenagers and runaway children. As the numbers of AIDS cases decline, thanks to effective HIV treatment, and the epidemic's spread decreases in the adult gay white male population, evidence at both local

and national levels shows it is expanding in other groups.

"It's extremely serious," says Dr. Helene Gayle, director of all the CDC's HIV/AIDS programs.

A Rand Corp. study presented early last month at the 12th World Conference on AIDS showed that a quarter of the nation's current diagnosed HIV population is female. More than half of those are African-American, Latino or other people of color. Ten years ago, about 80 percent of HIV-positive people were gay men; today, gays account for less than half.

The Rand study shows that because they tend to be poorer, black and Latino HIV patients are far less likely than whites to seek treatment and twice as likely as whites to get the bulk of their HIV care in emergency rooms. While more than 75 percent of white patients receive drugs to prevent lethal opportunistic pneumonia, only 63 percent of blacks and 65 percent of Latino HIV patients receive that preventive treatment.

Rand's data, because it is based on actual case figures from managed-care companies nationwide, suggests the CDC's estimate of the undiagnosed, unreported HIV population is probably way off. If Rand is correct, it's more like 41 percent, not 30 percent.

In a presentation 10 months ago in Toronto, a team of CDC HIV-epidemiology experts described its 30 percent guess as "a minimum estimate, since persons who were tested anonymously were excluded."

In anonymous testing, the identity of the subject is not recorded. If a person tests positive for HIV, he or she is referred to a doctor. Only cases of AIDS, not HIV infection, must be reported to the CDC by the state. At other testing sites, records of identity are maintained, but the identity of the subject is kept confidential.

Anonymous testing appears to be on the upswing in New York. In 1992, nearly 190,000 New Yorkers had an HIV test in a publicly funded facility. In 1996, that number was less than 40,000. There can be only two explanations: Either New Yorkers switched to private, anonymous testing, such as home HIV kits and commercial laboratories, or there has been a 79 percent decrease overall in HIV testing in New York State.

BUT AT THE SAME time, experts say, all indications point to an increase in activities that spread HIV.

For example, New York City is in the grip of a hepatitis A epidemic among gay men. The outbreak appears to have begun in 1996 and has spread at such a pace that the incidence of the disease in gay men more than tripled last year in gay neighborhoods, such as Chelsea. The rapid spread of hepatitis provides proof that thousands of gay men are not using condoms.

The bulk of those hepatitis A cases are gay men under 25 years of age. Researchers at the University of California in San Francisco have followed a group of 600 gay men under 29 , noting a dramatic increase in self-reported unsafe sexual activity during the past five years. Earlier this year 42 percent said they had had sex with more than 10 men annually without using a condom - a near doubling of the number who did so in 1994.

David Hansell, New York City associate commissioner for HIV services, has applied for a $1.7 million grant from the CDC to set up outreach programs for young gay men, African-Americans, Latinos and IV-drug users. The message: Get tested, and if HIV-positive, get treated. If the federal grant comes through, Hansell's office expects to spend about $20,000 for each HIV-positive person it finds. It's a lot of money, Hansell says, "but if you consider the potential savings to society, it's a good investment."

A University of Wisconsin study published in this month's American Journal of Public Health found that intervention that seeks to get people in for HIV testing and counseling costs about $17,000 per person and saves $65,000 for every new HIV infection that is prevented. That, the researchers concluded, means mass efforts to promote testing and counseling are cost-effective.

NATIONALLY, Gayle said, the CDC plans to mount a massive ad campaign that tells Americans, "In this day and age there are more and more reasons to get tested, and fewer and fewer not to. There's a personal benefit as well as a societal benefit to get tested."

In New York City, Dr. Mary Ann Chiasson, who heads HIV epidemiology for the health department, says her message is very simple: "Get tested - get treated!"

But it's on just that point - treatment, and specifically funding for treatment - that Jeffrey Reynolds, policy director for the Long Island Association of AIDS Care, has problems. More than 70 percent of the nation's identified HIV population receive care through taxpayer-supported programs such as Medicare, Medicaid and Veteran's Affairs .

"There's a problem with bringing in large numbers of people for services we don't have funding to provide," Reynolds insists. "Testing has to be a complete promise. It can't be, `Get tested. Now we're going to walk away from you.' "

Seventy-five percent of Nassau County's HIV cases are in the Town of Hempstead, Reynolds says. If testing is going to take place on a large scale in Hempstead, the state must support the community in its efforts to provide treatment. The same can be said for other HIV hot spots on Long Island, Reynolds continued: Freeport, Roosevelt, Bay Shore, Brentwood and Patchogue.

And the numbers of people who might flood into the Long Island health-care system far exceed the GMHC estimates, Reynolds says. GMHC upper estimates are that 895 people are undiagnosed in Nassau County, 1,869 in Suffolk.

"Why are the numbers so different for Nassau and Suffolk?" Reynolds asks. "Through 1997, Nassau reported 2,820 AIDS cases. Suffolk reported 2,978. Assuming the trends will continue, then why is there such disparity in undiagnosed cases in the two counties?"

Reynolds suggests that the difference in the GMHC figures for the two counties is a red flag, indicating underestimation. "My guess is that if you take the GMHC combination of Nassau and Suffolk - 2,764 - I wouldn't be surprised if it were twice that."

One guess on the discrepancy is that HIV patients on Long Island are less likely to use Medicaid services, because they are wealthier, particularly in Nassau. And because the GMHC estimates are based on Medicaid reports, Long Island's HIV burden may be underestimated.

Key to slowing the spread of HIV, Reynolds says, is school-based education about testing. Dr. Donna Fudderman, who runs the Adolescent AIDS Program at Montefiore Medical Center in the Bronx, says one out of four people in the nation currently living with AIDS was infected as a teenager. And most were carrying HIV for a decade before they got a diagnostic test.

"We really think the lack of HIV estimates has been a serious public health barrier," Fudderman said in an interview, "because we don't know how many kids are out there who should be in care."

Fudderman's team has a campaign in the Bronx, called "Kickin' Boots," that uses teenage slang to reach youngsters in schools and encourage testing. She is certain that New York State experts "grossly undercount teenagers" with HIV.

But no one knows for sure. Perry Smith, director of the state's epidemiology division, thinks his Albany office will be in a better position to gauge the size of the HIV epidemic - including its undiagnosed component - after 2000. That's because starting next January, every New York physician will be required to report - by name - all diagnosed HIV cases. Smith figures it will take a couple of years to get the state's reporting system in gear. And then, he says, he'll have numbers to count.

Chiasson is similarly hopeful that the new mandatory reporting will put New York City's database in a better position.

But Link and Reynolds say mandatory HIV name-reporting may drive the undiagnosed epidemic further underground.

"It's yet another challenge that's been thrown up," Reynolds concluded.

17 August 1998 pp C06.

•Relayed as an informational Courtesy• August 18th,1998

MEMORANDUM TO BRUCE REED

FROM: Sandy Thurman, Coordinator for National AIDS Policy

SUBJECT: Draft Memorandum on HHS International Studies To Reduce Maternal-Infant HIV Transmission

Attached is a draft memo outlining the issues involved in U.S.-sponsored international clinical trials to reduce perinatal HIV transmission. I have prepared it as an information memo without recommending a specific position to the President. Attached are Q&A's and talking points in support of the HHS position.

If the President were to be questioned on this issue, my recommendation would be to prepare a response that he has asked Secretary Shalala to look into this issue carefully and report back to him. I do not think this is an issue he should be asked to defend at this time. I've prepared a second set of talking points along these lines.

Let me know if you would like this or other revisions to the memo.

QUESTIONS AND ANSWERS

Q: **Did you know about the NIH supported clinical trials using AZT and placebos in HIV infected pregnant women in developing countries?**

A: I am aware that NIH is funding some research into how to improve prevention of mother to infant transmission of HIV in some developing countries. I understand that AZT is the drug that is being used in these studies.

I have asked the Secretary of Health and Human Services to provide me with a report on these NIH studies. I also asked for an evaluation of how these studies will help the women and infants involved and how the studies are helping to curb maternal transmission of HIV in these countries.

Q: **Some of the women in these studies are not receiving AZT, they are getting a placebo. How does this comport with the U.S. position that all HIV infected pregnant women and their infants should be offered AZT?**

A: That question will be addressed in Secretary Shalala's report. Just let me say that in many developing countries no HIV treatment at all is available for pregnant women or their infants. It is a totally different situation than what we have in this country where AZT is readily available.

Q: **Some critics are saying that the NIH funded AZT studies in developing countries are not different from what happened in the Tuskegee study where treatment was withheld from some of the participants. How do you answer that?**

A: Well, I will need to see the report from HHS before I can fully address that. But I must emphasize that in the Tuskegee study, treatment that was widely available in this country was deliberately withheld from some of the participants. In the AZT studies oversees, the only AZT treatment available is the treatment provided to participants in the study.

Q: **Some critics are saying that there is an issue of violation of international ethical codes in the AZT studies. Is this true.**

A: I will know more about the studies and the specific concerns surrounding it when I review Secretary Shalala's report. Until then, I can't say anything further on this. I can assure you that we will not support any studies where such violations occur.

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Let me know if you would like this or other revisions to the memo.

THE WHITE HOUSE

WASHINGTON

MEMORANDUM FOR THE PRESIDENT

FROM: Bruce Reed, Assistant to the President for Domestic Policy
Sandra Thurman, Coordinator for National AIDS Policy

SUBJECT: International Studies on Reducing Maternal-Infant HIV Tranmission

This memorandum will provide background on the controversy over an ongoing group of U.S.-supported international clinical trials studying options to reduce maternal transmission of HIV in developing countries. A brief overview of current knowledge, the rationale for further research, the World Health Organization position, concerns of domestic public interest groups, and the Department of Health and Human Services' position will be covered. Attached separately are talking points and Q&A's prepared by HHS on the issue.

Perinatal Transmission The World Health Organization (WHO) estimates over 1,000 HIV+ infants are born each day. Women with HIV disease have a 15%-40% risk of transmitting HIV to their baby with each pregnancy. The National Institutes of Health demonstrated that this transmission risk can be lowered to 8.3% by the administration of the drug AZT to women orally during pregnancy and intravenously during labor, and to their newborn infants orally for 6 weeks. This NIH study, known as ACTG 076 - comparing AZT with a placebo - was halted and published in 1994 when these dramatic results were evident. It has become the standard of care to offer all HIV+ pregnant women AZT therapy in the U.S.

An important unanswered research question is at what point during pregnancy or birth do women transmit HIV to their babies -- and if it is necessary to administer AZT over many months to prevent HIV infection in infants. Because many developing countries cannot afford expensive drug therapies for their citizens, pinpointing the critical period in which to administer AZT to prevent perinatal transmission is important so that the greatest number of women could be offered treatment.

Research Study Design Issues The public health leadership of several WHO member countries collaborated with the NIH and Centers for Disease Control and Prevention (CDC) to design and develop research studies to prevent perinatal HIV transmission in countries with limited health care infrastructure and resources. Each research study included an informed consent document outlining the research question, the randomization to an AZT or placebo group, and a detailed description of potential risks study participants may incur. All study protocols were reviewed and approved by the NIH and CDC Institutional Review Boards (IRBs) and the host countries. The political leadership of each host country were also fully informed of the study methodologies and concurred with their implementation. The first studies proposed by this international collaborative group began in 1993 with funding support from the U.S. (NIH, CDC) and France.

World Health Organization Activity In June 1994, the WHO hosted a meeting of researchers and public health practitioners from the U.S., Europe, and countries in Africa, Asia and the Carribean which have a high incidence of HIV disease. The purpose of the meeting was to examine the results of the NIH ACTG 076 trial in terms of their applicability internationally. The following recommendations were issued from this meeting:

1) Encourage the use of AZT as outlined by the NIH ACTG 076 study in industrialized countries; and

2) Immediate exploration of alternative regimens that could be used to achieve prevention of perinatal HIV prevention in the developing world.

WHO participants established parameters for the conduct of research studies in developing countries. The studies supported by the U.S. and France were consistent with these parameters.

Concerns of Some U.S. Public Interest Groups Dr. Sidney Wolfe of the Public Citizen Health Research Group wrote a long critique of U.S. involvement and support for these international perinatal HIV prevention studies in a letter to Secretary Shalala. The letter was broadly distributed to the media. Key concerns raised were:

- Some research designs include a placebo arm when AZT has proven benefit. Such a research design would never be allowed in the U.S.

- The studies violate major international ethical guidelines, specifically: the World Medical Association's 1975 Declaration of Helsinki; four of the Nuremberg codes for human experimentation; and the International Ethical Guidelines for Biomedical Research Involving Human Subjects designed to address ethical issues in developing countries

- There is no guarantee that women and infants in host countries will benefit from the research knowledge gained

- The lack of appropriate care in host countries does not justify study designs with placebo arms that have no benefit. The standard of care in many countries does not include access to prenatal care, medications, hospital births or intravenous infusions

- Comparison of these studies to the Tuskeegee syphilis study; criticism that IRBs should ensure that risks to subjects are minimized and subjects are not unnecessarily exposed to risk; this is colonialism at its worst

Senator Carol Moseley-Braun (D-IL) has also voiced her concern regarding study designs with a placebo arm when there is a known effective treatment for HIV prevention. She is alarmed that such studies are supported with U.S. funds, and thinks it is inappropriate to continue such funding in face of the apology being offered to the Tuskeegee survivors this Friday.

Department of Health and Human Services The Department of Health and Human Services has conducted a review of the U.S.-funded studies in question and continues to support both the study designs and public health importance of completing them. They are ongoing as of this date. HHS testified to this effect before the House Government Reform and Oversight Committee last week. There was very little discussion of the issue among Representatives present.

In brief, the HHS position maintains:

o The studies address a pressing need in the global control of the spread of HIV, defining interventions that will result in reductions in maternal-infant transmission which can be safely and routinely implemented in the developing world;

o The studies are based on the assumption that the NIH ACTG 076 regimen is not a feasible therapeutic intervention in developing countries due to lack of medical infrastructure and cost constraints; the research design examines options for treatment which are viable and affordable within the medical care delivery systems of the study countries

o All ongoing studies are in full compliance with U.S. and in-country regulations and laws, have gone through extensive in-country and U.S. ethical review processes and an international ethical review, and all studies have strong in-country support; an independent Data and Safety Monitoring Board continues to provide oversight of research findings at regular intervals

o Broadly accepted ethical principles for international research recognize a role for the local standard of care when testing the effectiveness of a new intervention. In the case of developing host countries, the local standard is minimal to no health care access. Studying new research options of AZT administration at specific times during pregnancy offers a new benefit to individuals who would not otherwise have had it, while defining research knowledge that may allow many individuals to benefit if shorter courses of AZT prove effective for HIV prevention. The placebo arm is equivalent to the local standard of care.

Attached are Q&As and talking points which support the HHS position on this issues.

THE WHITE HOUSE

WASHINGTON

QUESTIONS AND ANSWERS

Q. Did you know about the NIH supported clinical trials using AZT and placebos in HIV infected pregnant women in developing countries?

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I have asked the Secretary of Health and Human Services to provide me with a report on these NIH studies. I also asked for an evaluation of how these studies will help the women and infants involved and how the studies are helping to curb maternal transmission of HIV in these countries.

Q. Some of the women in these studies are not receiving AZT, they are getting a placebo. How does this compare with the U.S. position that all HIV infected pregnant women and their infants should be offered AZT?

A. That question will be addressed in Secretary Shalala's report. Just let me say that in many developing countries no HIV treatment at all is available for pregnant women or their infants. It is totally different situation than what we have in this country where AZT is readily available.

Q. Some critics are saying that the NIH funded AZT studies in developing countries are not different from what happened in the Tuskegee study where treatment was withheld from some of the participants. How do you answer that?

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TALKING POINTS

* OUR GOAL IN SUPPORTING THESE STUDIES IS TO FIND EFFECTIVE WAYS TO PREVENT MOTHER-TO-CHILD TRANSMISSION OF HIV THAT CAN BE USED IN DEVELOPING COUNTRIES. THAT MEANS FINDING A REGIMEN THAT IS EFFECTIVE FOR THE SPECIFIC POPULATION AND AFFORDABLE IN THAT COUNTRY.

* THE FULL AZT-076 REGIMEN, WHICH IS THE STANDARD OF CARE IN THE UNITED STATES, IS NOT FEASIBLE FOR THESE COUNTRIES. IT IS EXPENSIVE AND REQUIRES SOPHISTICATED MEDICAL MONITORING.

* WE HAVE WORKED WITH THE WORLD HEALTH ORGANIZATION, UNAIDS AND THE HOST GOVERNMENTS TO DESIGN THESE TRIALS. THEY ARE FULLY SUPPORTED BY THE INTERNATIONAL BODIES AND BY THE HOST GOVERNMENTS

* THESE TRIALS HAVE BEEN REVIEWED FROM AN ETHICAL STANDPOINT BY THE CDC AND NIH INSTITUTIONAL REVIEW BOARDS, AND BY REVIEW BOARDS IN THE HOST COUNTRIES. WE AGREE THAT THESE ARE DIFFICULT AND COMPLEX ISSUES, BUT THAT IS EXACTLY WHY WE WENT TO SOME LENGTHS TO ACHIEVE MEDICAL AND ETHICAL CONSENSUS ON THE RESEARCH NOT ONLY WITHIN HHS, BUT WITH INTERNATIONAL ORGANIZATIONS AND THE HOST COUNTRIES THEMSELVES.

* WE ARE DEDICATED TO FINDING AN EFFECTIVE THERAPEUTIC INTERVENTION THAT CAN REALISTICALLY BE ADMINISTERED IN THE HOST COUNTRIES AND IS AFFORDABLE.

QUESTIONS AND ANSWERS
MOTHER-INFANT TRANSMISSION OF HIV

Q. Why is the U.S. government supporting these studies around the world?

A. HHS has been criticized for conducting 9 studies in different parts of the developing world.

All nine were designed in cooperation with public health officials in the countries themselves.

All are aimed at finding ways to reduce mother-infant transmission of HIV in those specific countries. They were devised after completion of the AIDS Clinical Trial Group (ACTG) protocol 076 showed dramatic, positive results of an AZT treatment regimen in the U.S.

All nine were developed following a June 1994 WHO meeting in Geneva at which researchers and public health practitioners from around the world called for 1) use of the 076 regimen in the industrialized world where feasible and, 2) immediate exploration of alternative regimens that could be used in the developing world. They were designed in accord with guidelines developed at that meeting.

Q. Why can't the 076 regimen be used everywhere?

A. According to consensus among researchers and public health practitioners in all the cooperating countries, the 076 regimen is imply not feasible as a standard of prevention in much of the developing world. Let me explain:

* The regimen requires that women be reached early in pregnancy and have blood drawn and tested for HIV. Once the woman knows she is positive for HIV she must take AZT three times daily for weeks, then receive AZT intravenously during labor and delivery. Once the baby is born the newborn must receive AZT in syrup for 6 weeks. In the developing world women are most often not seen in health care delivery systems before delivery.

* Drug costs alone for the 076 AZT regimen are estimated to be $800, an amount that is 80 times the annual health budget per person in many countries involved in these studies, and not available outside the research setting.

* In addition, the 076 regimen simply cannot be assumed to work everywhere. The U.S. study looked at women with greater than 200 CD4 counts who were not breast feeding, while most of the women in host countries would breast feed their infants. In addition, the biology of the HIV virus itself (different strains) may be significantly different in other countries.

Q. Why do some of these studies use a placebo control arm? The Public Citizen groups says this is wrong.

A. The panel convened in Geneva recommended that since the 076 regimen is not applicable in the developing world, "placebo-controlled trials offer the best option for obtaining rapid and scientifically valid results."

They explained that in parts of the world where the 076 regimen is not applicable, the choice of a placebo for the control group in a trial would be appropriate as there is currently no available effective alternative for HIV-infected pregnant women in these countries. This is the quickest way to find appropriate interventions that can be used to benefit the people in these countries.

Although it has been argued that we could use a low dose of AZT in these studies, we believe that low dose AZT would not be an appropriate control because 1) it offers no known benefit to the individual (low dose AZT has not been prove useful anywhere) and 2) this type of study could fail to achieve useful results.

Q. Why is the placebo arm in some studies no intervention at all?

A. Unfortunately, the current standard of perinatal care in much of the developing world is no prevention intervention at all. That is a fact of life. Using this standard care as the placebo control in these studies will result in the most rapid, accurate, and reliable assessment of the value of the intervention being studied compared to the local standard of care.

Q. Are these studies ethically acceptable?

A. They are. The ethical dilemmas are complex and difficult. But the human subjects issues of these studies have been reviewed intensively since the 1994 Geneva meeting. These matters have been discussed in many formal meetings and at forums; reviews have been conducted in the U.S. and the countries where the clinical trials are being carried out (or where they will be carried out).

Q. Public Citizen says that it is unethical to conduct a trial unless it offers all participants a chance to receive an effective intervention if such is available anywhere in the world, not just at the site of the clinical trials. What is your response to that?

A. After thorough review, HHS, and WHO agree that to meet the standards of the World Medical Association Declaration of Helsinki, these studies must employ the best current diagnostic and therapeutic methods available in the country where they are to be performed. Holding other countries accountable to a standard of care unavailable

to its citizens and denying the opportunity for research advances that might benefit them raises another set of difficult ethical issues not addressed by advocacy groups.

Q. Are you going to have these studies re-reviewed or modified, as many have suggested?

A. No. The ethical review of these studies has been rigorous. It has included community and scientific participation in reviews by the relevant institutional review boards (IRBs) in the U.S. and the local IRBs in the countries where the trials are carried out. Support from local governments is obtained and review by an independent Data and Safety Monitoring Board is required when deemed appropriate.

Q. How are these studies any different than the Tuskeegee study?

A. The fundamental difference is that the Tuskeegee study witheld treatment of known benefit in a country where the treatment was widely available. The AZT trials are being conducted in certain developing countries where the standard of care for HIV+ pregnant women does not include treatment for HIV or any prevention options for perinatal transmission.

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FAX TRANSMISSION
IMPORTANT INFORMATION
FROM THE
NATIONAL MINORITY AIDS COUNCIL

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COMMENTS: ATT Daniel Montoya

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Public Citizen

NEWS RELEASE

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1000 FOREIGN INFANTS TO DIE UNNECESSARILY IN US-FUNDED HIV STUDIES

HUMAN EXPERIMENTS ARE TUSKEGEE PART TWO, SAY HEALTH GROUPS

Washington, D.C., April 22, 1997 – The U.S. Government is funding experiments in some of the world's poorest countries which will allow over 1000 children to die unnecessarily from HIV infections, Public Citizen's Health Research Group revealed today, based on documents obtained from the government.

"The American government is paying for--and in at least one case conducting--experiments on African, Asian and Caribbean women which would never be tolerated in this country. It is a clear-cut double standard and for these babies it will be lethal," said Dr. Peter Lurie of Public Citizen's Health Research Group. Public Citizen and other public health experts said that they are not opposed to randomized, controlled trials of different kinds of arguably effective interventions to reduce mother-to-infant HIV transmission *per se* but that they strongly object to such trials if they deny women access to any intervention already proved effective, such as AZT. The discovery that AZT can reduce the transmission of HIV from mother to baby by about two-thirds dates to early 1994 and since then providing AZT has been standard care for HIV-infected pregnant women in the U.S.

Public Citizen produced evidence showing that at least 1002 newborn babies will die as a result of HIV infections they will contract from their mothers in nine unethical experiments funded by either the National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC). An additional 502 infants can be expected to die in six other experiments funded by foreign governments including Belgium, Denmark, France and South Africa and the UN AIDS program.

In the HIV experiments in Burkina Faso, Cote d'Ivoire, Ethiopia, Kenya, Malawi, Uganda, Tanzania, Thailand, Zimbabwe, and the Dominican Republic, some of the women are given either placebos or drugs that have not been proven effective, instead of AZT. Some of the experiments are already under way.

"Two U.S. studies of anti-HIV drugs to prevent transmission to infants are listed in the documents obtained from the government. While both studies in the U.S. offer effective anti-HIV drugs like AZT to *all* the women involved, 15 experiments abroad--including nine funded by the U.S.--do not. It's Tuskegee Part Two and this time many more people will die," said Dr. Sidney Wolfe, Director of Public Citizen's Health Research Group, referring to a U.S. Public Health Service study in which African-American men were denied access to effective treatment for syphilis for several decades.

The health experts including Public Citizen, Wilbert Jordan, M.D., MPH, Chairman of the Black Los Angeles AIDS Consortium, Michael Grodin, M.D. and George Annas, J.D., MPH of Boston University's Health Law Department and George Silver, M.D. of Yale School of Medicine have appealed to Secretary of Health and Human Services Donna Shalala to order the researchers to provide the women in the experiments with AZT immediately and save the infants' lives. "The research violates at least four of the ten principles of the Nuremberg Code," said the letter. They also stated that the experiments may violate the Department's regulations on human research and demanded an investigation by the Department's Office of the Inspector General.

Public Citizen is a non-profit, member-supported, consumer advocacy organization founded by Ralph Nader in 1971. Public Citizen fights for safe foods, drugs and medical devices; for greater consumer control over personal health decisions; and for universal access to quality health care.

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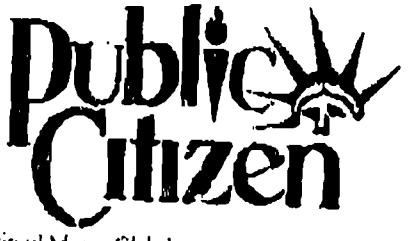

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

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 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*." [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).

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, Msellati 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.

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 woman 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 8,055 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. A8.

[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.

THE WHITE HOUSE

WASHINGTON

MEMORANDUM TO BRUCE REED

FROM: Sandy Thurman, Coordinator for National AIDS Policy

SUBJECT: Draft Memorandum on HHS International Studies To Reduce Maternal-Infant HIV Transmission

Attached is a draft memo outlining the issues involved in U.S.-sponsored international clinical trials to reduce perinatal HIV transmission. I have prepared it as an information memo without recommending a specific position to the President. Talking points and Q&A's in support of the HHS position follow the memo.

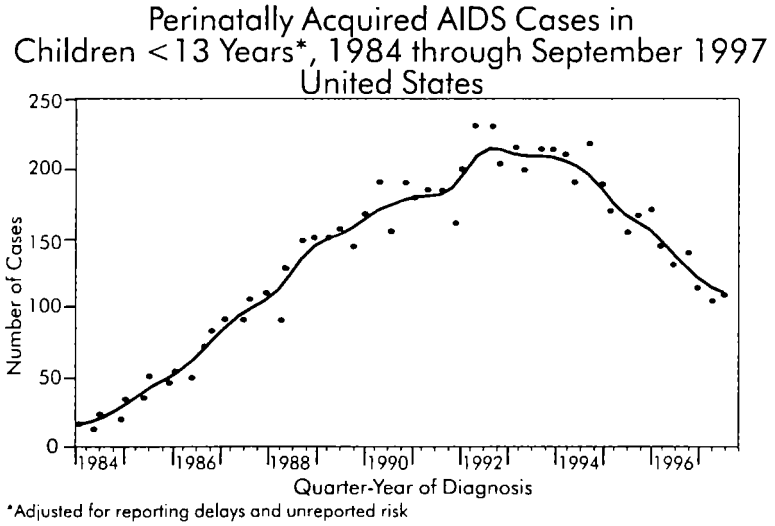
If the President were to be questioned on this issue, my recommendation would be to prepare a response that he has asked Secretary Shalala to look into this issue carefully and report back to him. I do not think this is an issue he should be asked to defend at this time.
I've prepared a separate set of talking points up front along these lines.

Let me know if you would like this or other revisions to the memo.

COMBATING COMPLACENCY
HIV PREVENTION
GENEVA '98

Status of Perinatal HIV Prevention
U.S. Declines Continue:
Hope for Extending Success to Developing World

During the early 1990s, before perinatal preventive treatments were available, an estimated 1,000-2,000 infants were born with HIV infection each year in the United States. Today, the U.S. has seen dramatic reductions in mother-to-child, or perinatal, HIV transmission rates. These declines reflect the widespread success of Public Health Service (PHS) recommendations made in 1994 and 1995 for routinely counseling and voluntarily testing pregnant women for HIV, and for offering zidovudine (AZT, also called ZDV) to infected women during pregnancy and delivery, and for the infant after birth.



Perinatal Prevention Saves Lives and Dollars

On a national level, and in numerous states, studies continue to demonstrate that perinatal HIV prevention is making a difference, both in terms of lives and resources saved:

- Between 1992 and 1996, perinatally acquired AIDS cases declined 43% in the U.S. In 1997, this trend continued with a 30% decline.
- A four-state study (Michigan, New Jersey, Louisiana, and South Carolina) found that the

proportion of pregnant women voluntarily tested for HIV increased from 68% in 1993 to 79% in 1996. The percentage of women offered AZT increased from 27% in 1993 to 85% in 1996.

- Among women in CDC's Perinatal AIDS Collaborative Transmission Study (PACTS), AZT use increased following the publication of PHS guidelines, and the rate of perinatal transmission dropped from 21% to 11%. The PACTS study includes women from four cities - New York City, Newark, Atlanta, and Baltimore.

- In North Carolina, perinatal HIV transmission dropped from 21% in 1993 to 6.2% in the first half of 1996.

- Prenatal care that includes HIV counseling and testing and AZT treatment for infected mothers and their children, saves lives and resources. Without intervention, a 25% mother-to-infant transmission rate would result in the birth of an estimated 1,750 HIV-infected infants annually in the United States, with lifetime medical costs of $282 million.

  Researchers estimate that the annual cost of perinatal prevention is $67.6 million. This investment prevents 656 HIV infections and saves $105.6 million in medical care costs alone, for a net cost-savings of $38.1 million annually.

Despite these successes, challenges remain for further reducing HIV transmission to children in the United States, and for extending opportunities for perinatal prevention to nations in the developing world. Perhaps the greatest barriers in the U.S. are the continuing spread of HIV infection among minority women and the lack of early prenatal care for many of these women.

HIV Remains a Significant Problem for U.S. Women and Their Babies, Especially for Minority Women and Children

HIV infection in children is closely associated with the HIV epidemic in women. HIV transmission from mother to child during pregnancy, labor, and delivery or by breast-feeding has accounted for 91% of all AIDS cases reported among U.S. children. Obviously, the best way to prevent infection among children is to prevent infection in women.

Women of color and their children have always been disproportionately affected by the HIV epidemic. In 1997, of the 13,105 total AIDS cases reported among U.S. women, 10,458 (80%) were among African-American and Hispanic women. Of the 473 children reported with AIDS last year, 402 (85%) were African American and Hispanic. We must continue to improve HIV prevention efforts for women of color and ensure that interventions provide the information, skills, and support needed to reduce their HIV-related risks.

Moreover, perinatal HIV prevention efforts must work to ensure that all HIV-infected women are reached early in pregnancy with the opportunity to learn their HIV status and, if infected, to

consider preventive therapy to improve the chances that their children will be born free of infection. Achieving this goal will require increased access to and utilization of prenatal care.

- A 1995 study analyzed data on approximately one-sixth of all HIV-exposed children born in the United States and found that only about half (53%) received the benefit of the full AZT treatment regimen (for the mother during pregnancy and delivery and for the infant following birth). *The main reason for babies not having the advantage of therapy was that more than one-fourth of the mothers (26%) did not get prenatal care.*

In addition to increasing access to preventive therapy in the U.S., efforts must also focus on extending perinatal prevention to the developing world.

Critical Need to Extend Perinatal Prevention to the Developing World

Until recently, the only AZT regimen proven effective for perinatal HIV prevention was essentially out of reach for the countries where more than 90% of worldwide HIV infections occur. The AZT regimen used in the United States and other industrialized nations is costly and requires several months of treatment for the mother and the infant, and an intravenous dose during delivery that is not feasible in many developing countries. Additionally, HIV-infected mothers in these nations often have no practical alternative to breast-feeding, and this poses an additional risk of transmitting the virus to their newborns.

Earlier this year, researchers from CDC and the Ministry of Public Health in Thailand announced dramatic findings that offer real hope for extending perinatal prevention successes to many developing nations that previously had no realistic preventive options. Researchers found that a short course of AZT given late in pregnancy and during delivery reduced the rate of HIV transmission to infants of infected mothers by half and is safe for use in the developing world. However, the study did not address the efficacy of the regimen among women who breast-feed. Ongoing studies in Africa are expected to provide this critical information.

Policy makers believe that this regimen, using a much shorter course of AZT during pregnancy, an oral dose rather than an intravenous dose during delivery, and no infant dose, can more realistically be implemented in the developing world. The provision of safe alternatives to breast-feeding will still need to be addressed in every setting. The United Nations is now working with public health agencies around the globe to help make this short-course regimen available for as many women as possible and to continue to identify practical solutions for reducing the toll of the epidemic on women and children worldwide.

CDC Presentations Related to Perinatal Transmission

Orals:

"Implementation of Recommendations for the Medical Care of HIV-Exposed Infants in the First Year of Life, U.S.A.," Jeanne Bertolli

"Study Drug Adherence and Tolerance Within a Randomized Clinical Trial to Evaluate a Short-Course Regimen of Zidovudine to Reduce Mother-to-Child Transmission of HIV-1 in Abidjan, Côte d'Ivoire," Ehounou Ekpini

"Randomized Placebo-Controlled Trial of Short-Course Oral ZDV to Reduce Perinatal HIV Transmission, Thailand," Nathan Shaffer

"RNA and DNA PCR for Early Diagnosis of Infants Born to HIV-Infected Mothers, Thailand," Nancy Young

Posters:

"Clinical Outcome and Survival Associated with Perinatal HIV-1 Subtype E, Bangkok, Thailand," Kulkanya Chokephaibulkit

"Safety, Tolerance and Adherence of Late Oral ZDV to Reduce Perinatal HIV Transmission, Bangkok," Rutt Chuachoowong

"Adequacy of Prenatal Care and Perinatal Zidovudine Use to Prevent HIV Transmission," Amy Lansky/Jeffrey Jones

"Viral and Host Genetic Characterizations of Possible Transient Infections in Perinatally Exposed Infants," Marcia Kalish

"Prevalence of HIV and Syphilis Infections Among Pregnant Women Attending Urban Antenatal Clinics in Côte d'Ivoire," Sidibé Kassim

"Declining Seroprevalence of HIV-1 Among Childbearing Women in Upper Northern Ireland," Peter Kilmarx

"Changes in Plasma Viral Load Related to Short-Course Oral Zidovudine (ZDV) During Late Pregnancy," Anuvat Roongpisuthipong

"Cord Blood ZDV Concentration After Intermittent Oral Administration During Labor, Thailand," Wimol Siriwasin

"Utility of Single or Dual Rapid Tests in the Detection of HIV in Pregnant Women, Kenya," Richard Steketee

"HIV and Malaria Overlap and Do Interact in Sub-Saharan African Pregnant Women," Richard Steketee

"Prevention of Perinatal Transmission on the U.S.: A Population-Based Evaluation of Prevention Efforts in 4 States," Pascale M. Wortley