NLWJC - Kagan

DPC - Box 001 - Folder 023

AIDS - Africa Testing/AZT Studies

Aids - Africa AZT

Sandra Thurman 02/18/98 01:45:43 PM

Record Type: Record

To: See the distribution list at the bottom of this message

cc:
Subject: Statement of Short Course AZT

FYI - Here's some very good news on the AIDS front.

Sandy

STATEMENT BY SANDRA THURMAN
DIRECTOR, WHITE HOUSE OFFICE OF NATIONAL AIDS POLICY

WHITE HOUSE AIDS CZAR HAILS NEW TREATMENT TO REDUCE MOTHER-TO-CHILD TRANSMISSION OF HIV

I would like to offer my heartfelt thanks and congratulations to researchers from Thailand and the United States who have found an effective and more affordable treatment regimen for reducing the transmisison of HIV from mothers to children. They have brought a bright ray of hope to the darkness of the AIDS pandemic.

This morning, the Centers for Disease Control (CDC) in Atlanta announced preliminary results from a controversial clinical study, showing that a "short course" of zidovudine (AZT) resulted in a reduction by half of the transmission of HIV from infected mothers to their newborn children.

This study has tremendous implications for helping curb the spread of the AIDS epidemic. Most importantly, it demonstrates the efficacy of a treatment regimen of AZT that is far more affordable and deliverable than the standard course used in the United States.

With 5.8 million new infections occuring each year, most of which are in the developing world, there is a desperate need for strategies to reduce infections. Unfortunately, most of these countries have neither the funds nor the infrastructure to support the long course of AZT that is the standard treatment regiment for pregnant women in the developed world. The new short course costs a fraction of the long course ($50 versus $800) and does not require the intravenous treatments that would be virtually impossible in most developing nations.

Based upon these preliminary results, the CDC (in conjunction with the National Insitutes of Health, the Agence Nationale De Recherches Sur le Sida and UNAIDS) are recommending that controversial placebo control arms of all similar studies be replaced by this new short course regimen.

This is a story about researchers, governments, and communities working together to battle this epidemic. We now know about a tool to save hundreds of thousands of children that would otherwise be lost. The challenge ahead is to figure out how to make this tool available as widely as possible. The United States will continue its leadership in addressing the global epidemic, particularly in implementing this exciting new treatment strategy.

#30#

Message Sent To:

Bruce N. Reed/OPD/EOP
Elena Kagan/OPD/EOP
Christopher C. Jennings/OPD/EOP
Sarah A. Bianchi/OPD/EOP
Toby Donenfeld/OVP @ OVP

Copied Reed. Thurman COS

5-20-97

AIDS — Africa testing

'97 MAY 16 PM 1:53

THE WHITE HOUSE
WASHINGTON

MEMORANDUM FOR THE PRESIDENT

and return

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

opportunity. I think this letter Eric E-mailed us about will provide it. Elena

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?

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 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?

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'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.

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.

AIDS - AZT Studies

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.

- Not Tuskegee
  These ~~pts~~ - participants not denied std of care prevalent in community; here, the ~~[illegible]~~ no one is being harmed bec placebo is same as std of care that they would have gotten.
- Approved by numerous ethical oversight cmtes in US + international - have support of host countries
- Point of test is to figure out effective treatment in places where full course of AZT isn't possible.

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 plecebo. 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.

DRAFT

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.

DRAFT

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

DRAFT

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:

- 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;

- 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

- 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

- 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.

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.

Copied Reed Thurman COS

Eric - Could you answer this question? We'll put it in the weekly. cc: Bruce Elena

5-20-97

File: AIDS - Africa

THE WHITE HOUSE
WASHINGTON

'97 MAY 16 PM 1:53

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?

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 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?

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'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.

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.

AIDS - Africa Levels

NATIONAL SECURITY COUNCIL ID 9703257

REFERRAL DATE: 15 MAY 97

MEMORANDUM FOR: REED, B

DOMESTIC POLICY COUNCIL

DOCUMENT DESCRIPTION: TO: PRESIDENT

SOURCE: MOSELEY-BRAUN, CAROL

DATE: 30 APR 97

SUBJ: HHS FUNDING OF US AIDS TESTING IN AFRICA

REQUIRED ACTION: APPROPRIATE ACTION

DUEDATE:

COMMENT:

FOR JOHN W. FICKLIN

NSC RECORDS MANAGEMENT OFFICE

5-16-17

CAROL MOSELEY-BRAUN
ILLINOIS

3257

COMMITTEES:
BANKING, HOUSING, AND URBAN AFFAIRS
FINANCE
SPECIAL AGING

United States Senate

WASHINGTON, DC 20510–1303

April 30, 1997

MAY 2 11:37

The Honorable William J. Clinton
President
The White House
Washington, D.C. 20500

Dear Mr. President:

An April 23, 1997 article in the Washington Post titled "Medical Group Condemns U.S. AIDS Drug Tests in Africa for Using Placebo" raises some very serious concerns.

The article was based on information released by the Public Citizen Health Research Group. The article reported that the federal government is sponsoring nine medical studies in Africa, Asia, and the Caribbean meant to determine the effects of the brief use of the drug azidothymidine (AZT), or other active drugs, on the mother-to-child transmission of the human immunodeficiency virus (HIV). AZT was found to reduce HIV transmission from mother to infant by two-thirds as part of the Protocol 076 studies in 1993, but the regimens used as part of Protocol 076 may not be feasible in the developing countries. Therefore, the studies that are the subject of the Washington Post article are intended to test alternative regimens.

The problem, however, is that some of the HIV-infected women are being randomly selected to only receive placebos during the studies. According to Public Citizen, this decision will cause at least 1000 children to die unnecessarily from HIV infections.

I am astonished to learn that the Department of Health and Human Services is funding such research, particularly on the eve of the federal government offering an apology to the survivors of the Tuskegee experiments. It is not reasonable to conclude that denying AZT to the participants is consistent with treatment otherwise available in the developing country. The fact remains that we are conducting these studies and we know that AZT has proven results.

MAY 9 13:55

I hope that you will give this matter your immediate attention and ensure that any U.S. funded research provides known effective treatment to all participants.

Yours truly,

Carol Moseley-Braun
United States Senator

CMB:jj