FOIA Number: 2018-0756-F

FOIA MARKER

This is not a textual record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

Collection/Record Group: Clinton Presidential Records

Subgroup/Office of Origin: National AIDS Policy Office

Series/Staff Member: Kristine Gebbie

Subseries:

OA/ID Number: 8299

FolderID:

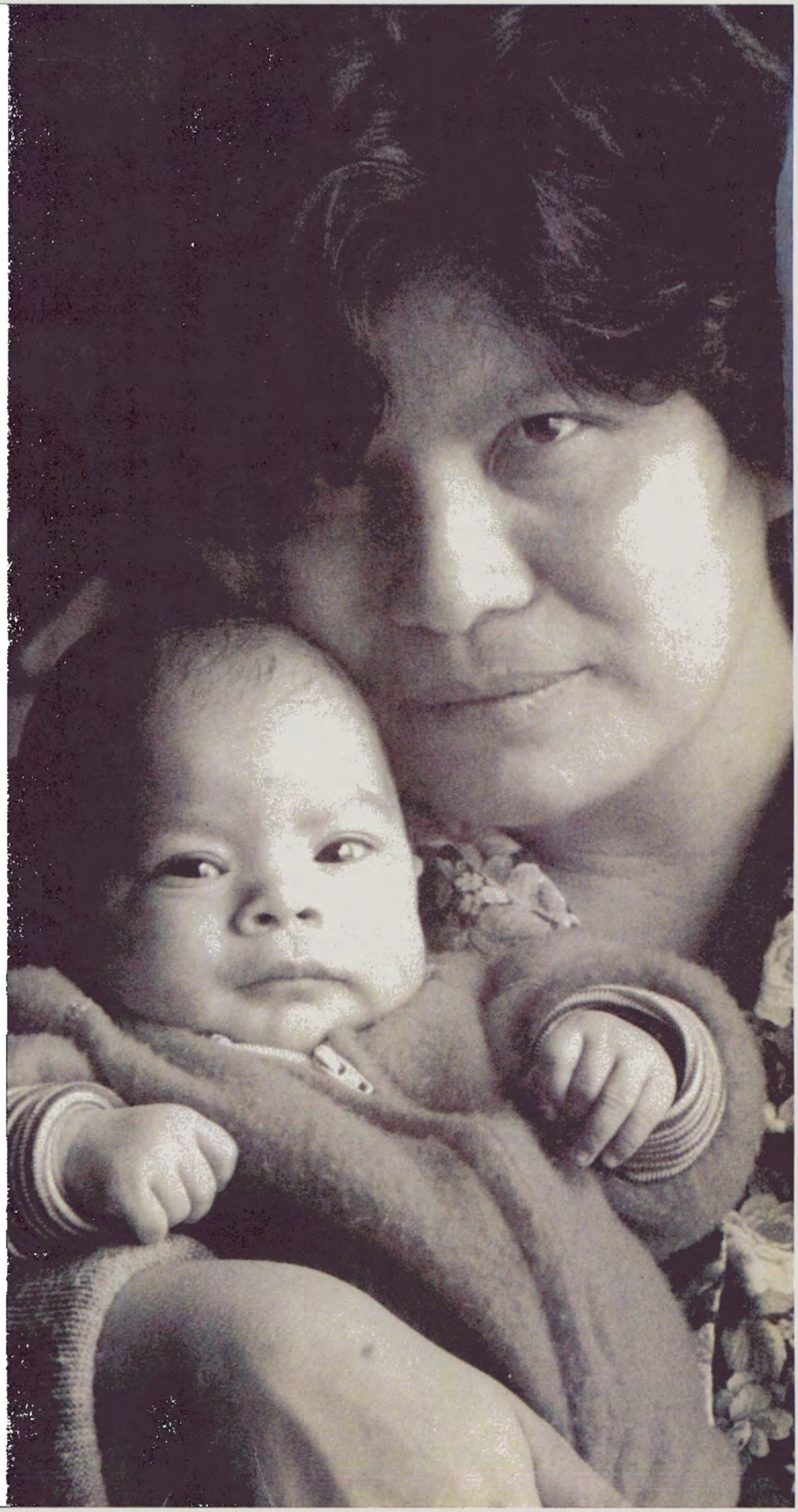
Folder Title:
Meeting with March of Dimes 6/22/94

Stack:	Row:	Section:	Shelf:	Position:
S	66	5	5	2

DAY: WEDNESDAY
DATE: JUNE 22, 1994
TIME: 11:30 AM - 2 PM
LOCATION: NEW YORK TIMES BLDG
229 WEST 43rd ST
EVENT: SPEECH - MARCH of DIMES

MOFD US

March of Dimes
Birth Defects Foundation



March of Dimes
Preventing Birth Defects

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

Join Our Campaign for Healthier Babies

41-61200

EXECUTIVE SUMMARY & QUESTIONS-AND-ANSWERS

FOR THE ACTG 076 STUDY*

(A Phase III Randomized, Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerance of Zidovudine (ZDV)** for the Prevention of Maternal-Fetal HIV Transmission)

* Prepared by the National Institutes of Health (NIH)

** Also known as AZT

EXECUTIVE SUMMARY:ABSTRACT ACTG 076

A Phase III Randomized, Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerance of Zidovudine (ZDV) for the Prevention of Maternal-Fetal Transmission

BACKGROUND

Currently, there are approximately 10-20,000 HIV-infected children and approximately 7,000 infants are born annually to HIV-infected women in the United States. It is estimated that by the year 2000, 10 million children globally will have been infected.

The vast majority of HIV-infected infants and children acquire the virus by maternal-infant transmission; either in utero, during labor and delivery, or postpartum via breastfeeding. In the developed world, antepartum and intrapartum routes account for nearly all of the cases. The risk of maternal-infant HIV transmission in pregnant women has been associated with advanced disease stage, low CD4+ lymphocyte count, and high viral burden.

Zidovudine (ZDV) has been demonstrated to be an effective treatment to decrease viral burden and delay disease progression for HIV-infected adults and children. An uncontrolled survey of some pregnant women treated with ZDV for their own medical care revealed no significant untoward effect.

The risk of maternal-infant transmission of HIV theoretically could be reduced by ZDV treatment of pregnant women. To test this hypothesis, in April, 1991, a Phase III randomized, double-blind, placebo-controlled clinical trial (ACTG 076) was initiated to evaluate whether ZDV therapy could reduce the risk of maternal-fetal transmission in HIV-infected pregnant women. An additional study objective was to evaluate the safety of the ZDV regimen for mothers and infants.

METHODS

Eligible patients were HIV-infected pregnant women (between 14 and 34 weeks gestation) who had no antiretroviral treatment during the current pregnancy, had baseline CD4+ lymphocyte counts greater than 200 cells/mm^3, and had no clinical indications for maternal antepartum ZDV therapy. The target sample size was 748 women (636 fully assessable mother-infant pairs). This was chosen so as to provide 80 percent power to detect a reduction in the probability of transmission to 20 percent for the ZDV group compared with 30 percent for the placebo group, using a two-sided, alpha=0.05 test. Women were stratified according to gestational age (14-26 weeks; >26 weeks) and randomized to receive either ZDV or placebo.

The ZDV regimen consisted of antepartum ZDV (100 mg p.o. five times daily) plus intrapartum ZDV (IV loading dose, 2 mg/kg, followed by continuous infusion, 1 mg/kg/hr, until delivery) plus newborn ZDV (syrup, 2 mg/kg q. 6 hr for six weeks beginning 8-12 hours after birth). Pregnant women were seen frequently during pregnancy, through delivery, and for six months postpartum, and were carefully assessed for evidence of drug toxicity, HIV disease progression, and fetal well-being. Infants were carefully monitored through 78 weeks of age for evidence of HIV infection and to assess safety. HIV infection status was determined by viral culture from the infants at birth, 12 weeks, and 78 weeks of life, and samples were obtained for HIV serology at 72 and 78 weeks. A protocol modification added an additional culture at 24 weeks. Infants were defined as HIV infected for the primary analysis based on one positive viral culture obtained from peripheral blood.

On February 17, 1994, the ACTG Data and Safety Monitoring Board (DSMB) reviewed the interim analysis based on information in the database as of December 20, 1993, and concluded that there was significant evidence of treatment efficacy. On February 18, 1994, the Pediatric AIDS Clinical Trials Group Executive Committee approved the DSMB recommendations to: (1) discontinue new patient enrollment; (2) offer open-label ZDV as per protocol regimen to all individuals on the study; and (3) continue long term follow-up of all infants participating in ACTG 076 to monitor for possible development of unknown late effects of the study treatment.

RESULTS

Thirty-five NIAID sponsored sites, 15 NICHD sponsored sites, and nine centers in France enrolled patients in ACTG 076. Four hundred seventy-seven women were enrolled as of the December 20, 1993 data cut-off. The median age was 25 years (range, 15-43), the median CD4+ lymphocyte count was 550 cells/mm^3 (range, 200-1818), and 41 percent of women had CD4+ lymphocyte counts between 200 and 500 cells/mm^3. The median gestational age at entry was 26 weeks. Maternal demographics revealed a predominantly minority population: only 19 percent were white/non-Hispanic.

Four hundred twenty-one babies have been born; 409 singletons and 6 sets of twins. The median gestational age at delivery was 39 weeks (range, 27-43 weeks). Three sets of twins and 23 singletons were premature (<36 weeks gestation). The median 1-minute Apgar score was 8 (range, 0-10), the median 5-minute Apgar was 9 (range, 5-10), and the median birth weight was 3160 grams (range, 1040-5267 grams). Seven infants (1.7 percent) weighed <1500 grams at birth, 14 (3.4 percent) weighed between 1500 and 2000 grams, and 44 (10.7 percent) weighed between 2000 and 2500 grams.

Three hundred sixty-four births were included in this interim efficacy analysis, 180 in the ZDV group and 184 in the placebo group. Two hundred thirty-three infants had information about HIV infection status as of 24 weeks

of life, and 75 of these had confirmation at 18 months. Thirteen babies in the ZDV group and 40 in the placebo group were defined as HIV-infected. The estimated percentages infected based on Kaplan-Meier analysis were 8.3 percent (s.e.: 2.25 percent) in the ZDV group and 25.5 percent (s.e.: 3.60 percent) in the placebo group. The estimated absolute difference in percentage infected between the two groups was 17.2 percent, with 95 percent confidence interval 8.9 to 25.5 percent. This corresponded to a 67.5 relative reduction in transmission risk. This risk reduction is highly statistically significant (z=4.03; two-sided p=0.000056).

Reported maternal and infant side effects were balanced between the two randomized groups, with one exception that hemoglobin levels were lower for infants in the ZDV group. The mean decrease in hemoglobin was less than 1 g/dl, did not require transfusion, and resolved after completion of ZDV therapy.

CONCLUSIONS

A treatment regimen consisting of ZDV given to the mother both antepartum and intrapartum, as well as to the newborn during the first six weeks of life, significantly reduced the risk of maternal-infant transmission of HIV for women with baseline CD4+ lymphocyte counts >200 cells/mm^3. Further follow-up of mothers and infants is being conducted to determine if there are any late adverse effects of this treatment regimen. Any decision to institute therapy regimens for the prevention of maternal-fetal transmission must be made after careful consideration of the potential unknown long term risks.

February 20, 1994
Distributed with Site Instructions

Prepared by:
Richard D. Gelber, Ph.D.
Pavel Kiselev, Ph.D.
Edward Connor, M.D.
Rhoda Sperling, M.D.
John Moye, M.D.
Mary Culnane, M.S., C.R.N.P.
Bethann Cunningham, M.S.

ACTG 076
QUESTIONS AND ANSWERS

WHAT IS STUDY ACTG 076?

ACTG 076 is a Phase III, randomized, double-blind, placebo-controlled clinical trial, designed to evaluate whether zidovudine (AZT) administered to HIV-infected pregnant women and their infants could reduce the rate of transmission from mother to infant.

The primary objective was to determine if zidovudine given to HIV-infected women during pregnancy and to their infants for the first six weeks of life can reduce the HIV infection rate in the infants. The study also evaluated the safety of AZT when administered to pregnant women and to their infants during the first 6 weeks of life.

WHY WAS ACTG 076 CONDUCTED?

Vertical transmission of HIV (infection of an infant through exposure to maternal virus during pregnancy or labor and delivery) accounts for the vast majority of HIV infection in infants and children worldwide. In the U.S. over 5000 children have developed AIDS. Approximately 7000 infants are born to HIV-infected women each year in the U.S. Not all infants born to infected women become infected. Vertical transmission rates vary in different regions and different patient populations. The overall transmission rate in the U.S. is about 20 to 25 percent.

WHAT WAS THE RATIONALE FOR THE TREATMENT REGIMEN USED IN THIS STUDY?

At the time ACTG 076 was designed there was very little information regarding when the greatest risk of transmission occurs during gestation and delivery. Since transmission is known to occur in some infants early in gestation, the investigators believed that institution of therapy as early as possible in pregnancy might be important in order to achieve the maximum possible effect on the transmission rate consistent with a reasonable safety profile. Thus, it was decided to begin treatment of the women no earlier than the end of the first trimester of pregnancy. Similarly, since one of the mechanisms which was hypothesized to be potentially important for a reduction in transmission was a reduction of the circulating HIV load in the mother, it was decided that women in the study should begin therapy no later than 34 weeks, so that most of the women would have at least four weeks of therapy before delivery.

Since there was some preclinical data to suggest that AZT could reduce the risk of infection in animal models when treatment occurs before exposure, it was thought important that the fetus and infant should be exposed to adequate levels of AZT during the period at risk. The intravenous AZT

regimen during labor was designed to ensure these levels were maintained. The data to support the regimen was obtained in a phase I trial ACTG 082 conducted by the NIAID sponsored AIDS Clinical Trials Group.

A regimen of AZT for the six weeks following birth was included because of the potential for significant blood exposure and mixing at birth and because circulating maternal HIV infected cells might be present in the infant for some time after delivery. The oral treatment of the infant was started at 8-12 hours after delivery based on pharmacokinetic data on the half life of AZT in newborns. The dose used in the infants was derived from data obtained in the phase I trial of AZT in infants, ACTG 049.

WHAT ARE THE POSSIBLE MECHANISMS BY WHICH AZT REDUCES TRANSMISSION?

AZT causes a significant reduction in the level of infectious virus in the maternal circulation, and likely in other fluids such as vaginal secretions as well. It is probable that this reduces the amount of virus to which the infant is exposed.

The presence of AZT in the infant before and during exposure to virus may reduce the risk of an exposure resulting in an established infection.

There is no data to suggest which of these mechanisms plays the most significant role in the effect observed in this study.

WHO SPONSORED THE STUDY?

ACTG 076 was conducted by the AIDS Clinical Trials Group sponsored by the National Institute of Allergy and Infectious Diseases. Study trial sites contracted by the National Institute of Child Health and Human Development participated in the trial. In addition, women enrolled at sites under the auspices of the Institut National de la Sante et de la Recherche Medicale (INSERM), and Agence Nationale de Recherches sur le SIDA (ANRS), France. Burroughs Wellcome Co. provided zidovudine for the study.

WHEN AND WHERE WAS THE STUDY CONDUCTED?

Study enrollment opened in April 1991. The study was conducted at 59 sites of the AIDS Clinical Trials Group (ACTG). As of December 20, 1993, 477 women had been randomized and the births of 421 infants have been recorded in the database.

WHO PARTICIPATED IN THE STUDY?

The study was open to HIV-infected pregnant women who had not taken any antiretroviral therapy during the current pregnancy, had baseline CD4+ lymphocyte counts greater than 200 cells/mm^3, and had no clinical indications for maternal antepartum ZDV therapy. The women were between 14 and 34 weeks of their pregnancy when they entered the study.

WHAT WAS THE DESIGN OF THE STUDY?

Eligible women were randomized to either an active drug arm containing ZDV or a control arm containing placebo. The zidovudine regimen included 100mg capsules five times a day initiated between the 14th and 34th weeks of pregnancy and continued throughout the remainder of pregnancy. During labor, intravenous ZDV was administered (loading dose 2mg/per kilogram of body weight followed by continuous infusion 1mg/kg/hour until delivery). When the mothers received ZDV, their infants received ZDV, and when mothers received the placebo, their infants received the placebo. The zidovudine regimen for the infants (syrup 2mg/kg by mouth every six hours) began 8 to 12 hours after birth and continued for 6 weeks.

The ability of zidovudine to prevent the transmission of HIV in infants born to HIV-infected mothers was evaluated by comparing the rates of HIV infection in infants born to mothers who had received zidovudine and those who received placebo.

WHAT WERE THE RESULTS OF THE STUDY?

As of December 1993, 421 infants were born to women enrolled in the trial. Of those, 364 infants had at least one culture result available.

Of the 364 evaluable infants, 53 had HIV infection. Of those 53, 13 had received zidovudine and 40 had received the placebo. The estimated rate of transmission in the group that received zidovudine is 8.3%, whereas the rate of transmission in the group that received the placebo was 25.5%. These results are statistically significant (p=.00006) and indicate that if zidovudine is used in a similar population, only 8 out of 100 infants will be infected, compared to 25 out of 100 infants when zidovudine is not used. All 53 HIV-infected infants had at least one HIV-positive culture. There was no evidence that zidovudine delayed time to detection of infection.

There were no significant short time side effects to either mother or infants resulting from AZT use other than mild anemia in the infants which reversed shortly after treatment ended.

There is no information regarding any long term effects on the infants or mothers treated in this study.

HOW WAS HIV INFECTION DETECTED IN THE INFANTS?

All infants were checked for evidence of HIV infection at birth and at 12, 24, and 78 weeks. A positive viral culture was considered indicative of HIV infection. Infants were also tested for HIV antibodies at 15 and 18 months.

HOW OLD WERE THE WOMEN IN THE TRIAL AND WHAT WERE THEIR CD4+ CELL COUNTS?

The average age of the women who participated in the trial was 25.6 years old. The average CD4+ cell count was 586 cells/cubic millimeter of blood (mm3). Forty-one percent of women had CD4+ lymphocyte counts between 200 and 500 cells/mm^3.

WHAT WERE THE ETHNIC BACKGROUNDS OF THE WOMEN ENROLLED?

Of the women enrolled, 51% were African American, 29% Hispanic and 0.2% Asian. The ethnic and racial distribution of the trial participants is comparable to that in the population of HIV-infected women in the U.S.

WERE SIGNIFICANT SIDE EFFECTS SEEN IN THE MOTHER THAT COULD BE ASSOCIATED WITH ZIDOVUDINE USE?

The drug was tolerated well by women enrolled in the trial. No significant differences in side effects between the zidovudine and placebo groups were reported. The most common side effects reported were blood related toxicities with equal numbers reported in both groups. Six women discontinued treatment due to toxicities. Three of these were receiving zidovudine and the other three were receiving placebo.

WERE SIGNIFICANT SIDE EFFECTS SEEN IN THE INFANTS THAT COULD BE ASSOCIATED WITH ZIDOVUDINE USE?

Overall, zidovudine was tolerated well. During the six weeks of treatment the most common side effects reported for both treatment groups were low hemoglobin (anemia), low white blood cells (neutropenia) and a high bilirubin level. While significant anemia was rare, the values of hemoglobin for the zidovudine group were lower than those for the placebo.

However, the mean decrease in hemoglobin was less than one gram/dl, did not require transfusion, and resolved within several weeks after completion of ZDV therapy.

WERE ANY CONGENITAL ANOMALIES IN THE INFANTS ASSOCIATED WITH ZIDOVUDINE USE?

Congenital anomalies were seen equally in the ZDV treated and placebo groups of infants (7 infants and 8 infants, respectively). The rate of congenital anomalies that did occur does not differ from what one would expect in the general population. No congenital anomalies were believed to be related to ZDV.

HAVE ANY WOMEN OR INFANTS ON THE STUDY DIED?

No women on the study have died. Most women on ACTG 076 are at a relatively early stage of HIV disease. Seven infants in the treatment group and seven infants in the control group died. Infant deaths were attributed to serious congenital anomalies present at birth or were due to rapid progression of HIV disease.

WHAT HAPPENED TO THE WOMEN AFTER THEY DELIVERED?

The mothers' health was monitored for six months after delivery. At six months postpartum, there was no significant difference in CD4+ T lymphocyte cell counts by treatment group and 95% of women had CD4+ lymphocyte counts >300 cells/mm^3.

HOW WILL THE MANAGEMENT OF MOTHERS AND THEIR INFANTS WHO ARE NOW IN THE STUDY CHANGE?

All participants will be informed of the study results. Women who are currently enrolled in Study ACTG 076 will be informed of the trial results and be offered zidovudine for the remainder of their pregnancy and for their infants during the first six weeks of life. Infants within the first 6 weeks of life in both the ZDV and placebo groups also will be offered zidovudine. Data will continue to be collected as outlined in the protocol. This means that all women will be seen at six months after delivery and their infants will be followed until they are 18 months old.

Infants also will be followed for an extended period of time for potential late-appearing side effects of treatment.

WHAT ARE THE IMPLICATIONS OF THE RESULTS?

The results of this study indicate zidovudine treatment as administered in this study can greatly reduce the risk of transmission of HIV infection from mother to infant. However, because long term effects of therapy on infants exposed to the treatment regimen used in this trial are unknown, general recommendations regarding treatment must await consensus on the balance between known benefit and unknown risk.

DOES THIS MEAN THAT ALL PREGNANT HIV-INFECTED WOMEN SHOULD BE TREATED WITH ZIDOVUDINE?

The results of this study are directly applicable only to women who initiate ZDV treatment between 14th and 34th weeks of pregnancy, receive no other antiretroviral treatment during the current pregnancy, have baseline CD4+ lymphocyte counts greater than 200 cells/mm^3, and have no clinical indications for maternal antepartum ZDV therapy.

Many clinical situations will differ from that of the women who were treated in ACTG 076. However, the study provides no data that directly address either alternative clinical situations or therapeutic regimens.

Answers to questions that involve other treatments and other patient populations will require additional research.

DOES THIS NOW MEAN THAT AN HIV-INFECTED WOMAN CAN DECIDE TO HAVE A CHILD AND BE SURE IT WILL BE BORN WITHOUT HIV INFECTION?

No. In this study population, 8 out of every 100 infants born were infected with HIV even though both mothers and infants received zidovudine.

WILL THERE BE LATE CONSEQUENCES FOR WOMEN AFTER USING ZDV DURING PREGNANCY TO REDUCE PERINATAL TRANSMISSION?

Further studies are needed to address questions about ZDV efficacy and safety in mothers for whom ZDV will be indicated at a later time,

following an interval off-treatment after their treatment during pregnancy.

WILL USING ZIDOVUDINE CAUSE CANCER OR SOME OTHER PROBLEMS LATE IN LIFE?

There is no human data to answer the question of whether treatment with zidovudine may cause unforeseen problems later in life. Infants who have been followed for at least one year in ACTG 076, show no indication of a late side effect associated with zidovudine, but it is far to soon after therapy to draw any conclusions regarding the long term effects, if any. Additional data are absolutely essential from longer follow-up of more infants. The NIAID and ACTG Pediatric Executive Committee plan rigorous efforts to ensure long term follow-up for all the infants who have participated in this study. Through this long term follow-up, data will be gathered on possible long term effects of zidovudine.

CAN THE RESULTS OF ACTG 076 BE EXTRAPOLATED TO OTHER SITUATIONS IN WHICH PREEXPOSURE OR POSTEXPOSURE PROPHYLAXIS MIGHT BE CONSIDERED?

There are no useful data to extrapolate from this study to other situations where one is trying to prevent transmission. The transmission of virus from mother to infant is a unique route of infection.

WHERE IS MORE INFORMATION AVAILABLE?

Further information about this trial is available from the AIDS Clinical Trials Information Services, 1-800-TRIALS-A.

General information about HIV disease, testing or treatment options may be obtained from your health care provider, your local and state health department or by calling any of the national organizations. Some of these include:

- National AIDS Information Hotline (1-800-342-AIDS)
- National AIDS Information Clearinghouse (1-800-458-5231)
- National Pediatric HIV Resource Center (1-800-362-0071)

February 20, 1994
Distributed with Site Instruction Package

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100
Direct Line 914 997 4622
FAX 914 997 4662

Join Our Campaign for Healthier Babies

Andrea Heller Ziltzer
Manager
Magazine Media Relations

MARCH OF DIMES BIRTH DEFECTS FOUNDATION PRACTICE AND POLICY ON PERINATAL TRANSMISSION OF HIV

March Dimes Practice

The mission of the March of Dimes Birth Defects Foundation is to improve the health of babies by preventing birth defects and infant mortality. Perinatal AIDS and HIV can cause birth defects (i.e., the consequences of the infections that occur in infancy) and infant mortality. The Foundation provides health education materials on HIV prevention to women and men of childbearing age. Chapters have participated in and sponsored professional education: An exemplary project in New York City uses a medical residency training curriculum on substance abuse, with emphasis on HIV-related concerns. The March of Dimes also provides general support for the work of the Salk Institute in La Jolla, California, where basic research is being conducted to develop a vaccine to prevent HIV-AIDS.

March of Dimes Policy

The March of Dimes urges all persons at risk for HIV to be tested before trying to conceive. Prenatal care providers should routinely offer all pregnant women effective HIV counseling and voluntary testing because detection can increase opportunities for effective treatment of mother and infant. Four studies in urban areas found that approximately 90% of pregnant women agreed to HIV screening when the service was routinely offered. Policies viewed as coercive or stigmatizing discourage prenatal care use.

The March of Dimes believes that prenatal testing for HIV infection or other conditions should not be mandatory at this time. This policy will be reviewed periodically as new data becomes available.

The March of Dimes urges research aimed at preventing HIV and understanding the effects of treatment, as well as policies and programs that promote access to preconception and prenatal care. (June 22, 1994)

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes Preventing Birth Defects

Public Health Education Information Sheet

Perinatal AIDS

What is HIV/AIDS?

HIV stands for Human Immunodeficiency Virus, the virus that causes AIDS. After HIV enters a person's blood stream, an AIDS test will indicate that he or she is "HIV positive." This does not necessarily mean that he or she has AIDS. But it does mean that the person is carrying the virus and can transmit it to others. It can take up to 10 or more years for an HIV-positive person to actually develop AIDS.

AIDS stands for Acquired Immune Deficiency Syndrome. When a person has AIDs, he or she cannot fight off other diseases and so is abnormally susceptible to infections, cancer, and other serious problems that can be life-threatening or fatal.

A person with AIDS can infect others through sexual intercourse, sharing drug needles or, in the case of a pregnant woman, by infecting her baby during pregnancy or delivery. When a mother passes the AIDS virus on to her baby, the baby's condition is referred to as perinatal HIV infection.

How extensive is the problem of perinatal AIDS?

AIDS is a rapidly growing problem among infants and children. As of December 1992, a total of 4,249 cases of pediatric AIDS had been reported to the Centers for Disease Control and Prevention (CDC). Of these cases, 3,432 involved children under age 5. Most of the children were infected before or during birth by their infected mothers. Thousands more babies carry HIV but have not yet developed AIDS.

The rapidly growing number of babies with AIDS reflects the rise in the number of women who have AIDS. As many as 80,000 women of childbearing age in the United States may carry the virus, according to a study by the CDC. Approximately 6,000 HIV-infected women now give birth each year — and many will pass the virus on to their babies.

How do babies get AIDS?

More than 85 percent of children with AIDS were born to mothers who either had AIDS or were HIV-positive during pregnancy. These children became infected while in the uterus, during labor or delivery or, in a few cases, from breastfeeding. Most studies indicate that babies born to infected mothers have about a 30 percent chance of acquiring HIV; however, a recent European study reported a rate of only 13 percent.

Since a person who has HIV often has no symptoms, it is possible for a woman to be unaware that she is infected with the virus until her baby develops AIDS.

What are the symptoms of perinatal AIDS, and when do they appear?

About 20 percent of HIV-infected infants develop symptoms of AIDS within the first few months of life, and the majority develop symptoms within two years of birth. Some, however, may not develop symptoms for years.

Babies with AIDS suffer frequent infections, such as ear infections and meningitis, and often suffer from diarrhea. They often fail to thrive and gain weight. Enlargement of the spleen, liver, and lymph and salivary glands are common. Because the virus damages the brain, many children suffer delays in learning to sit up, crawl, walk and speak.

Most adults with AIDS are plagued by diseases that occur rarely in people whose immune system is not weakened. Such diseases, called opportunistic infections, are found less frequently in children with AIDS. The children's health is more likely to be threatened by common bacteria, such as strep.

One opportunistic infection, however, is common in babies as well as adults with AIDS. This is Pneumocystis carinii pneumonia (PCP). This infection occurs in about 40 percent of children with AIDS, and is often the first AIDS-related illness to appear in infants. PCP is more often fatal in infants than adults and is a major cause of death in the first year of life among babies with AIDS.

Life is often short for infants who have AIDS. Babies who develop symptoms in the first six months of life often do not survive beyond 1 year of age. However, some children with the virus do better than expected. Some do not become sick until age 5 or 6, and a few have survived until age 12 or 13. It is not yet known why some children with the AIDS virus can remain symptom-free for years, while others succumb rapidly.

Does the AIDS blood test tell if a newborn is infected?

The AIDS screening test, which detects HIV antibodies, is not reliable for an infant born to an infected mother. This is because the mother's antibodies may be present in her baby's blood for up to 15 months, even if the baby has not been infected.

However, new tests have begun to lead to earlier diagnosis of infected babies. A test that measures an immune system protein called IgA is proving accurate in diagnosing HIV in babies between the ages of 3 and 6 months. Other new tests that detect the AIDS virus itself, instead of the antibody, often make it possible to detect infected newborns; however, tests of this type are complex and not widely used. Researchers recently reported the development of a simpler test that detected the virus in 80 percent of infected newborns. This could pave the way for earlier, more effective treatment for babies with AIDS.

How are infants with AIDS treated?

Infants with AIDS are closely monitored and treated with antibiotics, immune globulin (a blood ingredient rich in antibodies that help ward off infections), and antiviral drugs. A study by the National Institutes of Health (NIH) found that children who receive monthly doses of intravenous immune globulin have fewer bacterial infections and longer infection-free periods than other children with AIDS. The CDC recommends that HIV-infected children whose white blood cell counts drop below a specified level receive antibacterial drugs on a regular basis to help prevent Pneumocystis carinii pneumonia.

While there currently is no way to eliminate HIV or prevent it from damaging the immune system, the AIDS drug zidovudine (also called azidothymidine or AZT) has shown promise for prolonging the lives of infected babies. Early studies with another AIDS drug, didanosine (also called dideoxyinosine or DDI, led to improvement of some symptoms in infected children.

What research is being done on perinatal AIDS?

Researchers are investigating whether giving zidovudine to a pregnant woman who tests positive for HIV can prevent her baby from becoming infected. The NIH is conducting a large study to test whether zidovudine given in the second and third trimesters of pregnancy can reduce transmission of the virus from infected mothers to their babies. Newborns will continue to receive the drug for the first six weeks of life.

Other researchers are looking at whether giving an infected pregnant woman gamma globulin containing concentrated antibodies against HIV can reduce the risk to her newborn. Also under investigation is a vaccine that may reduce transmission of the virus from an HIV-infected pregnant woman to her baby.

What is the best way to prevent perinatal HIV infection today?

In some urban areas, 1 to 4 percent of women of childbearing age carry the HIV virus. Thousands of infants will develop AIDS unless women at special risk for the infection receive counseling and testing before becoming pregnant. A woman should get tested for HIV if she:

- Has symptoms of HIV infection.
- Has a positive HIV antibody screening test. (This may have caused rejection as a blood donor, for example).
- Has used intravenous drugs for nonmedical reasons.
- Is from a country where AIDS is widespread among heterosexuals.
- Has engaged in unprotected sex with multiple partners.
- Is or was the sexual partner of an intravenous drug user, a bisexual man, a man with hemophilia or another condition requiring treatment with whole blood or pooled-blood products, a man from an area with epidemic heterosexually transmitted AIDS or a man who shows evidence of HIV infection.
- Has had blood transfusions or treatment with pooled-blood products between 1977 and early 1985.
- Has a current or past history of sexually transmitted diseases.

Women who would like counseling and testing can contact their state or local health department. In many cities, anonymous testing is available. If a woman is found to be infected, she can avoid having a baby with AIDS by avoiding or delaying pregnancy until more is known about transmission of the virus during pregnancy and delivery.

Uninfected women can avoid all known or likely sources of infection before and throughout pregnancy. Known sources of infection include needles, razors or other items contaminated with the blood of infected persons, and sexual contact with infected persons. The Surgeon General has suggested that the proper use of condoms offers protection from AIDS and other sexually transmitted diseases.

What is the March of Dimes doing about perinatal AIDS?

The March of Dimes supports research on the prevention and treatment of perinatal AIDS, including a study aimed at pinpointing the times during pregnancy, labor and delivery that the virus is most likely to be transmitted to the fetus. This information could be used to develop ways to block transmission from mother to baby.

The March of Dimes also works to educate the public about the threat the AIDS virus poses to unborn babies. A brochure for teens called "AIDS: What We Need to Know" is available from local March of Dimes chapters or the national office.

For more information, call the National AIDS Hotline at 1-800-342-AIDS. For information in Spanish, call: 1-800-344-SIDA. If you are hearing impaired, call: 1-800-243-7889.

This information sheet is made possible by donations to the March of Dimes and its Campaign for Healthier Babies.

09-362-00 12/93

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100
Fax: 914 428 8203

March of Dimes

National Communications Advisory Council

Editorial Luncheon

PREVENTING HIV TRANSMISSION: THE LATEST NEWS ABOUT MOTHERS AND BABIES

The New York Times Executive Dining Room
229 West 43rd Street, 11th Floor
New York City

Wednesday, June 22, 1994
12 - 2 p.m.

Presenters:

Kristine Gebbie
White House AIDS Policy Advisor

Howard Minkoff, M.D.
Director, Maternal-Fetal Medicine
State University of New York Health
Science Center at Brooklyn

Nancy Dubler, LL.B.
Director, Division of Bioethics
Montefiore Medical Center

Moderator:

Alan Fleischman, M.D.
Director of Neonatology
Albert Einstein College of Medicine

KRISTINE M. GEBBIE, R.N., M.N.
National AIDS Policy Coordinator
Appointed by President Bill Clinton

Kristine M. Gebbie is President Clinton's National AIDS Policy Coordinator, overseeing the nation's HIV and AIDS agenda in research, services and prevention. Prior to her appointment, Ms. Gebbie served as Secretary of the Department of Health for the State of Washington. She was a member of the Presidential Commission on AIDS chaired by Admiral Watkins, which was the first national body to make comprehensive recommendations for the national response to HIV and AIDS.

Ms. Gebbie has a lengthy career history in the health field and public policy. She has served as the public health administrator in the State of Oregon, and was the coordinator of ambulatory care for St. Louis University Hospitals. Ms. Gebbie taught health courses at the University of Washington, the Oregon Health Sciences University in Portland, the University of California at Los Angeles, and St. Louis University.

Ms. Gebbie is active in many professional organizations, and has served as a member of the Executive Board of the American Public Health Association. She has been a member of the HIV Committee of the Association of State and Territorial Health Officials, and she has chaired the Centers for Disease Control and Prevention Advisory Committee on the prevention of HIV infection and the Environment, Safety, and Health Advisory Committee of the U.S. Department of Energy. She is a member of the Institute of Medicine, and she has served on its AIDS Oversight Committee.

Ms. Gebbie has a Bachelor of Science degree in nursing from St. Olaf College, a Masters of Nursing from the University of California at Los Angeles, and is a doctoral candidate at the University of Michigan School of Public Health. She is the mother of three and resides in Washington, D.C.

###

HOWARD L. MINKOFF, M.D.

Dr. Howard L. Minkoff is Director of Maternal-Fetal Medicine and Distinguished Professor of Obstetrics and Gynecology at the State University of New York Health Science Center at Brooklyn.

Dr. Minkoff is active on various national and state committees related to the health of pregnant women and children, particularly in the area of perinatal HIV infection. He is a member of the Surgeon General's Task Force on Pediatric AIDS, the Subcommittee on Maternity & Family Planning of The New York Academy of Medicine, the Department of Health Task Force on Perinatal AIDS and the Department of Health Task Force on HIV Among Pregnant Women.

Dr. Minkoff has published numerous peer-review articles about perinatal HIV transmission and pregnancy outcomes. He has served as a research investigator for several National Institutes of Health (NIH) studies on obstetrics and HIV disease. Dr. Minkoff recently chaired a national task force to develop guidelines for implementation of results from the 076 study on perinatal HIV transmission into clinical practice.

Dr. Minkoff earned his B.A. degree in biology from the State University at Binghampton in New York and his M.D. from the State University at Pennsylvania. He completed his residency in obstetrics and a fellowship in maternal-fetal medicine at the State University of New York Health Science Center at Brooklyn.

He is a member of a number of societies, including the American College of Obstetricians/Gynecologists, the Infectious Disease Society of Obstetrics and Gynecology, and the Infectious Disease Society of America.

###

NANCY NEVELOFF DUBLER, LL.B.

Nancy Neveloff Dubler is Director of the Division of Bioethics, Department of Epidemiology and Social Medicine at Montefiore Medical Center and Professor of Bioethics at the Albert Einstein College of Medicine.

Ms. Dubler founded and currently serves as Director for the Law and Ethics Consultation Service at Montefiore Medical Center, which provides support to the hospital for analysis in difficult cases. She is also editor of the Journal of Prison and Jail Health: Medicine, Law, Corrections and Ethics, which she founded in 1978.

Previously, she held positions with the Vera Institute of Justice, South Brooklyn Legal Services and Bank Street College of Education.

Ms. Dubler serves on various ethics committees and institutional review boards at major medical centers. She consults frequently for federal agencies, national working groups and bioethics centers, most recently serving as co-chair of the working group on "Ethical Foundations of the New Health Care System" for the National Health Care Reform Task Force in Washington, D.C.

Ms. Dubler lectures often about, and is the author of numerous articles and books on, issues surrounding termination of care, home- and long-term care, geriatrics, the care of adolescents, prison and jail health care, AIDS and tuberculosis policy.

She is currently a Woodrow Wilson Visiting Scholar, and a Fellow at The Hastings Center. She has received Fellowships for research from the World Health Organization and the Ford Foundation.

Ms. Dubler earned her B.A. at Barnard College in New York, N.Y., where she was Phi Beta Kappa and received a Woodrow Wilson Fellowship. She earned her LL.B. from Harvard Law School in Cambridge, MA.

She is a member of a number of societies, including the American Public Health Association, the American Society of Law, Medicine and Ethics and the New York Academy of Medicine.

###

ALAN R. FLEISCHMAN, M.D.

Dr. Fleischman is Director of the Division of Neonatology, and Professor of Pediatrics and Professor of Epidemiology and Social Medicine, in the Department of Pediatrics of the Albert Einstein College of Medicine and the Montefiore Medical Center. After 19 years at Einstein-Montefiore, Dr. Fleischman will become Senior Vice President at the New York Academy of Medicine in July of 1994.

In his new position, Dr. Fleischman will be responsible for initiatives focusing on urban health, education, public policy and public health. He will maintain academic appointments at the Albert Einstein College of Medicine. He is also a Fellow of The Hastings Center in Briarcliff Manor, New York, where he participates in research and education in the area of ethics.

Dr. Fleischman has written extensively about neonatal and fetal physiology with a research emphasis on nutrition. He has written, taught and lectured about all aspects of bioethics, emphasizing the rights of individual patients and the responsibilities of health care providers.

Dr. Fleischman is a member of the American Academy of Pediatrics National Provisional Committee on AIDS and the New York State Bioethics Commission-the Governor's Task Force on Life and the Law. He is a consultant to the March of Dimes Birth Defects Foundation and President of the Eastern Society for Pediatric Research. He is also a member of the American Pediatric Society, the Ambulatory Pediatrics Association, the American Public Health Association and the Association for Health Services Research.

Dr. Fleischman graduated Phi Beta Kappa from the City College of New York and first in his class from the Albert Einstein College of Medicine. He continued his education in Pediatrics at the Johns Hopkins Hospital in Baltimore, MD and in Neonatal-Perinatal Medicine at the National Institutes of Health in Bethesda, MD and through a Royal Society of Medicine Foundation Scholarship at Oxford University in England.

###

critical unasked ?'s —
separate 3 parts of therapy ?

III What are the issues

Temptation - to focus on the eventual child,
not the mother

Focusing on the mother:

1) her decisions regarding her own health
AZT resistance develops —
if she takes now (when she doesn't need it)
what are her risks later

2) the questions of testing —
Mandates on providers to offer
if any mandates at all

Don't lose sight of longer term ?'s for child

most infants born to infected moms
are uninfected — this increases the
% —
long term impact on child unknown

1 known for sure —
we've increased the # of health kids
living w HIV+ parent
& likely to be orphaned prior to
adulthood

We were already producing
100,000 + HIV orphans -

March of Dimes –

HIV, Women & Children

I. The connection is real:
women & children do get HIV
worldwide: 3.5 million women infected
US: 7000 infected women give birth each year –
Their experience is complicated
by the stereotyping
that only gay men get it
that only certain women get it
"druggies" / sex for $'s
by the silence

II. "1st good news about prevention"
Take issue –
1st good news ~~this is a preventable disease~~ was behavioral prevention
the complication news? which we don't do well.
But in fact – it's good news

It is possible, ~~for a woman who is~~ an infected
woman to receive a medication
(zidovudine) & reduce the
risk of an infected child from
25.5% to 8.3%

MEMORANDUM

To: Kristine Gebbie

From: Francess E. Page

Re: Talking Points for ACTG 076 Discussion at the March of Dimes Editorial Luncheon

1. Maternal/fetal transmission of HIV

* Worldwide there are estimated 3.5 million women, many of childbearing age, that are infected with HIV. Estimates include 3000 who become infected each day.

* In the U.S. serosurveys indicate that annually 7,000 HIV infected women give birth. With a 20-30% transmission rate, that adds up to 1,400 to 2,100 infected infants born each year.

* Preventing HIV transmission among women is ideal, yet new infections still occur. Refraining from breast feeding decreases the risk of mother to infant transmission in the post partum period.

* Prevention of transmission of HIV to the fetus, in uetero or intrapartum was the intent of clinical trial 076. There is the possibility of transmission before birth or in the birth process when the child is exposed to copious amounts of the mother's blood and other body fluids which contain HIV.

2. How such transmission may be reduced as in ACTG 076 study

* Under this study ZDV (AZT) was given to HIV infected pregnant women with no prior history of ZDV use. These women were between 14 to 34 weeks of pregnancy and continued through pregnancy and labor. The infant was given ZDV for six weeks following delivery. Other women were given placebo regiments.

* The risk of perinatal transmission was reduced from 25.5% in the group receiving the placebo to 8.3% in ZDV recipients.

* The study was discontinued in February, 1994 due to the very convincing reduction in the vertical transmission of HIV.

* Even though there was a significant reduction, transmission of HIV occurred despite ZDV therapy in 13 out of 180 infants.

3. Ethical and social issues

* There are many unknowns in this study:

  - What is the efficacy of this therapy in women with advanced HIV disease and/or prior antiretroviral therapy.

  - What about the possibility of ZDV resistant virus?

  - What are the long term risks of ZDV exposure in utero and early infancy to the children--those who may have become infected and those who would not have been infected anyway?

  - What will the impact of ZDV use during pregnancy have on the woman's ability to use the therapy when it becomes indicated for her own health.

  - What about the infected child's ability to use this therapy when indicated for their own health?

  - Is this therapy indicated when the woman is in the third gestational period or presents in labor? What is the impact on the child?

* Even if HIV disease is reduced in these infants, what will happen to them when they are orphaned due to their mother's disease? Are we preparing for additional children to be added to the foster care system.

* ZDV was given in several periods, ante-partum, intra-partum, and post partum. There is no indication that if ZDV is effective if administered in only one or two of these periods. This is especially critical if the woman delivers outside the clinical setting.

* Who will pay for these women to receive ZDV if they are unable to afford this therapy? Who will provide services for the child?

* In some communities there has been a push for policies toward mandatory testing of all pregnant women without regard for their rights, based on the need to "save the babies". This does a disservice to the mother, father, siblings and the baby who may not become infected anyway. Counseling should be offered in all settings. The woman should be allowed to make her own decision regarding her future treatment options.

4. Issues women should discuss with the health care provider

* Options regarding HIV counseling and kinds of testing--confidential and anonymous

* If you provide the testing, will you provide the obstetrical services?

* Is this therapy indicated for me based on my CD4 levels and gestational period?

* What are the potential long term effects for me and my child?

* How long will my child and I have to take this drug?

* If I choose not to take this drug, will you still provide medical services for me?

* What will happen if my child becomes infected even though he received ZDV?

* What are my options for additional pregnancies?

* Will I be followed for a long period of time to determine if there are any long term effects of ZDV?

5. Steps women can take for themselves and their babies.

* Insist that they get all information necessary to make informed choices regarding their health and that of their child.

* Seek counseling regarding ZDV complications for herself and the child.

* First of all, practice safer sex so that they do not become infected with different strains of HIV.

* Do not breast feed the baby if HIV infected.

* Practice good nutritional habits, exercise, reduce stress, seek adequate prenatal and post natal care.

* Ensure that your child receives all necessary medical care and follow up to prevent opportunistic infections.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

To Dr. F41

IMPORTANT

FAX TRANSMISSION

TO: Frances Page (202-690-5560) fax 202 690-7560

FROM: Lynne Mofenson MD

DATE: 6/16/94

NUMBER OF PAGES TRANSMITTED (INCLUDING THIS PAGE): 39

SUBJECT: Treatment document - please review
Comments due by 3PM Monday June 20

PLEASE CALL Sandy AT (301) 496-7339 TO CONFIRM RECEIPT OF THIS MATERIAL.

PEDIATRIC, ADOLESCENT AND MATERNAL AIDS BRANCH
CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN
NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
6100 BUILDING, ROOM 4B11
6100 EXECUTIVE BOULEVARD
ROCKVILLE, MARYLAND 20892

FAX REPLY NUMBER (301) 496-8678

PLEASE NOTE THAT OUR ADDRESS HAS CHANGED. THANK YOU.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Child Health
and Human Development
Bethesda, Maryland 20892

TO: Members of the Public Health Service/Health & Human Services Task Force on Use of Zidovudine to Reduce Perinatal Transmission

FROM: Lynne M. Mofenson, M.D.

DATE: June 16, 1994

RE: Treatment Recommendation document

Enclosed is a revised Treatment Recommendation document that has been written following the evening meeting of the Executive (Writing) Committee on June 6.

This document reflects revisions to the original document that was provided on June 10 to the Executive Committee for review, and has taken into account all comments provided by the Committee to me by June 15 (the final date for comments).

I have spoken with both Drs. Lee and Varmus, who have committed themselves to a rapid review process for the recommendations. In order to have the document published in a supplement to the MMWR in August, we need to have final approval by Dr. Lee's office by mid-July.

Therefore, I am asking that you review this document over the weekend, and provide your comments to me by 3 p.m. **MONDAY, JUNE 20, 1994.** It has been suggested that the document might be reviewed by Agency Directors at their routine meeting with Dr. Lee, thus we need to have a finalized document by early next week.

After I receive your comments, I plan to try to incorporate then and provide a revised document to you on June 21 for you to review at each of your Agency levels. If you have any questions or wish to talk with me, I will be in my office (TELEPHONE: 301-496-7339; FAX: 301-496-8678) on Monday June 20 and until about 1 p.m. on Tuesday June 21. I will then be at a WHO meeting in Geneva June 21-26, although my secretary will have numbers to reach me. I plan to have agency level review completed by the week of June 27 if at all possible.

The meat of the recommendations are listed in Table 3, if you want to first directly read them before the text. I realize that the references may repeat themselves; this is due to the reference software I am using and will be fixed prior to the final MMWR publication.

I appreciate your rapid review of this material. If I do not receive comments from you by 3 p.m., **MONDAY, JUNE 20,** I will assume that you have approved the document.

DRAFT ~~CONFIDENTIAL~~

RECOMMENDATIONS ON THE USE OF ZIDOVUDINE TO REDUCE HIV TRANSMISSION FROM MOTHER TO CHILD

INTRODUCTION

Worldwide, the vast majority of HIV infections in children occur secondary to mother to infant transmission. An estimated 3.5 million women, the majority of childbearing age, are infected with HIV, and it is estimated that an additional 3,000 women become infected every day[1]. This increase in HIV infection in women is mirrored by a similar increase in HIV infection in children. In the United States, serosurveys indicate that an estimated 7,000 HIV-infected pregnant women give birth annually; given a 20-30% transmission rate, 1,400 to 2,100 newly infected infants are born each year[2]. HIV is currently the fifth leading cause of death in children under 15 years of age in the United States, and fourth among women of reproductive age.[3]

The ideal approach to the reduction of perinatal transmission would be to prevent HIV infection among women. However, while efforts to provide education regarding HIV risk to women and men are ongoing, infections are still occurring and are increasing rapidly in women of reproductive-age.[4] Some women who are HIV-infected may become pregnant, and while refraining from breastfeeding may prevent postpartum HIV transmission, it will not prevent transmission occurring *in utero* or intrapartum. With this in mind, researchers have turned toward development of additional strategies to reduce perinatal HIV infection.

The recently reported interim results of AIDS Clinical Trials Group (ACTG) Protocol 076, a clinical trial sponsored by

the National Institutes of Health in collaboration with the National Institute of Health and Medical Research (INSERM) and the National Agency of Research on AIDS (ANRS) of France, indicate that zidovudine (ZDV) given to HIV-infected pregnant women with early stage HIV infection (CD4+ lymphocyte count >200 cells/μL and limited or no prior antiretroviral therapy) and their infants can significantly reduce the risk of perinatal HIV transmission[5]. A regimen of ZDV begun between 14 to 34 weeks gestation and continued through pregnancy and labor and in the infant for six weeks following delivery (Table 1) reduced the risk of perinatal transmission from 25.5% in the group receiving placebo to 8.3% in ZDV recipients.

These results have the potential to significantly reduce the rate of mother to child transmission, which would in turn have a major effect on child mortality. However, transmission was still observed despite drug therapy. The efficacy of this therapy in HIV-infected pregnant women with advanced disease, prior antiretroviral therapy, or ZDV-resistant virus is unknown. The long-term risk of ZDV exposure <u>in utero</u> and early infancy for the child is not known. Similarly, it is not known if use of ZDV in this context during pregnancy will affect the drug's ultimate utility for the woman when it becomes clinically indicated for her own health. Some HIV-infected women present for prenatal care late in pregnancy or in labor when the full ZDV regimen used in ACTG 076 cannot be administered. In addition, many pregnant women are not aware of their risk for HIV infection, are not

tested before or during pregnancy, and remain undiagnosed. As a consequence, they do not receive information about therapy that could significantly reduce the risk of HIV transmission to their infants.

Many questions remain regarding optimal, safe and rational recommendations for HIV-infected pregnant women and their health care providers on the use of the ACTG 076 ZDV regimen to reduce mother to child transmission. While HIV-infected women should be informed of the substantial potential benefits and short-term safety of ZDV given during pregnancy and the newborn period, they also must be made aware that long-term risks of such therapy to themselves and their children are unknown at this time. A woman's decision to use ZDV to reduce the risk of HIV transmission to her infant involves a balance of the benefits and potential risks of the regimen to the woman herself and to her child.

On June 6-7, 1994, the U.S. Public Health Service held a Workshop, composed of individuals from the medical, scientific, public health and lay community and representatives from interested professional, community and advocacy organizations, to address two issues related to the results of ACTG 076: 1) what recommendations can be made for the use of ZDV to reduce HIV transmission from an infected woman to her child, and 2) what are the implications of the trial results for counseling and HIV testing. This report summarizes the conclusions of the Workshop on Treatment Implications, held on June 6. The goal of this meeting was to evaluate the available scientific and clinical

information on the use of ZDV in pregnancy and to develop recommendations for women and their providers regarding use of ZDV to reduce perinatal transmission. A separate summary on counseling and HIV testing is planned.

Although perinatal transmission of HIV infection is an international problem, alternative strategies may be appropriate in some other countries[6]. Hence, it is recognized that these recommendations are made for the United States. Policy and practice in other countries will depend on local considerations such as availability of ZDV, access to facilities for intravenous infusion during labor, and alternative interventions that may be under evaluation.

PURPOSE OF RECOMMENDATIONS

These recommendations have been formulated to provide a basis for discussion between the woman and her health care provider when making decisions about the use of ZDV to reduce perinatal transmission. The final decision to accept or reject a recommended treatment for herself and her child is the right and responsibility of the woman. A decision not to receive treatment should not result in punitive action or denial of care, nor should ZDV be denied to a woman who decides to receive the regimen. As information becomes available from additional research over the course of time, these recommendations may be updated. This document provides guidance regarding 1) treatment options for pregnant women; 2) recommendations on medical monitoring of pregnant women and neonates receiving the ACTG 076 ZDV

regimen ; and 3) issues regarding long-term follow-up of women and their children who have received the ACTG 076 ZDV regimen.

1) IN WHAT CLINICAL SITUATIONS SHOULD USE OF ZDV TO REDUCE PERINATAL TRANSMISSION BE CONSIDERED?

General Issues

The results of ACTG 076 are directly applicable only to women who meet the entry criteria for the study (Table 2). The study examined women who had CD4+ lymphocyte counts above 200/μL; the mean CD4+ lymphocyte count was 586 cells/μL. Also, because this was a placebo-controlled study, entry into the study was restricted to women who did not have clinical indications for ZDV use for their own health. Prior ZDV use during the current pregnancy resulted in exclusion from the study. Very few women (19 of 477) had ZDV exposure prior to the current pregnancy, and most of that was of very limited duration.

Women were not enrolled prior to the 14th week or after the 34th week of gestation. Exclusion prior to 14 weeks gestation avoided exposure during the first trimester, when fetal organogenesis is maximal. The 34 week limit allowed most women to have several weeks of ZDV before delivery to allow time for reduction of circulating maternal viral load, a presumed important determinant of transmission risk.

Information regarding benefit and short-term risks is available from this trial only for women who met the entry criteria of the study. Recommendations regarding use of the ZDV regimen for women whose clinical conditions differ from the ACTG

protocol 076 eligibility criteria were derived from consensus interpretation of available scientific data.

Various circumstances which will commonly occur in clinical practice are enumerated below (Table 3), and the factors influencing treatment considerations are highlighted. It is not possible to enumerate every potential clinical situation, and in many cases, definitive evidence upon which to base a recommendation is not currently available. Therefore individualized consideration by each pregnant woman and her provider of the potential benefits, short-term safety, unknown long-term effects, and gaps in knowledge relating to her clinical situation is necessary. Finally, it is important that providers and institutions provide an environment that is conducive to cultural considerations of the HIV-infected woman and provide adequate information and counseling to ensure that informed decisions are made.

Clinical Scenarios

I. Pregnant women with CD4+ lymphocyte count > 200/μL who are between 14 and 34 weeks gestation and who have no clinical indication for ZDV and no extensive history (< 6 months) of prior therapy.

Recommendation:

The full ACTG 076 ZDV regimen should be recommended to all HIV-infected pregnant women in this category. This recommendation should be presented in the context of a risk/benefit discussion with the pregnant woman. The long-term adverse consequences

of the regimen are not known, and the decision regarding use of this regimen by the pregnant woman should be the woman's choice after discussion with her health care provider.

Rationale and Considerations:

This group of women have similar characteristics to the ACTG 076 study population. The data from that study indicate that the complete ACTG 076 ZDV regimen will likely result in about a two-thirds reduction in the risk of transmission. The observed short-term toxicity for the woman was minimal. Reported side effects such as anemia, neutropenia, thrombocytopenia, and liver chemistry abnormalities were as frequent in women receiving placebo as in women receiving ZDV, and there were no clinical or immunologic differences between the two groups at 6 months postpartum.

There was also no difference in fetal growth and amniotic fluid volume between pregnant women who had received placebo or ZDV. Birth parameters (gestational age; birth weight, length, and head circumference; Apgar scores) were similar in infants born to both groups of mothers, and the presence of major or minor congenital abnormalities was balanced between the two groups, nor was any pattern in the type of abnormalities observed. Similarly, in a recent report from the Antiretroviral Pregnancy Registry run by the Wellcome Foundation in conjunction with the Centers for Disease Control and Prevention, no increase in the risk of birth defects above that expected for all pregnancies was observed in infants born to over 120 HIV-infected women

who received ZDV during pregnancy, nor was there any unusual pattern of birth defects.[7]

Infant ZDV therapy was also well tolerated. The only adverse effect occurring more frequently in the ZDV-treated infants was a mild, transient anemia that was resolved by 12 weeks of age without therapy.

While significantly reducing transmission, ZDV did not completely prevent perinatal transmission; 13 of 180 infants from the ZDV group were infected. Reasons for transmission in these infants are under evaluation but have not yet been identified. Several case reports have also described perinatal transmission despite ZDV therapy first started during pregnancy.[8 9 10 11]

Long-term effects of transient ZDV treatment in women or of fetal and neonatal
ZDV exposure are not known at present. ZDV is a nucleoside analogue that inhibits HIV replication by interfering with HIV RNA-dependent DNA polymerase. ZDV triphosphate also can inhibit human cellular DNA polymerases, but only at concentrations significantly higher than those required to inhibit HIV polymerase; gamma DNA polymerase, required for mitochondrial replication, is also inhibited by ZDV at lower concentrations.

Major concerns related to potential long-term toxicity of nucleoside analogues include potential mutagenic and carcinogenic effects, possible effects on tissues with high mitochondrial content, such as hepatic and cardiac tissue, and possible teratogenicity and effects on the reproductive system.

ZDV has been shown to be a weak mutagen in vitro.[12] Rodent studies have demonstrated a small number of noninvasive squamous epithelial vaginal tumors after 19-21 months of continuous high dosing. Certain unique features of these animal models may increase ZDV and glucuronyl-ZDV concentration in rodent urine, thereby causing contact of high concentrations of the drug with vaginal mucosa and increasing the potential for ZDV-associated vaginal irritation and tumors. The applicability of rodent carcinogenicity studies to humans is limited. In humans, an increased incidence of non-Hodgkin's lymphoma has been reported in patients with AIDS receiving ZDV, but is believed to be due to increased survival in the setting of severe immunodeficiency and not to a direct effect of ZDV.[13] Potential for carcinogenesis will need to be further assessed through continued follow-up of children with in utero exposure.

Myopathy and cardiomyopathy have been reported with ZDV therapy, but it is not clear if such effects are secondary to ZDV itself or a consequence of HIV infection. A prospective study of cardiac function in HIV-infected children did not find that ZDV therapy improved or diminished cardiac function.[14]

Reproductivity/fertility studies in animals have not shown adverse effects on male or female fertility in rats or the reproductive capacity of their progeny.[15] In a murine animal model, ZDV given early in gestation was associated with an embryotoxic effect and fetal resorptions; however, ZDV given at

or beyond midgestation in mice had no detectable effect on the murine fetus.[16] [17]

ZDV is assigned FDA pregnancy category "C" status. This indicates that safety in human pregnancies has not been determined, that animal studies are either positive for fetal risk or have not been done, and that the drug should not be used unless the potential benefit outweighs the potential risk to the fetus. FDA ratings range from "A" for drugs tested for teratogenicity that do not show evidence of fetal damage to "D" for drugs that are teratogenic but have no safer alternative; an "X" rating is reserved for drugs that should never be used during pregnancy. Most animal studies of ZDV in pregnancy have not demonstrated teratogenicity; one study in pregnant rats given massive doses of ZDV (3 grams per kg per day) found developmental malformations and skeletal variations in 12% of fetuses.[18] Data from ACTG 076 and from uncontrolled reports indicate that ZDV does not appear to be teratogenic in humans.[19] [20] [21] [22] [23] However, continued surveillance is necessary.

Although long-term toxicity to infants is unknown, this must be weighed against the decreased risk of transmission of a fatal disease, HIV infection. Currently, there is no way to predict if an individual pregnancy will be associated with HIV transmission; therefore, each fetus must be viewed as having an approximate one in four risk of developing a life-threatening infection. Since transmission was lowered by two-thirds (from 25.5% to 8.3%), long-term ZDV-related toxicity would have to be very severe (such

as untreatable malignancy or profound developmental delay) and relatively common in ZDV-exposed infants to outweigh the substantial benefit.

For the pregnant woman, there is concern that transient use of ZDV could be associated with the development of ZDV-resistant virus, which in turn could lead to loss of ZDV therapeutic benefit for the woman when it is needed for her own health. However, the development of ZDV resistance is uncommon in patients with early stage disease until after 18 to 24 months of continuous therapy.[24] An increase in ZDV susceptibility has been observed in initially ZDV-resistant isolates obtained from some patients following withdrawal of ZDV therapy, although persistence of resistance for more than a year after discontinuation has also been reported.[25] [26] Considerations for the woman's future health care should include the current and future availability of alternative drugs for treatment of HIV infection (ie., didanosine, zalcitabine).

II. Pregnant women who present at >34 weeks gestation who have not received extensive prior ZDV (<6 months) and do not require ZDV for their own health.

Recommendation:

This patient population has clinical characteristics similar to that of women enrolled in ACTG 076; the major potential difference is duration of antenatal therapy. The full ACTG 076 regimen should be recommended; however, the woman should be informed that ZDV efficacy may be less than that seen in ACTG 076

because they are initiating the regimen late in the third trimester.

Rationale:

Current estimates are that between 50-70% of perinatal transmission may occur near to or during delivery.[27] It is reasonable, therefore, to believe that the ACTG 076 ZDV regimen might have some effect when started later than 34 weeks gestation, although the utility of this intervention is likely to decrease as the duration of antenatal ZDV administration is reduced. Studies evaluating the effect of ZDV on circulating viral load indicate that maximal effect is observed after 8 to 16 weeks of therapy.[28] At best, an effect for reduction of perinatal transmission similar to that in ACTG 076 might be observed; at worst, little or no effect might be observed. Potential risks for the woman and her infant would be assumed to decrease the closer to delivery that the ZDV regimen is started because of the more limited length of exposure to ZDV.

III. Pregnant women with CD4+ lymphocyte count < 200/μL who are between 14 and 34 weeks gestation and who have no other clinical indication for ZDV and no extensive history of prior therapy (under 6 months of ZDV therapy).

Recommendation:

Initiation of antenatal ZDV therapy should be advised for the woman for her own health benefit.[29] Although this population of pregnant women was not studied in ACTG 076, it is reasonable to extrapolate that addition of the intrapartum and neonatal

components of the ACTG 076 ZDV regimen to antenatal maternal therapy may provide some reduction in the risk of transmission. The ZDV regimen used in ACTG 076 should be recommended until other information becomes available. Alternatively, enrollment into available perinatal clinical trials could be considered.

Rationale:

This group of pregnant women meet the current standard of care for ZDV treatment of HIV infection for their own benefit, and therefore administration of ZDV during pregnancy in this scenario provides direct benefit to the woman as well as potential benefit to her infant.[30] [31] A variety of published studies document that HIV-infected pregnant women with low CD4+ lymphocyte count (ranging from under 700 cells/μL to below 200 cells/μL) have a greatly increased risk of HIV transmission to their infants, ranging between 31% to 60%.[32] [33] [34] [35] [36] [37] Additionally, viral load has been shown to increase as CD4+ lymphocyte count decreases[38]; thus, baseline maternal viral load would be expected to be high in this population.

Because of the limited (or no) prior exposure to ZDV, although viral replication and therefore capacity for mutations is high, it is unlikely that pre-existing ZDV-resistant viral strains would be present. Therefore, it is expected that ZDV will provide an acute reduction in circulating maternal viral load analogous to that observed in women with higher CD4+ lymphocyte number. Additionally, maternal CD4+ lymphocyte count would not be expected to affect ZDV levels in the newborn and infant

following administration of ZDV during labor and during the first 6 weeks of life. Hence, maternal CD4+ lymphocyte count should not affect the potential utility that neonatal levels of systemic ZDV might provide for reduction of intrapartum transmission.

Because ZDV therapy is clinically indicated in these women for their own health, the additional risk of the ACTG 076 regimen is the discomfort to the woman of an additional intravenous infusion during labor, and the additional 6 weeks of ZDV exposure to the infant after delivery.

IV. Pregnant infected women with significant prior ZDV (> 6 months of ZDV therapy) and/or other antiretroviral therapy prior to pregnancy.

Recommendation:

There are insufficient data to extrapolate potential efficacy of the ACTG 076 regimen in this population of women. Some of the issues that should be discussed with the pregnant woman include the clinical and immunologic stability of the woman on ZDV therapy or the reasons why she was receiving an alternative antiretroviral (eg. ZDV therapeutic failure or intolerance) and the likelihood of ZDV resistance. Consultation with experts in HIV infection may be warranted. Because the utility of the full ACTG 076 ZDV regimen in this setting may vary depending on the clinical status of the woman, the regimen should be available to the woman following discussion with her health care provider. Further clinical trials should evaluate alternative approaches for such women.

Rationale:

Women who have received extensive prior ZDV therapy may have viral strains with reduced susceptibility to ZDV. It is known that ZDV-resistant strains can be transmitted from mother to fetus, however, the frequency with which such transmission occurs is unknown.

Resistant mutant virus appears to emerge more quickly at later stages of disease.[39] The appearance of ZDV resistance mutations follows a temporal pattern, and the level of resistance is proportional to the number of mutations in the reverse transcriptase-coding region of HIV.[40] Phenotypically and genotypically diverse HIV viral populations can coexist in patients during ZDV therapy.

In one study, ZDV-resistant strains appeared earlier in the course of ZDV therapy in patients with AIDS or advanced ARC. After 12 months of ZDV therapy, viral isolates from 89% of patients with late-stage disease and 31% of those with early disease were resistant.[41] However, isolates from only 33% of late-stage patients showed high-level resistance. Resistant virus was also more likely to be isolated from patients with low CD4+ cell count at start of therapy: 1-year estimated rates of resistance in patients with baseline counts of >400, 100-400 and <100 cells/μL were 27%, 41%, and 89%, respectively. In patients with advanced disease, high-level resistance develops after 6 to 18 months of therapy; however, in patients with early disease,

high level resistance appears delayed until after 24 months of therapy.[42]

It is possible that ZDV would have a decreased ability to reduce transmission of virus from mothers who carry a significant burden of resistant strains, particularly if high-level resistance has developed, although data to support this assumption are lacking. Further studies are needed.

V. Pregnant infected women who have not received antepartum ZDV and present to the health care provider in labor.

Recommendation:

There is a wide range of patients in this group, including both term and pre-term pregnancies. For women with HIV infection who come to care in labor without having received the antepartum component of the ACTG 076 ZDV regimen (either because of no prenatal care or because they did not wish to receive antepartum therapy), when the clinical situation permits, the intrapartum and neonatal components of the ACTG 076 regimen should be discussed and offered. It is recommended that clinical trials be designed to address the efficacy of this approach.

Rationale:

There are no human data to bear on the effectiveness of ZDV in this situation. Because maternal ZDV therapy would be very limited, no effect on the level of maternal virus in blood or genital secretions would be expected. However, administration of the intravenous loading dose and continuous infusion of ZDV during labor will result in the infant being born with circulat-

ing levels of ZDV similar to levels seen with the complete ACTG 076 treatment regimen. To the extent that the presence of systemic levels of ZDV in the infant prior to HIV exposure from the mother's blood and genital secretions during delivery plays a role in preventing intrapartum transmission, ZDV may have some utility in this scenario.

The intravenous route was chosen for drug dosing during labor in ACTG 076 because intravenous, continuous infusion of drug following an initial loading dose gives definitive, predictable levels that under optimal circumstances provide a significant fetal blood level during the birth process, a time of presumed extensive exposure to HIV in maternal blood and secretions. During labor, orally administered drugs have unpredictable absorption due to delayed gastric emptying.[43] Therefore, it was hypothesized that oral administration of ZDV during labor might produce widely variable systemic levels in the mother and infant. In the absence of data regarding the pharmacokinetics of oral ZDV during labor, there is no information to support oral rather than intravenous administration of ZDV during labor.

Infections that occur prior to labor (as much as 50% of transmission may occur <u>in utero</u>) would not be prevented by this regimen. If the majority of transmission occurs during the last few weeks of pregnancy rather than during labor, ZDV administered only during labor and to the newborn may not prove effective.

Since maternal therapy would be limited only to the period of labor, the risk to the woman for development of resistant

virus or ZDV toxicity would be minimal, and the primary risk is that associated with an intravenous catheter. The risk to the infant would be limited to the toxicity associated with 6 weeks of oral ZDV therapy, without in utero exposure to the drug.

VI. Infants who are born to HIV-infected women who have not received any intrapartum ZDV therapy.

Recommendation:

If the clinical situation permits and ZDV therapy can be started within 24 hours of birth, the ACTG 076 postpartum component of 6 weeks of neonatal ZDV therapy should be discussed and offered for the infant. ZDV efficacy in this situation is likely to be significantly less than observed in ACTG 076. Based on data from animal prophylaxis studies, therapy started as soon as possible (within hours) following delivery is preferable. If therapy cannot begin until after 24 hours of age and no maternal therapy was given, there are no data to support offering therapy to the infant. Further studies are recommended to evaluate efficacy of a neonatal approach.

Rationale:

Infants whose mother's have not received ZDV during late pregnancy and/or labor will not have a circulating ZDV level present during birth, a period of presumed intense viral exposure. Data from post-exposure prophylaxis of retroviral infection in animal models indicates that very early treatment (within hours) is essential to prevent infection, and that even with early therapy initiation, such prophylaxis may not be protective.

For example, in a simian immunodeficiency virus (SIV) model in rhesus monkeys, initiation of ZDV therapy (given subcutaneously for 28 days) within 1 hour of inoculation with SIV prevented infection; initiation within 8 hours prevented antigenemia, and only transient culture positivity was observed. However, initiation of therapy 24 hours or more post-inoculation was not successful in preventing infection.[44] Similarly, in a SCID-hu mouse model of HIV infection, a time-dependent effect of ZDV prophylaxis was observed.[45] All animals given ZDV within 2 hours of inoculation were free of detectable virus at 2 weeks; 80%, 40% and 20% were free of virus if ZDV was given at 8, 24 and 36 hours, respectively. No protection was observed if ZDV was administered 2 days post inoculation. In a mouse model using the Friend leukemia retrovirus, administration of ZDV beginning as early as 10 minutes after initial viral exposure did not prevent low levels of persistent retrovirus in the mice, although it was effective in preventing retrovirus-induced mortality in the mice.[46]

In humans there have been several anecdotal reports of failure of prophylactic ZDV to prevent HIV infection following accidental or deliberate HIV inoculation, even with rapid administration and intensive dosing.[47] [48] [49] [50] [51] While these anecdotes do not disprove potential post-exposure efficacy of ZDV, clearly any protection offered would not be absolute.

2) **WHAT IS RECOMMENDED REGARDING MONITORING OF THE ZDV REGIMEN FOR MOTHER AND INFANT?**

General Issues:

Maternal ZDV therapy in ACTG 076 was well tolerated. Reported adverse events were minimal, and largely recorded as unrelated to treatment or of unknown relation to treatment. Drug dose was modified during pregnancy due to perceived toxicity in 60 women receiving ZDV and in 73 women receiving placebo. Six women discontinued ZDV treatment due to perceived toxicity; 3 were receiving ZDV and 3 placebo. Reports of grade 3 or 4 hematologic (hemoglobin <8 gm/dL, absolute granulocyte count <750/μL, platelets <50,000/μL) or serum chemistry toxicities were balanced between ZDV and placebo recipients; hematologic toxicity was observed in only 35 women and serum chemistry abnormalities in only 15 women.

Serial sonogram evaluation for fetal growth and amniotic fluid volume as conducted in the study (entry and every 4 weeks from 28 weeks gestation) did not provide helpful management information. Reports of new-onset polyhydramnios or oligohydramnios were balanced between ZDV and placebo groups; overall, polyhydramnios was reported in only 9 women, and oligohydramnios in only 25 women.

Median gestational age at birth was 40 weeks for the ZDV group and 39 weeks for placebo patients; mean birth weight was 3147 gm and 3160 gm, respectively. No significant difference was observed between ZDV and placebo groups in the number of infants born with birth weight <2500 gm, small or large for gestational

age, or born prematurely (16 infants in the ZDV group compared to 13 in placebo were born <36 weeks gestation).

Infant ZDV therapy was well-tolerated. The only adverse event occurring more frequently in ZDV group infants was a mild, transient anemia. Drug was discontinued due to perceived toxicity in 11 infants receiving ZDV and 11 receiving placebo. Hemoglobin values for infants receiving ZDV were significantly lower than those receiving placebo. The maximum mean difference was 1 gm/dL, occurring at 3 weeks of age. The lowest mean value in infants receiving ZDV was 10.0 gm/dL at 6 weeks of age. By 12 weeks of age, hemoglobin values for both ZDV and placebo groups were comparable without therapy. Reports of absolute neutrophil count <1000 cells/μL and grade 3 or 4 serum chemistry toxicity were balanced between ZDV and placebo groups of infants; no differences in the pattern of chemistry abnormalities were observed.

Diagnosis of HIV infection did not appear to be delayed by treatment with the ACTG 076 ZDV regimen. The time to first positive culture was similar between infected infants in the ZDV and placebo groups. Infection was diagnosed by 6 months of age in all infants found to be infected, and none of the over 100 infants who received ZDV and had negative cultures up to 6 months of age were found to be infected after this time.

Recommendation:

Ideally, follow-up of women and their children should occur in a family-centered setting, with both mother and infant seen at

the same time at a single site, and with coordination of care between gynecologic, pediatric and internal medicine health care providers. A comprehensive program of support services is necessary to assist maintenance of both mother and child in the health care setting.

Maternal monitoring:

Monitoring of HIV-infected pregnant women should be consistent with previously published guidelines.[52] [53] Monitoring should include assessment for ZDV-associated hematologic and liver chemistry abnormalities. Indications of toxicity that might require dose interruption or reduction include a hemoglobin less than 8 gm/dL and absolute granulocyte count <750 cells/μL.

CD4+ lymphocyte count should be monitored for determination of need for initiation of prophylaxis for Pneumocystis carinii pneumonia (PCP). Pregnant HIV-infected women with CD4+ lymphocyte count <200 cells/μL or <20% of total lymphocytes should receive appropriate PCP prophylaxis. Current guidelines suggest CD4+ determination does need not be repeated during pregnancy if the count is >600 cells/μL: if CD4+ count is below 600 cells/μL, evaluation should be repeated each trimester. CD4+ lymphocyte count should be assessed at 6 weeks and 6 months postpartum to evaluate need for continued antiretroviral therapy.

Fetal Monitoring:

Sonogram and non-stress testing should be performed only as clinically indicated.

Infant Monitoring:

Complete blood count and differential should be performed at birth as a baseline evaluation. Repeat measurement of hemoglobin is recommended at 6 and 12 weeks of age. ZDV should be administered with caution to infants born with severe anemia (hemoglobin < 8 gm/dL), and treatment of the anemia and more intensive monitoring is warranted should the drug be given.

Evaluation of the infant for diagnosis of HIV infection, need for initiation of PCP prophylaxis, and, if found to be HIV-infected, need for antiretroviral therapy should be consistent with previously published guidelines.[54] [55] [56] There are no data to address potential efficacy or lack of efficacy of ZDV therapy in HIV-infected children who require antiretroviral therapy and who have had <u>in utero</u> and early infancy treatment with ZDV. Consultation with a specialist in pediatric HIV infection may be considered if therapy is necessary in infected children treated with an ACTG 076-like ZDV regimen. Further research is needed regarding response to therapy and disease progression in such infants.

<u>3) WHAT ARE POTENTIAL LONG-TERM EFFECTS ON WOMEN AND INFANT AND WHAT FOLLOW-UP IS NECESSARY?</u>

<u>General Issues:</u>

Women enrolled in ACTG 076 were seen at 6 weeks and 6 months postpartum. There was no evidence that treatment during pregnancy was associated with adverse effects on maternal CD4+ count or rate of HIV disease progression at 6 months postpartum. Only 2

of 403 women were prescribed open-label ZDV prior to delivery, one in each group.

As would be expected from data regarding changes in CD4+ count during pregnancy and immediately postpartum, statistically significant increase in CD4+ count from baseline to 6 weeks postpartum was observed for women in both ZDV and placebo treatment groups; this increase was greater among women in the ZDV group. At 6 months postpartum, CD4+ count for both groups had decreased and had similar distributions. CD4+ counts fell below 200/μL during the study in only 1 woman receiving ZDV and 3 receiving placebo.

No maternal deaths occurred during the study. At 6 months postpartum, 19 women who had received ZDV and 21 who had received placebo were receiving open-label ZDV from their physicians.

Comparison of longitudinal anthropomorphic evaluations in uninfected children from ACTG 076 has demonstrated no differences up to 18 months of age in growth between ZDV and placebo group infants, including measurements of head circumference, weight and length. No data exist at the present time to address any effect <u>in utero</u> ZDV exposure might have on risk for neoplasia or organ system toxicities.

Concerns regarding potential longer-term adverse effects in women include development of ZDV-resistant virus when ZDV therapy is used transiently for reduction of perinatal transmission, particularly if used during more than one pregnancy, and the potential effect such resistance could have on disease progres-

sion for the woman. Whereas studies to date have associated emergence of ZDV resistance with total duration of ZDV exposure, none have specifically addressed the effect of intermittent therapy on development of resistance. Concerns regarding long-term adverse effects in the infants have been delineated previously.

Observational data collection of short-term pregnancy outcome of women who receive ZDV during pregnancy is being collected through the international Antiretrovirals in Pregnancy Registry. The purpose of the registry is to monitor for possible teratogenicity among infants born to women who have received ZDV during pregnancy. Health care providers who care for women treated with ZDV can register patients by calling the registry, (800) 722-9292, extension 8465, in the United States, or by calling (919) 315-8465 for registrations from countries outside the United States. Written reports are available from Antiretrovirals in Pregnancy Registry, P.O. Box 12700, Research Triangle Park, NC 27709.

Continued follow-up of women who participated in ACTG 076 and their infants is planned. A woman's protocol to provide prospective evaluation of the health of women enrolled in ACTG 076 is under design by the Women's Health Committee of the ACTG, and will evaluate virologic, immunologic and clinical parameters in participating women.

ACTG 219 is an ongoing protocol designed to provide prospective evaluation until age 21 years of children who have had <u>in utero</u>

exposure to antiretrovirals or to HIV vaccines through ACTG protocols. This protocol will provide intensive evaluation of multiple organ system functions, neuropsychologic testing, and information regarding quality of life.

Information regarding potential long-term effects of the complete or partial ACTG 076 ZDV regimen on women and children receiving the regimen outside of a clinical trial protocol may also be provided from evaluation of prospectively followed federally-funded cohort studies of HIV-infected women and their infants.

Recommendations:

Further research is needed regarding the long-term effects of the ACTG 076 ZDV regimen on women and children. Particular focus on issues of viral resistance and disease progression should be addressed in women receiving ZDV during pregnancy for the sole purpose of reduction of perinatal HIV transmission. Routine monitoring for HIV-infected women should include annual Pap smear and gynecologic examination.

Long-term follow-up of uninfected as well as infected infants born to mothers receiving ZDV during pregnancy is also important, with an emphasis on assessment of organ system toxicities, neurodevelopment, pubertal development, reproductive capacity and development of neoplasms.

Special studies will need to be developed to provide intensive evaluation of these issues, and innovative methods and

support systems developed to assist in follow-up of these women and their children.

CONCLUSION

These recommendations have been developed in recognition of the urgent need to provide guidance to women and health care providers regarding the use of ZDV to prevent perinatal transmission. They have been formulated using the available data from ACTG 076 and current information regarding factors associated with transmission. It is recognized that the knowledge base upon which these recommendations are based is incomplete and additional information is needed to optimize use of ZDV for this purpose.

The decision to use the ACTG 076 regimen for prevention of perinatal transmission is complex, and requires weighing benefits and potential risks to the HIV-infected woman and her child in the face of many uncertainties. Further research is a high priority, including clarification of long-term risks of the ZDV regimen to the woman and/or her child, elucidation of the reasons for transmission despite use of the optimal ZDV regimen, delineation of the relative efficacy of the various components of the ACTG 076 ZDV regimen for the reduction of transmission and of efficacy of the regimen in women with characteristics that differ from those enrolled in ACTG 076, and evaluation of additional types of interventions for the reduction of perinatal transmission. As further information becomes available on these issues, these recommendations may need to be modified.

Additionally, development of appropriate methods and materials for communicating treatment options, risks, and benefits to women and health care providers is necessary, so that informed treatment decisions can be made.

Drft3.Rec LM [ver 0.1 Exec Comm:MY:AB:MJO:WP:ID:JL:AW 06.10.94]
[ver 0.2 AN:JB:HM:ID:ML:MY:RJS:AB:WP [AR:JM] 06.16.94)

Table 1.

Zidovudine Regimen from AIDS Clinical Trials Group Protocol 076

- Oral administration of 100 mg zidovudine (ZDV) five times daily, initiated at 14 to 34 weeks gestation, and continued for the remainder of the pregnancy.

- During labor, intravenous administration of ZDV, in a loading dose of 2 mg per kg body weight given over 1 hour, followed by a continuous infusion of 1 mg per kg body weight per hour until delivery.

- Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg body weight per dose given every 6 hours) for the first 6 weeks of life, beginning 8 to 12 hours after birth.

Table 2.

Eligibility Criteria for HIV-Infected Pregnant Women Participating in AIDS Clinical Trials Group Protocol 076

- Pregnancy between 14 weeks but not more than 34 weeks gestation.
- Has not received zidovudine (ZDV) during the current pregnancy for any indication.
- Has no clinical indications for maternal antiretroviral therapy in the judgement of her health care provider.
- Has CD4+ lymphocyte count >200 cells/mm^3 at initial assessment.

Table 3.

Summary: Recommendations for Use of Zidovudine in HIV-Infected Pregnant Women to Reduce Perinatal HIV Transmission

I. **Pregnant women with CD4+ lymphocyte count > 200/μL who are between 14 and 34 weeks gestation and who have no clinical indication for ZDV and no extensive history (< 6 months) of prior therapy.**

Recommendation:
The full ACTG 076 ZDV regimen should be recommended. This recommendation should be presented in the context of a risk/benefit discussion with the pregnant woman.

II. **Pregnant women who present at >34 weeks gestation who have not received extensive prior ZDV (<6 months) and do not require ZDV for their own health.**

Recommendation:
The full ACTG 076 regimen should be recommended. This recommendation should be presented in the context of a risk/benefit discussion with the pregnant woman. In addition, the patient should be informed that ZDV efficacy may be less than observed in ACTG 076 because they are initiating the regimen late in the third trimester.

III. **Pregnant women with CD4+ lymphocyte count < 200/μL who are between 14 and 34 weeks gestation and who have no other clinical indication for ZDV and no extensive history of prior therapy (under 6 months of ZDV therapy).**

Recommendation:
Initiation of antenatal ZDV should be advised for the woman for her own health benefit. In addition, the intrapartum and neonatal components of ACTG 076 regimen should be recommended until other information becomes available. This recommendation should be presented in the context of a risk/benefit discussion with the pregnant woman.

IV. **Pregnant infected women with significant prior ZDV (> 6 months of ZDV therapy) and/or other antiretroviral therapy prior to pregnancy.**

Recommendation:
There are insufficient data to extrapolate potential efficacy of the ACTG 076 regimen in this population of women, and consultation with experts in HIV infection may be warranted. Because the utility of the full ACTG 076 ZDV regimen in this setting may vary depending on the clinical status of the

woman, the regimen should be available to the woman following discussion with her health care provider. Further clinical trials should evaluate alternative approaches for such women.

V. Pregnant infected women who have not received antepartum ZDV and present to the health care provider in labor.

Recommendation:
For women with HIV infection who come to care in labor without having received the antepartum component of the ACTG 076 ZDV regimen (either because of no prenatal care or because they did not wish to receive antepartum therapy), when the clinical situation permits, the intrapartum and neonatal components of the ACTG 076 regimen should be discussed and offered. It is recommended that clinical trials be designed to address the efficacy of this approach.

VI. Infants who are born to HIV-infected women who have not received any intrapartum ZDV therapy.

Recommendation:
If the clinical situation permits and ZDV therapy can be started within 24 hours of birth, the ACTG 076 postpartum component of 6 weeks of neonatal ZDV therapy should be discussed and offered for the infant. Therapy started as soon as possible following delivery is preferable (within hours). If therapy cannot begin until after 24 hours of age and no maternal therapy was given, there are no data to support offering therapy to the infant. Further studies are recommended to evaluate efficacy of a neonatal approach.

REFERENCES

1. United National Development Programme. Young women: silence, susceptibility, and the HIV epidemic. Pediatr AIDS & HIV Infect: Fetus to Adolescent. 1994;5:1-9.

2. Centers for Disease Control and Prevention. National HIV serosurveillance summary: results through 1991. Vol 3. Atlanta: US Department of Health and Human Services, Public Health Service, 1994.

3. Centers for Disease Control. Update: mortality attributable to HIV infection among persons aged 25-44 years - United States, 1991 and 1992. MMWR 1993;42:869-872.

4. Centers for Disease Control. Update: HIV infection/AIDS among women aged 25-44 years (United States, 1990 and 1991). MMWR 1993;42:481-486.

5. Centers for Disease Control and Prevention. Zidovudine for the prevention of HIV transmission from mother to infant. MMWR 1994;43:285-287.

6. Newell ML, Peckham CS. Working towards a European strategy for intervention to reduce vertical transmission of HIV. Brit J Obstet Gynecol 1994;101:-192-196.

7. Centers for Disease Control. Birth outcomes following zidovudine therapy in pregnant women. MMWR 1994;43:409-412.

8. Chavanet P, Diquet B, Waldner A, Portier H. Perinatal pharmacokinetics of zidovudine (letter). N Engl J Med 1989;321:1548-1549.

9. Lyman WD, Tankaka KE, Kress Y, Rubenstein A, Soeiro R. Zidovudine concentrations in human fetal tissue: implications for perinatal AIDS (letter). Lancet 1990;335:1280-1281.

10. Bernard N, Boulley AM, Perol R, Rouzioux C, Colau JC. Failure of zidovudine prophylaxis after exposure to HIV-1 (letter). N Engl J Med 1990;323:916.

11. Barzilai A, Sperling RS, Hyatt AC, et al. Mother to child transmission of human immunodeficiency virus 1 infection despite zidovudine therapy from 18 weeks gestation. Pediatr Infect Dis J 1990;9:931-933.

12. Ayers KM. Preclinical toxicology of zidovudine: an overview. Am J Med 1988;85(Suppl 2A):186-188.

13. McLeod GX, Hammer SM. Zidovudine: five years later. Ann Int Med 1992;117:487-501.

14. Lipshultz SE, Orav EJ, Sanders SP, Hale AR, McIntosh K, Colan DS. Cardiac structure and function in children with human immunodeficiency virus infection treated with zidovudine. N Engl J Med 1992;327:1260-1265.

15. Comprehensive information for investigators: retrovir (March 1990). Available from Burroughs Wellcome Company, Research Triangle Park, NC.

16. Toltzis P, Marx CM, Kleinman N, Levine EM, Schmidt EV. Zidovudine-associated embryonic toxicity in mice. J Infect Dis 1991;163:1212-1218.

17. Toltzis P, Mourton T, Magnuson T. Effect of zidovudine on preimplantation murine embryos. Antimicrob Agents Chemother 1993;37:1610-1613.

18. Letter to investigators, June 1992. Burroughs Wellcome Company, Research Triangle Park, NC.

19. Sperling RS, Stratton P, O'Sullivan MJ, et al. A survey of zidovudine use in pregnant women with human immunodeficiency virus infection. N Engl J Med 1992;326:857-861.

20. O'Sullivan MJ, Boyer PJJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: Phase I ACTG study (protocol 082). Am J Obstet Gynecol 1993;168:1510-1516.

21. Watts DH, Brown ZA, Tartaglione T, et al. Pharmacokinetic disposition of zidovudine during pregnancy. J Infect Dis 1991;163:226-232.

22. Ferrazin A, De Maria A, Gotta C, et al. Zidovudine therapy of HIV-1 infection during pregnancy: assessment of the effect on the newborns. J Acquir Immune Defic Synd 1993;6:376-379.

23. Boyer PJJ, Dillon M, Navaie M, et al. Factors predictive of maternal-fetal transmission of HIV-1: preliminary analysis of zidovudine (ZDV) given during pregnancy and/or delivery. JAMA 1994 (in press).

24. Richman DD, Grimes JM, Lagakos SW. Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. J Acquir Immune Defic Syndr 1990;3:743-746.

25. Hirsch MS, D'Aquila RT. Therapy for human immunodeficiency virus infection. N Engl J Med 1993;328:1686-1695.

26. Smith MS, Koerber KL, Pagano JS. Long-term persistence of zidovudine resistance mutations in plasma isolates from human immunodeficiency virus type 1 of didexoyinosine-treated patients removed from zidovudine therapy. J Infect Dis 1994;169:184-188.

27. Mofenson LM. Epidemiology and determinants of vertical HIV transmission. Sem Pediatr Infect Dis 1994 (in press).

28. DeGruttola V, Beckett LA, Coombs RW, et al. Serum p24 antigen level as an intermediate end point in clinical trials of zidovudine in people infected with human immunodeficiency virus type 1. J Infect Dis 1994;169:713-721.

29. Sperling RS, Stratton P, and the members of the Obstetric-Gynecologic Working Group of the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Treatment options for human immunodeficiency virus-infected pregnant women. Obstet Gynecol 1992;79:443-448.

30. Sande MA, Carpenter CCJ, Cobbs G, et al. Antiretroviral therapy for adult HIV-infected patients - recommendations from a state-of-the-art conference. JAMA 1993;270:2583-2589.

31. Sperling RS, Stratton P, and the members of the Obstetric-Gynecologic Working Group of the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Treatment options for human immunodeficiency virus-infected pregnant women. Obstet Gynecol 1992;79:443-448.

32. St. Louis ME, Kamenga M, Brown C, et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic and placental factors. JAMA 1993;269:2853-2859.

33. European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. Lancet 1992;339:1007-1012.

34. Ryder RW, Nsa W, Hassig SE, et al. Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive women in Zaire. N Engl J Med 1989;320:1637-1642.

35. Burns DN, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes and vertical transmission of HIV-1 among women with low CD4+ levels. J Acquir Immune Defic Syndr 1994 (in press).

36. Tibaldi C, Ziarati N, Salassa B, D'Ambrosio R, Sinicco A. Asymptomatic women at high risk of vertical HIV-1 transmission to their fetuses. Brit J Obstet Gynecol 1993;100:334-337.

37. Pitt J, Landy A, McIntosh K, et al. Prenatal maternal circulating leukocyte HIV predisposes to HIV culture positivity in their infants: progress from a North American cohort. (Abst 598) Program and Abstracts 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Anaheim, CA, October 11-14, 1992.

38. Yerly S, Chamot E, Hirschel B, Perrin LH. Quantitation of human immunodeficiency virus provirus and circulating virus: relationship with immunologic parameters. J Infect Dis 1992;166:269-276.

39. Richman DD, Grimes JM, Lagakos SW. Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. J Acquir Immune Defic Syndr 1990;3:743-746.

40. Boucher CAB, O'Sullivan E, Mulder JW, et al. Ordered appearance of zidovudine resistance mutations during treatment of 18 human immunodeficiency virus-positive subjects. J Infect Dis 1992;165:105-110.

41. Richman DD, Grimes JM, Lagakos SW. Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. J Acquir Immune Defic Syndr 1990;3:743-746.

42. Hirsch M, D'Aquila RT. Therapy for human immunodeficiency virus infection. N Engl J Med 1993;328:1686-1695.

43. Avery G.S., editor. Drug treatment: principles and practice of clinical pharmacology and therapeutics. 2nd edition. New York: ADIS Press, 1980.

44. Martin LM, Murphey-Corb M, Soike KF, Davison-Fairburn B, Baskin GB. Effects of initiation of 3'-azido, 3'-deoxythymidine (zidovudine) treatment at different times after infection of rhesus monkeys with simian immunodeficiency virus. J Infect Dis 1993;168:825-835.

45. Shih CC, Kaneshima H, Rabin L, et al. Postexposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. J Infect Dis 1991;163:625-627.

46. Morrey JD, Okleberry KM, Sidwell RW. Early-initiated zidovudine therapy prevents disease but not low levels of persistent retrovirus in mice. J Acquir Immune Defic Syndr 1991;4:506-512.

47. Lange JMA, Boucher CAB, Hollack CEM, et al. Failure of zidovudine prophylaxis after accidental exposure to HIV-1. N Engl J Med 1990;322:1375-1377.

48. Durand E, Le Jeunne C, Hughes FC. Failure of prophylactic zidovudine after suicidal self-inoculation of HIV-infected blood (letter). N Engl J Med 1991;
324:1062.

49. Looke DFM, Grove DI. Failed prophylactic zidovudine after needlestick injury (letter). Lancet 1990;335:1280.

50. Jones PD. HIV transmission by stabbing despite zidovudine prophylaxis (letter). Lancet 1991;338:884.

51. Anonymous. HIV seroconversion after occupational exposure despite early prophylactic zidovudine therapy. Lancet 1993;341:1077-1078.

52. U.S. Department of Health and Human Services. Public Health Service. Agency for Health Care Policy and Research. Evaluation and management of early HIV infection. AHCPR Publication No. 94-0572, January 1994.

53. Sperling RS, Stratton P, and the members of the Obstetric-Gynecologic Working Group of the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Treatment options for human immunodeficiency virus-infected pregnant women. Obstet Gynecol 1992;79:443-448.

54. U.S. Department of Health and Human Services. Public Health Service. Agency for Health Care Policy and Research. Evaluation and management of early HIV infection. AHCPR Publication No. 94-0572, January 1994.

55. Working Group on Antiretroviral Therapy: National Pediatric HIV Resource Center. Antiretroviral therapy and medical management of the human immunodeficiency virus-infected child. Pediatr Infect Dis J 1993;12:513-522.

56. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with human immunodeficiency virus. MMWR 1991;40:RR-2.

KRISTINE GEBBIE SPEAKING POINTS

1. Broader issues of HIV in women and children

   - e.g., women are fastest growing group with AIDS
   - e.g., children must be taught the right health messages

2. 076 study raises more questions than it answers

   - e.g., impact on children who may not have been infected anyway, long-term health problems

3. Women aren't just carriers who can transmit HIV to babies

   -- own bodies and selves are important

4. Additional implications for HIV-infected mothers

   -- Even children born HIV-negative being left as orphans

KG-
Your talking
@3 2
relayed.

Draft materials

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

Put in my March of Dimes file

CSA Rep. 7-A-94

Subject: Maternal HIV Screening and Treatment to Reduce the Risk of Perinatal HIV Transmission

Presented by: Yank D. Coble, Jr., MD, Chair

Referred to: Reference Committee D
(Peter W. Carmel, MD, Chair)

Human immunodeficiency virus (HIV) infection, which causes acquired immunodeficiency syndrome (AIDS), is the fifth leading cause of death in children under the age of 15 years in the United States. Through December 1993 more than 4,700 children with AIDS have been reported who acquired their infection perinatally from their HIV-infected mother. This figure understates the problem of perinatal HIV infection, however. The Centers for Disease Control and Prevention (CDC) estimates that approximately 7,000 HIV-infected women in the United States give birth to infants each year, and that approximately one-fourth, or 1,750, of these infants are infected with HIV from their mother.

Zidovudine (also known as AZT) was the first licensed antiretroviral agent shown to be effective under at least some circumstances for the treatment of HIV infection. Zidovudine has been shown to reduce viremia in infected persons. This observation led to the hypothesis that it might be possible to reduce the risk of perinatal transmission of HIV if the woman were diagnosed with HIV infection early in pregnancy and treated throughout the remainder of gestation. The proposed study raised a number of ethical questions initially since approximately three-fourths of infants born to infected women would not ordinarily acquire infection and it was unknown whether the risk of teratogenicity or other toxicity of intrauterine exposure to zidovudine might be greater than the risk of infection. The study design was approved, however, and was implemented at multiple centers in the United States and France as Study 076 of the National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG). The clinical trial was sponsored by the National Institute of Allergy and Infectious Diseases, NIH, in collaboration with the National Institute of Child Health and Human Development, NIH, and the Institut Nationale de la Sante et de la Recherche Medicale (INSERM) and Agence Nationale de Recherches sur le SIDA (ANRS) of France.

Preliminary Results, ACTG Study 076

ACTG Study 076 was designed as a placebo-controlled double-blinded study. The study started in April 1991 with a target enrollment of 748 HIV-infected pregnant women who did not themselves need zidovudine as part of their medical care; enrollment in the study for each woman occurred between the fourteenth and thirty-fourth week of gestation. The study targeted women who were asymptomatic, had CD4 lymphocyte counts >200 cells per mm^3, and had not had previous antiretroviral treatment; 41% had CD4 counts between 200 and 500 cells, and 59% had CD4 counts >500 cells. The women received either a standard adult dose of zidovudine or placebo during pregnancy, and during labor and delivery the women receive a continuous

intravenous infusion of the same product. The actual length of treatment for the women in the study ranged from one to 29 weeks. Starting within 24 hours after birth and daily for six weeks after birth the infants received the same treatment as had their mothers (either zidovudine in an appropriate oral form and dosage or placebo). An independent Data and Safety Monitoring Board (DSMB) was established as part of the study design to review the preliminary findings periodically and to recommend if changes or discontinuation of the study was warranted based on those findings.

As of December 1993 almost 500 women had enrolled in the trial and more than 400 infants had been born; of these, at least one HIV culture had been completed for 364 infants. Forty infants born to women on placebo (25.5%) and 13 infants born to women on zidovudine (8.3%) were HIV infected. Based on these findings, the DSMB recommended to NIH in February 1994 that the trial be discontinued and that the pregnant women who were receiving placebo be offered zidovudine. The study's sponsors concurred with this recommendation and stopped the study.

Other preliminary results from the study found that zidovudine treatment caused no significant detectable problems for either mothers or infants, although some infants did have a mild anemia that was reversible after therapy was stopped. The study investigators will continue to follow the exposed infants for several years to determine if the intrauterine and early postnatal exposure to zidovudine has any long-term effects, including an impact on growth and development.

The findings of the study are being analyzed and prepared for submission to a peer-reviewed journal for publication.

Implications of the Preliminary Findings of ACTG Study 076

The finding that treatment of pregnant HIV-infected women with zidovudine initiated between the fourteenth and thirty-fourth week of gestation can substantially reduce the risk of perinatal transmission of HIV is the first documented demonstration of prophylaxis of this infection in humans by an antiretroviral agent. Based on the preliminary findings of the study, the crude relative risk of HIV infection in the infants born to treated mothers was 0.325 compared with infants born to mothers who were treated with placebo. Based on information available to date, no significant adverse effects from the treatment were evident in either the women or the infants. Since the long-term effects on the infants of intrauterine and early postnatal treatment with zidovudine is not known, however, neither the study investigators nor the NIH have issued recommendations at this time about routine treatment of HIV-infected pregnant women with zidovudine to reduce the risk of HIV transmission to the infants. Also, since this study included only women with CD4 counts >200 cells who had not previously been treated with an antiretroviral, the results may not apply to women who have CD4 counts <200 cells (i.e., those with a later stage of infection) or who have previously been treated with antiretroviral therapy. Additional data about risks of adverse consequences of the prophylactic treatment are being obtained during prospective follow-up of the infants, and this issue will be addressed in the future.

Even in the absence of specific recommendations to offer zidovudine treatment to pregnant HIV-infected women to reduce the risk of HIV transmission to their infants, the preliminary information from ACTG Study 076 reemphasizes the importance for physicians to assess the risk of HIV infection of pregnant women and to encourage women to have HIV antibody counseling and testing as part of prenatal care. Pregnant women found to be HIV infected should be medically evaluated and presented with current information about the potential for treatment during pregnancy to reduce the risk of HIV transmission to their infant and about potential risks of adverse events secondary to the treatment. A related issue is the added importance this information gives to the need for early and continued prenatal care for all pregnant women. Approximately 35% of HIV-infected pregnant women do not receive prenatal care, which precludes their being able to consider and receive zidovudine treatment if appropriate. The issues involved in HIV screening of pregnant women and newborns were examined by a special committee of the Institute of Medicine in 1990; although the results of ACTG Study 076 will modify some of the conclusions reached by this committee in 1990, the broad discussion of the issues, including ethical considerations, remains important.[1]

Recommendations

In view of the important preliminary results that have emerged from ACTG Study 076 of zidovudine in HIV-infected pregnant women to reduce the risk of transmission of HIV to their infants, the AMA Council on Scientific Affairs recommends that the following statements be adopted as policy and the remainder of this report be filed:

1. Since preliminary results of a study of antiretroviral therapy in HIV-infected pregnant women have shown that treatment can reduce the risk of transmission of HIV from infected mothers to their neonates, women who are pregnant or who may become pregnant should know their HIV serologic status. The decision to have serologic testing should be a voluntary, educated decision and not be mandatory.

2. Physicians should assess pregnant women for risk of HIV infection as part of routine prenatal care.

3. Pregnant women who are at risk of HIV infection should be strongly encouraged by their physicians to have HIV antibody counseling and testing. In particular, pregnant women who live in a community in which the prevalence of HIV infection is high (i.e., prevalence of one percent or more in the population) should be encouraged to have antibody counseling and testing. Risk factors for HIV infection include, but are not limited to, the following:

- Medical symptoms consistent with HIV-related illness;
- A history of illicit injection drug use, particularly if needles or other injection equipment have been shared or if used or unsterile equipment has been used;
- Past or present sex partners who are known or suspected to be HIV infected;
- Sexual contact with multiple partners or with a person who is at risk of HIV infection;
- A history of or current infection with a sexually transmitted disease;
- A history of receiving blood transfusions between 1978 and 1985, or a history of a clotting factor disorder, such as hemophilia, requiring treatment with blood products before 1985;
- Origin in another country in which the prevalence of HIV infection is high.

4. Post-test counseling for a pregnant woman with HIV infection should include current information about the potential for zidovudine treatment during pregnancy to reduce the risk of perinatal HIV transmission to her infant. Information about the potential for risks of adverse events secondary to treatment also should be discussed.

5. Medical evaluation should be arranged for all HIV-infected women to help determine what type of medical care is appropriate. If a woman's stage of HIV infection does not require zidovudine therapy, the use of zidovudine treatment during pregnancy to reduce risk of perinatal HIV transmission should be discussed and a decision about treatment reached jointly with the woman.

References

1. Institute of Medicine. HIV Screening of Pregnant Women and Newborns. LM Hardy, ed. Washington, DC: National Academy Press. 1991.

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 415
(A-94)

Introduced by: New York Delegation

Subject: AMA Study of the Consequences of AZT Intervention in Pregnancy

Referred to: Reference Committee D
(Peter W. Carmel, MD, Chair)

Whereas, On February 20, 1994 the press reported in a National Institutes of Health-French multi-center, double-blind clinical trial of HIV infected women enrolled within the 14th to 34th week of pregnancy, that zidovidine (AZT) treated pregnancies had only one-third the incidence of HIV infected infants when oral administration of the drug to the infants was continued until they were 6 week of age; and

Whereas, In an 18 month follow-up study no serious health hazard has been observed among the successfully treated children; and

Whereas, No serious adverse reaction has been observed in the AZT treated mothers or infants other than occasional neutropenia, anemia and elevated bilirubin level which disappeared when treatment ended; and

Whereas, The theory has been put forth that the relative success of this regimen may be due to the short-term use of AZT, limited as it is to the latter half of pregnancy and the perinatal period; and

Whereas, On ethical as well as biological grounds it appears that every fetus at risk of transmittal of HIV infection should be treated with a course of AZT at some point after the 14th week of pregnancy and the treatment should continue into the perinatal period; and

Whereas, It is not known what level of favorable outcome will be obtained in pregnant women at the more advanced stages of HIV infection, since all women admitted to the study had CD-4 cell counts above 200; and

Whereas, Since the press release some clinicians have intensified their counselling and HIV testing efforts to identify HIV infected women at any stage of the AIDS spectrum in the hope of delivery of an uninfected infant through using AZT; and

Whereas, The policy most protective for a healthy outcome for the infant would be to focus responsibility on the obstetrician or nurse-midwife as the final responsible agent required to both counsel and advise pregnant women about HIV and AZT, and whether to have an HIV test; and

Whereas, Consideration should be given to having a national regulation wherein it would be required to offer the HIV test and seek informed consent, and to note in the record whether consent was given or not; and

Whereas, The highest risk group for HIV infection consists of women admitted to hospital late in pregnancy with little or no prenatal care and where the mother's status is not known beyond the presence of risk factors of HIV infection; and

Whereas, Under emergency conditions, when prompt clinical decisions must be made on whether to initiate AZT treatment, all usual procedures shall be observed except that verbal consent for HIV testing may suffice; and

Whereas, In such emergency situations the appropriate medical decision would appear to be to offer to begin AZT treatment, do ELISA after informed consent, which may be written or verbal and recorded as such, and finally recommend continuing care of the newborn infant with AZT if indicated; therefore be it

RESOLVED, That the American Medical Association study AZT intervention in pregnancy from several aspects, including:

1. The guidelines for HIV diagnosis and AZT treatment needed to maximize favorable outcomes for mothers and infants;

2. The cautions to be observed;

3. Reclarification of the central role of physicians and nurse-midwives in professional decision making; and

4. Modification of the circumstances of practice, if any; and be it further

RESOLVED, That the AMA report its findings at the 1994 Interim Meeting.

Fiscal Note:

NEW YORK CITY
JUNE 21 - 26, 1994

DATE/TIME OF EVENT:	June 22, 1994 11:30am - 2:00pm
EVENT:	The March of Dimes/New York Times Editorial Board Luncheon
LOCATION:	The New York Times Bldg. 229 West 43rd Street
SPONSORED BY:	The March of Dimes
REMARKS REQUIRED:	Yes. You are expected to speak for 15 minutes (no more) on the subjects of: The broader issues of the 076 study, such as women being the fastest growing group and teaching our children what they need to know. Women are more than vessels, they have real needs that need to be addressed. The issue of orphans of HIV positive parents. The fact that the 076 study brings up more questions than answers.
ACCOMPANIED BY:	John Paul Gurrola (will meet you at NYT Bldg.)
BACKGROUND:	There are many various media organizations already confirmed to attend this event, including McNeil/Lehrer News Hour, Good Housekeeping Magazine, For additional list of those who will be attending, see attached list marked 1.
TRANSPORTATION:	Taxi to and from

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

June 2, 1994

Kristine Gebbie
White House AIDS Policy Advisor
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Ms. Gebbie:

Thank you so much for taking the time to participate in our upcoming editorial luncheon focusing on the transmission of HIV from mother to fetus, to be held on Wednesday, June 22. It is an honor to have you with us and we are looking forward to a successful event. The purpose of this letter is to provide background to you in preparing for the lunch. I will need to speak with you soon about your key messages so that we can pitch a story idea to the morning talk shows, and so that we can coordinate the remarks of the other speakers.

As Sheila may have explained, the purpose of this editorial luncheon is to provide the public -- particularly women of childbearing age -- with a general understanding of maternal/fetal transmission of HIV; how such transmission may be reduced (076 study); accompanying ethical and social issues; and what women should discuss with their health care providers and steps they can take for themselves and their babies.

The principal audience at March of Dimes editorial luncheons consists of reporters from women's and parenting magazines. If a topic is very current and of some urgency, as is the case with HIV transmission, select national newspapers, wire services and broadcast outlets may also attend. These reporters need information that:

- o is conveyed in a clear, simple manner for consumers;
- o applies to readers of different demographic profiles from all over the country;
- o provides some sort of action readers may take concerning the topic.

As our first and featured speaker, we are looking to you to provide an overview and definition of the issues for the lunch. Our other speakers include Howard Minkoff, M.D., Director of the Department of Maternal-Fetal Medicine at SUNY Health Science Center at Brooklyn, who will explain the meaning of the 076 study and the rationale for and process of effective counseling; and Nancy

-more-

Dubler, LL.B., Director of Bioethics at Montefiore Medical Center, who will present the ethical and social issues surrounding counseling and testing. Alan Fleischman, M.D., Director, Division of Neonatology at Albert Einstein College of Medicine will serve as moderator.

Additional background about the luncheon is attached, including information on timing and logistics of the event. We'll eventually need to know any audiovisual requirements for your presentation, keeping in mind that you have up to 15 minutes to present. We provide the media with press kits at our luncheons, and invite speakers to contribute materials for inclusion; please let us know in advance if there is anything in particular you would like included. We will also need a copy of your bio.

We typically cover travel and lodging expenses for speakers participating in March of Dimes editorial luncheons. We would be happy to coordinate your travel arrangements, and can also help arrange for a hotel stay the night before the event if we book an interview for you on a morning talk show. Please feel free to contact our travel agent, Shay Aungst, at 914/997-4683.

Our immediate need is to have a rough sense of your key messages. I will call your office in the next day or so to see how you would like to proceed -- we could make an appointment to talk on the phone, or if you would prefer, you could send me a brief written outline. I can be reached directly at (914) 997-4459. Thank you again for your participation, and I look forward to speaking with you.

Sincerely,

Mary Giammarino
Vice President, Communications

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes
Preventing Birth Defects

FAX
TELECOMMUNICATIONS

DATE: _____

_____ TOTAL NUMBER OF PAGES BEING TRANSMITTED (INCLUDING THIS PAGE)

TO: Gus Ventura

ORGANIZATION: _____

DEPARTMENT: _____

FAX NUMBER: ( ) _____ TELEPHONE: _____

FROM: Mary Giammarino
Vice President, Communications
March of Dimes Birth Defects Foundation
Telephone: 914/997-4459

COMMENTS: _____

NOTE:
PLEASE CALL IF YOU DID NOT RECEIVE THE TOTAL NUMBER OF TRANSMITTED PAGES SPECIFIED ABOVE

MARCH OF DIMES FAX #: 914/997-4662 (Communications Department)

#

March of Dimes
Birth Defects Foundation
National Headquarters
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes Preventing Birth Defects

FAX
TELECOMMUNICATIONS

DATE: June 21, 1994

6 TOTAL NUMBER OF PAGES BEING TRANSMITTED (INCLUDING THIS PAGE)

TO: John Gurula

ORGANIZATION: White House

DEPARTMENT:

FAX NUMBER: (202 632-1096 EXTENSION:

FROM: Andrea Heller Ziltzer, Manager of Magazine Media Relations
March of Dimes Birth Defects Foundation
Telephone: 914/997-4622

COMMENTS: As discussed, attached is a copy of the media (and other) attendees, and logistics for speakers, re: tomorrow's luncheon. Also attached is a copy of the March of Dimes policy on perinatal HIV transmission. The media typically wants the Foundation's position on editorial luncheon topics, so we will include this in the press kit.

-Andrea

NOTE:
IF YOU DID NOT RECEIVE THE TOTAL NUMBER OF TRANSMITTED PAGES SPECIFIED ABOVE, PLEASE CALL: 914/997-4622 OR 997-4616.

MARCH OF DIMES FAX #: 914/997-4662 (Communications Department)

March of Dimes Editorial Luncheon Attendees

June 22, 1994

- Tamar Bauer
  March of Dimes
- Donna Behen
  Good Housekeeping
- Denise Brodey
  Child
- Trina Chang
  American Health
- Elizabeth Crow
  Mademoiselle/
  Luncheon Chair
- Nancy N. Dubler
  Montefiore Medical Center
- Barry Ensminger
  March of Dimes
- Dr. Alan Fleischman
  Albert Einstein College of Medicine
- Amy Fleischman
- Kristine Gebbie
  White House AIDS Policy Advisor
- Mary Giammarino
  March of Dimes
- Josie Glausiusz
  Discover
- Freddi Greenberg
  Child
- John Gurrola
  White House

Pg. 2/March of Dimes List

o Allen Haveson
March of Dimes

o Andrea Heller Ziltzer
March of Dimes

o Dr. Jennifer L. Howse
March of Dimes

o Kay Johnson
March of Dimes

o Dr. Richard Johnston
March of Dimes

o Michele Kling
March of Dimes

o Malcolm Manber
Science Writer

o Megan McMorris
Working Mother

o Dr. Howard Minkoff
State Univ./NY Health Science Ctr at Brooklyn

o Mary Mohler
Ladies' Home Journal

o Patricia Olson
CBS This Morning

o Curtis Pesman
Self

o Paul Raeburn
Associated Press

o Malcolm Ritter
Associated Press

o Debbie Rubin
CBS Evening News

Pg. 3/March of Dimes List

o Stuart Schear
MacNeil/Lehrer News Hour

o Emma Segal
New Woman

o Marcia Stein
March of Dimes

o Theresa Tamkins
American Health

o Claudia Wallis
TIME

o Ann Whelan
Baby Talk

o Catherine Winters
Parents

March of Dimes Editorial Luncheon (Perinatal HIV Transmission)
June 22, 1994

Logistics for Speakers

11:30 - 12:30:

o Meet to discuss/review content of presentations

12:30:

o As sit-down lunch is served, Luncheon Chair Elizabeth Crow (Editor-in-Chief, Mademoiselle) briefly welcomes the media and introduces the head table, including the moderator and speakers.

1:00:

o As dessert is served, Dr. Fleischman steps to podium to welcome guests in role as moderator, briefly introduces Dr. Howse/March of Dimes.

o Dr. Howse introduces featured speaker Kristine Gebbie.

o After Kristine Gebbie's presentation (15 minutes), Dr. Fleischman introduces Dr. Minkoff and Nancy Dubler.

o Dr. Minkoff presents (10 minutes)

o Nancy Dubler presents (10 minutes)

o Dr. Fleischman moderates question-and-answer session for media.

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

MARCH OF DIMES BIRTH DEFECTS FOUNDATION PRACTICE AND POLICY ON PERINATAL TRANSMISSION OF HIV

March Dimes Practice

The mission of the March of Dimes Birth Defects Foundation is to improve the health of babies by preventing birth defects and infant mortality. Perinatal AIDS and HIV can cause birth defects (i.e., the consequences of the infections that occur in infancy) and infant mortality. The Foundation provides health education materials on HIV prevention to women and men of childbearing age. Chapters have participated in and sponsored professional education: An exemplary project in New York City uses a medical residency training curriculum on substance abuse, with emphasis on HIV-related concerns. The March of Dimes also provides general support for the work of the Salk Institute in La Jolla, California, where basic research is being conducted to develop a vaccine to prevent HIV-AIDS.

March of Dimes Policy

The March of Dimes urges all persons at risk for HIV to be tested before trying to conceive. Prenatal care providers should routinely offer all pregnant women effective HIV counseling and voluntary testing because detection can increase opportunities for effective treatment of mother and infant. Four studies in urban areas found that approximately 90% of pregnant women agreed to HIV screening when the service was routinely offered. Policies viewed as coercive or stigmatizing discourage prenatal care use.

The March of Dimes believes that prenatal testing for HIV infection or other conditions should not be mandatory at this time. This policy will be reviewed periodically as new data becomes available.

The March of Dimes urges research aimed at preventing HIV and understanding the effects of treatment, as well as policies and programs that promote access to preconception and prenatal care.

(June 22, 1994)

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes
Preventing Birth Defects

June 15, 1994

TO: Gus Ventura
FR: Andrea Ziltzer
RE: March of Dimes Editorial Luncheon Attendees

As discussed, here is a brief overview of reporters who typically attend our editorial luncheons, to guide Ms. Gebbie as she prepares her speaking points:

The majority of reporters, and the "core" of attendees, consist of health editors and editors-in-chief of national women's and parenting magazines. A sampling includes:

- Good Housekeeping
- Self
- Elle
- Vogue
- Child
- American Baby
- Parents

If a topic is of particular urgency and newsworthiness, as is perinatal HIV transmission, reporters from major daily newspapers and wire services, and weekly magazines, will attend or at least cover the event. A sampling includes:

- Associated Press
- The New York Times
- USA Today
- TIME

To date, we have positive responses to the upcoming luncheon from several women's and parenting magazines, as well as a reporter who covers HIV and AIDS for American Health. Reporters from TIME and the Associated Press are also planning to attend. We are continuing to follow-up with invited media.

Gus, feel free to call me at 914/997-4622 with any questions. (Also, please thank Jeff for sending the bio so quickly.)

NEW YORK MEDICAL COLLEGE
VALHALLA, NEW YORK 10595

GRADUATE SCHOOL OF HEALTH SCIENCES

FACSIMILE COVER SHEET

TO: Gus Ventura (Christine Gelbier's Office)

FAX #: 202-632-1096

FROM: New York Medical College
Graduate School of Health Sciences
Telephone: 914-993-4531
Fax #: 914-993-4292

NAME: Sheila M. Smythe

I'll plan to call you later this morning. This gives the details (attached)

June 22 - 12-2 pm
NY Times Bldg. - 229 West 43 St. - 11th Floor

Total Pages: 3 (including coversheet)

Date Sent: 5-24-94

Time Sent: 7:45 am

Fax

H - 202-387-0015
O - 202-632-1090
202-690-5471

March of Dimes
Birth Defects Foundation
National Office
1275 Mamaroneck Avenue
White Plains New York 10605
Telephone 914 428 7100

March of Dimes Editorial Luncheon
Maternal/Fetal Transmission of Human Immunodeficiency Virus (HIV)
12-2, June 22, 1994 (tentative)
The New York Times, 229 West 43rd Street, New York.

Background on Luncheon Topic

A Pediatric AIDS Clinical Trials Group study (ACTG 076) released earlier this year reported that an HIV-infected woman can significantly reduce the risk of her baby acquiring HIV by taking AZT during pregnancy. It is now even more important for a woman to know her HIV status as early as possible in pregnancy. The March of Dimes Editorial Luncheon in June will address the findings of the study, the implications for counseling and testing of women, and the ethical issues involved.

The ACTG study has contributed to legislative debates regarding HIV testing and screening, particularly in New York. The editorial luncheons involve national media and a broad national perspective, so the particular issues in New York or other states will not be a central focus of the lunch. In addition, the March of Dimes has long emphasized the importance of counseling and voluntary HIV screening during preconception and prenatal care, and will include its own updated policy on this issue in the press kit for the luncheon.

Background on Editorial Luncheon

The March of Dimes Media Council holds editorial luncheons twice a year for national media in New York. The goal of the lunch is draw media attention to critical issues related to pregnancy and infant health. Attendees at the luncheons are editors and writers from women's and parenting magazines, as well as select national newspaper and broadcast outlets, and depending on the topic, business or other trade press. Attendance is limited to no more than 60 people. The Media Council advises the March of Dimes on the topics to address at the luncheons. Media Council members include John Mack Carter, Editor in Chief of Good Housekeeping magazine, Judy Nolte, Editor of American Baby Magazine, and Judy Woodruff, Anchor and Senior Correspondent at CNN.

Our previous lunch in January, titled "Preventing Birth Defects Before Pregnancy: What Can the Vitamin Folic Acid Do?" included Dr. David Kessler as the featured speaker and resulted in extensive media coverage in newspapers and magazines, as well as an appearance by Dr. Kessler and March of Dimes President Dr. Jennifer Howse on ABC-TV's "Good Morning America".

Speakers for June lunch.

Kristine Gebbie, (invited feature speaker):

Overview and definition of the issue.

(15 minutes).

Howard Minkoff, Department of Obstetrics, SUNY Health Science Center (confirmed):

Results of 076 study.

Implications for counseling, testing, and obstetrical care of women.

(10 minutes).

Nancy Dubler, Director, Division of Bioethics, Montefiore Medical Center (confirmed):

Ethical issues.

(10 minutes)

The luncheon will be moderated by Alan Fleischman, Media Council member and Director of Neonatology at the Albert Einstein College of Medicine.

Speakers will take questions from the media after the presentations are complete.

Logistics

The luncheon is tentatively scheduled for June 22, 1994 from 12:00-2:00. It will be held in the private dining room on the 11th floor of the New York Times building, 229 West 43rd Street, New York, NY.