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COMMENTS TO THE PUBLIC HEALTH SERVICE TASK FORCE ON ESTABLISHING PRACTICE GUIDELINES TO IMPLEMENT THE FINDINGS OF ACTG 076

"It is sad to admit, but AIDS is not the worse thing that could happen to many of my clients." Mary Beth Cashetta

I. ETHICAL CONSIDERATIONS CONCERNING INFORMED CONSENT IN THE IMPLEMENTATION OF PRACTICE GUIDELINES FOR THE USE OF AZT TO REDUCE THE RISK OF PERINATAL TRANSMISSION

In our society, a fetus has greater status than a woman, a fetus has greater status than a child, and a child has greater status than a woman. This value system defines the way we deliver (or do not deliver) health services and how we determine the allocation of other vital social, economic and political resources. The current political pressure to institute welfare reform illustrates this point when it punishes **women** for having children, once again making women the cause for a social problem for which they have only partial responsibility. The loudest complaint heard from the Left on these issues is that society is "punishing children for the sins of the mother "

With regard to the HIV/AIDS epidemic the reality is that the population for whom policy makers are making decisions consists primarily of low-income, African-American and Latino women. In addition, the women who will be targeted for the 076 protocol are drug users, in prison, or undocumented residents. It is highly unlikely that these women will be given access to unbiased information that they will require in order to make reasoned decisions concerning their own welfare.

In addition, for the estimated 50% of HIV positive women who don't find out about their own serostatus until either their child becomes ill or they themselves become too ill to function, the hospitalization for their first illness becomes their final hospitalization and caregivers are left to scramble to make custodial arrangements for her children, some of whom are infected/ill themselves. How many of these women will actually receive prenatal care in settings that are qualified to institute the procedural recommendations to be constituted from this meeting by the second trimester of their pregnancies?

Given these realities, the possibilities for coercion of these women is clear. This coercion could arise via:

1. The actions of the health care providers who:
    a. Offer patients inadequate or incomprehensible information, and/or
    b. Overemphasize the potential benefits to be derived from this regimen and understate or neglect to offer information on the potential risks or areas of

indeterminacy. (Note the title of the conference. AZT does not *prevent* transmission, it reduces the risk of transmission.)

2. The barriers patients face due to:
   a. An inability to comprehend the information given them due to native limitations or to the manner in which the information is presented. [The presentation of the informed consent materials and forms for the 076 protocol do not inspire confidence in the ability of the establishment to adequately inform these women.], or
   b. The desire and right of HIV positive pregnant women to have an uninfected child.

These issues must be resolved. We recommend that the PHS immediately convene a limited cross-agency task force whose membership would include seropositive women (including adolescents), seropositive men (especially fathers), advocates for women and children, selected principal investigators, and representatives from HRSA, FDA, PHS, MCHB (and any other agency that may have the power to promulgate regulations or practice guidelines as a result of 076), as well as representatives of the national pediatrics, women's health, and OB-GYN organizations. This task force must have complete access to the 076 data and should be directed to create informed consent and community education materials to be used by care providers in instituting 076 procedural recommendations to serve as safeguards against the misuse of AZT in pregnant women.

Informed consent and non-directive treatment counselling must include, at minimum, the information that:

1. The 076 trial was conducted with less than 500 women and their children,
2. The regimen's success relates directly to women with CD4 counts between 200 and 500,
3. A majority of participants had CD4 counts greater than 500,
4. The details concerning the three clinical arms of the trial,
5. While the rate of vertical transmission may be *reduced* by following the 076 regimen from 25% to 8%, there is a clear risk of long term toxicity from AZT use even in children who are born HIV seronegative, and
6. There is evidence [touched on by presenters at the conference] to suggest that AZT may be a carcinogen, a mutagen, and a genotoxic drug and that there is an unknown risk to the reproductive system of the patient who may have other children.

II. TESTING AND EDUCATION

The manner of the release of the 076 data and the hype surrounding that release have redoubled attempts to make mandatory the HIV antibody testing of all pregnant women or the unblinding of newborn seroprevalence data. (See, for example, HR 4507 introduced by Representative Ackerman of New York on June 14, 1994.) In Congress, certain members may also seek to add provisions to that effect to any health care bill introduced for a vote.

Moreover, New York, which has barely finished instituting procedures created after an incredibly acrimonious fight to prevent mandatory testing of women and newborns, is being forced to expend scarce resources and political capital to revisit the issue. Many pediatricians, even those with compassionate track records on behalf of seropositive women and children, are joining in the call for mandatory testing because of inaccurate and/or misleading information about the 076 research and its implications.

If mandatory testing is instituted or if newborn serostatus records are opened, the population of HIV seropositive women will be harmed because:

- Many of these women have a well-founded fear of legal, governmental and medical authority. Mandatory testing will serve to frighten away the most vulnerable members of this most vulnerable population away from any responsible prenatal treatment and we will be faced with an ever-growing number of mothers who only receive information regarding their condition when their children present opportunistic infections.

- In addition, open serostatus records provided as a result of mandatory testing or mandatory names reporting are being used in an increasing number of jurisdictions to either prove elements in criminal charges or to prove an *a priori* case of parental unworthiness/neglect. Reports of these events are spreading quickly in the seropositive community and will inevitably result in fewer women being willing to undergo testing.

The often asserted rationale for mandatory testing concentrates on protecting the health of children by providing pregnant women with the earliest possible access to care. The experience of enlightened care providers, however, has shown that draconian measures are ineffective, counter-productive and unnecessary since an overwhelming majority of at-risk women are completely willing to undergo testing and education if they are treated with respect, if their privacy is protected, and if they are carefully educated on the facts around their own and their children's health.

Moreover, the emphasis placed on testing *pregnant* women further amplifies the overwhelming feeling of women that they are incidental to this process and that only their fetuses matter. This emphasis was brought home to many of the participants in 076 when they realized that, while their children will receive follow-up care for life, their last contact with 076 care will be one visit six months after delivery.

Therefore, we believe that *all* women and not just pregnant women should be educated regarding the behaviors that spread HIV and offered testing if they feel that their behaviors have put them at risk. Also, *all participants in the 076 trials must be offered long-term care and follow-up.* Only through long-term tracking of women's health will we get satisfactory answers to questions such as:

- Does long-term use of AZT pose any threat to the long term health of women?

- Would the early use of AZT in healthy pregnant women permit mutant viral strains to develop that prevent future antiviral efficacy?

Additionally, such long term care is critical to addressing the concerns about the quality of care these women will have after their final six-month post-partum follow-up visit?

III. DATA CONTENT AND RELEASE ISSUES

Both the nature of and the manner of the release of the 076 data have placed enormous pressures on women living with or at risk for HIV infection, on health care providers, and on policy makers. Since 076 exhibited the first sign in 14 years that it was possible to chemically interfere with the transmission of HIV, and since this first sign of success came in reducing the risk of perinatal transmission (thereby saving "innocent victims" from infection), the news has spread world wide in a matter of days.

The limited nature of the data released in February, however, raises as many questions as it answered. Why was the released data so thin? Why, to this day, has the FDA released such a small amount of the enormous data collected? There are, after all, numerous precedents for the comprehensive release of data pre-publication (Concorde, for example), especially when the incomplete nature of the reported data could encourage an extreme public reaction.

Many questions remain to be answered regarding the use of AZT in pregnant women. Some of these questions may be answered to some degree by the data that has already been collected but which remains unreleased. Some others may have to be answered by other studies. These crucial questions include:

1. Why were there discrepancies in the numbers reported in the data presented during the 6/6/94 meeting and the 2/20/94 Memo from the 076 Protocol Team to the Principal Investigators?

	2/20/94 MEMO	6/6/94 PRESENTATION
Total #	364	363
Pregnancy Loss	14	15
Placebo Group #	184	183

2. Among the premature births, what is the actual number of infected babies and to which groups (AZT or Placebo) do they belong?
3. When will stratified levels of CD4 counts be released?
4. When will the maternal virology data be released?
5. How many sites actually collected p24 maternal virology data?
6. Are data on cardiomyopathy, anecdotally reported to be a frequent side-effect in children taking AZT, being collected on ACTG 219?
7 Given Dr. Farrelly's presentation on June 6 on Nucleoside Analogs, including AZT, as carcinogenic, mutagenic and genotoxic, how will these risks be explained to women, especially considering that 75%-92% of babies born to healthy HIV-positive women taking

AZT will be negative?

8. When will a site-specific comparative analysis be released which reveals the breakdown of drug/placebo transmission rates to determine if a varying standard-of-care across the ACTG research sites influenced the overall results, as may have been the case in the V.A./AZT study?
9. When will data be released that analyze the effect of AZT on the racial and ethnic groups enrolled? Analyzing data by race and ethnicity is required by the NIH Reauthorization bill and guidelines have been published in the Federal Register.
10. Which components of the 076 protocol effectively decrease transmission?
11. Does the protocol reduce transmission of HIV to infants born to women who do not meet 076 inclusion criteria?
12. Will the development of resistant strains developed with previous use of AZT remove the advantages suggested by 076?
13. Does partial compliance with the treatment regimen either pre or post delivery affect the outcome?
14. Only 1% of the women involved in the trial were active IV drug users. How will this sparsity of clinical data be taken into account in the development of clinical guidelines?
15. Will the preliminary guidelines developed as a result of the June 6-7 meeting be made available to ALL conference participants for comment?
16. Were the data that the ACTG Pediatric Executive Committee received from the DSMB identical to the data presented in the 2/20/94 Memo?
17. Why was misleading and incomplete information about the trial released to the press?

A SECOND COMMUNITY MEETING MUST BE SCHEDULED TO DISCUSS THE ANSWERS TO THESE AND OTHER URGENT QUESTIONS!

The data from the protocol must be released immediately so that questions such as these may be answered and accurate information can be presented to patients. Only if clear and concise data is available to women, and only if that data is presented to women in the context of a clear treatment plan will patients be able to make well informed decisions about their care. Many at the conference spoke of the necessity of treatment decisions being made by women, themselves. That should be an absolute rule in any medical care setting. Without adequate information that is comprehensible, truthful and culturally competent, however, that rule becomes an empty exercise in rhetoric.

CONCLUSION

Many of the ethical problems detailed here could have been mitigated had the PHS included HIV positive women in the trial design and evaluation of 076. Instead, PHS and the FDA, by undervaluing the knowledge base available to them in the experiences of these women, continue to encourage the medical establishment to view women as the vessels for their wombs and/or as vectors for disease transmission.

Along with homophobia, racism, classism and an almost willful misunderstanding of the

mechanics of drug use, sexism is one of the root causes of the HIV epidemic in America. Until society as a whole is prepared to remove these virulent threads from the fabric of our society and to begin to treat all human beings with the respect that they deserve, we will continue to fail in our attempt to end the HIV epidemic. This reality must be acknowledged, and all decisions and actions taken with regard to 076 must be made in light of this reality.

Marian D. Banzhaf, Executive Director, New Jersey Women and AIDS Network
Aimee R. Berenson, Esq., Legislative Counsel, AIDS Action Council
Mary Beth Caschetta, M.A., Assistant to the Director, HIV Law Project
Gary R. Rose, Esq., Associate Director for Legislation and Regulations, National Association of People With AIDS
Toni Young, Executive Director, National Women HIV/AIDS Project

To: Kristine Debbie

Copy of Briefing
Package sent to Dr Lee.

also 2 other article
re OTC.

Sam Page.

RECOMMENDATIONS TO PHS TASK FORCE

HRSA Constituent Working Group on Prevention of Perinatal Transmission of HIV
May 25, 1994

- Expanded counseling and testing should be made available in all settings that provide care to women. Testing should **only** be performed after women give specific informed consent. Informed consent should include a clear, simple presentation of the benefits of early intervention services to women (and infants, if applicable). Counselors should be aware of local resources and services for women with HIV and provide referrals when results are given.

- Information on the risks and benefits of AZT use during pregnancy (results of ACTG 076) should be made available to all pregnant women in clear, simple language to enable women to make informed choices. PHS should develop a culturally sensitive protocol for presenting the risks and benefits to women.

- Providers of health care and services for women should make the 076 protocol available to women who choose this option, either on site or by referral.

- All women and infants treated according to 076 protocol should receive long term follow-up care.

- Resources should be made available for community planning to develop appropriate services and follow-up care for women and families.

- Health care services for women need to be expanded; this includes reproductive health, substance abuse treatment, and relapse prevention services.

- Caregivers must be sensitive to the high level of distrust and fear that many disenfranchised and minority populations have toward health care providers. Culturally appropriate interventions and provider training must be developed to increase trust, utilization of services and compliance with treatment.

- Training should be provided for health care workers on: 1) diagnosis and management of HIV disease in women; and 2) counseling and testing for women. This should include training in cultural sensitivity.

- Public meetings should be convened to enable affected communities to discuss the findings of 076 and their impact on policy.

- Women with HIV should be considered an important resource for community outreach, education, policy and planning.

- Additional research should be conducted to determine: 1) which components of the 076 protocol effectively decrease transmission; 2) whether the protocol reduces transmission of HIV to infants born to women who do not meet 076 inclusion criteria; 3) whether partial compliance with treatment regimen pre or post delivery affects the outcome; 4) whether AZT use during pregnancy facilitates development of viral resistance to AZT later in the course of disease?

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

Meeting on
Clinical Trial 076 Guidelines
June 28, 1994

AGENDA

1. Introductions

2. Message from the ASH

3. Presentation of Guidelines
   Lynne Mofenson, NICHD

4. Counseling and Testing Issues
   Jim Curran, CDC
   Martha Rogers, CDC

5. Labeling Issues
   Nancy Stanisic, FDA

6. Clinical Guidelines and Implementation
   Steve Bowen, HRSA

7. Discussion

8. Next Steps

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

TO: Assistant Secretary for Health

FROM: Acting Director, NAPO

SUBJECT: Meeting on 076 Therapeutic Recommendations, Tuesday June 28, 1994, 11:00 A.M., 729-G -- BRIEFING

PARTICIPANTS

Patsy Fleming, HHS
Lynne Mofenson, NICHD
William Paul, NIH
Wendell McConnell, CSAT, SAMHSA
Warren Hewitt, CSAT, SAMHSA
Jim Curran, CDC
Martha Rogers, CDC
Nancy Stanisic, FDA
Richard Kotomori, IHS
David Lanier, AHCPR
Steve Bowen, HRSA

BACKGROUND

In February 1994, NIH released preliminary results of clinical trial ACTG-076, which was designed to evaluate the efficacy, safety and tolerance of AZT (zidovudine or ZDV) for the prevention of maternal-fetal transmission of HIV. This study was conducted in 50 sites in the USA and 9 sites in France. There were 477 women and 364 infants enrolled in the study at the time of the analysis of the data presented. A total of 421 infants have been born since the study began in 1991. Of those, 364 infants had at least one culture result available.

The meeting on June 28 is intended to discuss the clearance process for the therapeutic recommendations developed by NIH on the implementation of the findings of Clinical Trial 076. Attached at Tab A is the proposed agenda for the meeting. Attached at Tab B is the NIH draft document regarding treatment issues and evaluation.

An HHS/PHS Task Force entitled, "The Public Health Service/Health and Human Services Task Force on the Use of Zidovudine to Prevent Perinatal HIV Transmission" has had its first meeting on April 14, 1994. This panel convened to discuss implications of ACTG 076 for the woman and child, specific treatment guideline issues, testing and counseling parameters and propose timelines for the development of recommendations and policies. August, 1994 is the

target month for publication of the recommendations from this task force. Attached at Tab C is the list of consultants that participated in the Task Force. Attached at Tab D are copies of the minutes of two meetings of this Task Force.

ISSUES OF CONCERN

* Although not all of the issues related to 076 implementation are addressed by the therapeutic recommendations, the publication of these will send a clear message to clinicians that the administration is taking the necessary steps to address the needs of pregnant women living with HIV and their babies. The issues not contained within the recommendations, counseling and testing, labeling indications and clinical recommendations must be addressed in the months to come.

* Primary among the issues that must be addressed in the future is the long term impact of ZDV on the children born after therapy. This can be studied through continued evaluation of the application of the recommendations. Periodic reviews of ZDV use with pregnant women must be conducted.

* CDC will draft a document on counseling and testing issues for pregnant women living with HIV, outlining issues regarding follow-up for infants exposed to ZDV in utero, and evaluation natural history studies to provide further information regarding the impact of this therapy on women and children. The exact process by which this document will be developed is still under review. There will be a period for public comment once this document has been drafted.

* HRSA is responsible for plans to implement the counseling, testing and clinical care recommendations. The implementation of the clinical findings of 076 into broader settings including Ryan White programs will require early identification of HIV infected women. The process by which this document will be developed is still under review.

* FDA will review the labeling indication assessment of ZDV for use in pregnancy. FDA has indicated that Burroughs-Wellcome (BW) has submitted an application for new labeling indication for pregnant women after a gestational period of 14 weeks. A draft of the response has been sent to BW for comment. The ACTG 076 review, the treatment draft recommendations, BW application and response document will be presented to the FDA Antiviral Advisory Committee meeting on July 28, 1994. During this meeting there will also be discussions of possible Phase IV monitoring of long term effects on mothers and infants that may be required of the company. August 24, 1994 is absolute target date for

completion of this process.

* There are concerns that if the administration does not take action as soon as possible, Congress may follow the lead of those legislators that have called for mandatory testing of all women seeking prenatal care. Publication of the recommendations will assure legislators that the Department is taking the lead on this critical issue.

* Financial issues must also be addressed in conjunction with the clinical recommendations being developed. It is essential that funding mechanisms are made available to pay for the ZDV therapy for women, and that support services are made available to care for the children in the mother's absence.

DISCUSSION

This document by itself is only a portion of the recommendations needed to fully make ZDV therapy available for the women and children it targets. The American College of Obstetrics and Gynecology and the Academy of Pediatrics are also reviewing the data in order to make treatment decisions regarding this therapy. It is, therefore, critical that this document be approved for publication in order to give heath care practitioners recommendations on the use of ZDV for HIV infected pregnant women, keeping in mind that CDC, HRSA, HCFA and FDA have crucial roles in the implementation of these therapeutic recommendations.

More extensive research is needed to determine the long term effects of ZDV therapy on the infants, some of whom do not become infected with HIV and those who do in spite of ZDV therapy. Additional studies are indicated to determine the efficacy and safety of ZDV therapy for the mother. The impact on the health and the progression of HIV disease in the mother needs to be considered in subsequent studies.

The implications of this study highlight the need to broaden our outreach efforts to women of childbearing years to seek HIV counseling and testing. Clinicians who provide services to these women must be alerted to the need to counsel them regarding the potential impact of ZDV therapy, benefits and risks. It is important to note that 8 out of every 100 babies in the study was HIV infected, even though the mother and infant had received ZDV.

For women who participate in high risk behavior, i.e., injecting drugs and unprotected sex with someone whose HIV status is unknown, it is imperative that they have access to adequate counseling, testing and treatment regardless of whether they are pregnant or not. The rights of the woman to adequate treatment should not be abrogated to the rights of the unborn child.

Evaluation of Title IV programs demonstrates remarkable success in identifying HIV positive youth and women, retaining them and their newborn infants in comprehensive care and supporting them to participate in early medical treatment. Early identification and follow up care for HIV exposed infants by Title IV programs reduces morbidity and mortality through a coordinated, comprehensive medical, social and family support programs.

RECOMMENDATION

Based on the complexity of the issues and the implications of implementation of these recommendations, the PHS agencies should be allowed to clear and formally sign-off on the NIH draft document. If the PHS agencies are in substantial agreement with the contents of the recommendations, clearance can be completed within a one week period.

If you have any questions, please feel free to contact Frances Page at 690-5560.

Arthur J. Lawrence, Ph.D.

Attachements:
Tab A - Proposed Agenda, June 28 Meeting
Tab B - Draft NIH Therapeutic Recommendations
Tab C - List of Consultants, NIH 076 Task Force
Tab D - Minutes of April 14 and May 20 Task Force Meeting

cc: Patsy Fleming
Jo Ivey Boufford, M.D.
Bill Corr

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

TO: Robert Rickard, Executive Secretary, OASH
Telephone: 202-690-6925

FROM: Lynne Mofenson, M.D., PAMA, NICHD

DATE: June 21, 1994

RE: Dr. Lee's July 6 Agency Director's Meeting - Review and approval of Draft PHS Document "Recommendations on the Use of Zidovudine to Reduce HIV Transmission From Mother to Child" for publication in MMWR

I understand that Patsy Fleming has spoken with you regarding inclusion of the above recommendation document as an agenda item in Dr. Lee's July 6 Agency Director's meeting.

This document will be published as a August 1994 supplement to the Morbidity and Mortality Weekly Report published by the CDC. Due to the short timeline until publication, this document needs approval by PHS by July 15. Dr. Lee has committed to expedited approval of this document.

The document has already gone through two stages of review. The last review included incorporation of comments from the PHS Agency members of the PHS 076 Task Force: Patricia Salomon from HRSA; Steve Gitterman from FDA; R.J. Simonds from CDC; David Lanier from AHCPR; James Balsley and myself from NIH. These Agency staff are now supposed to begin the process of additional clearance in their respective Agencies.

We need to have the document sent ahead of the July 6 meeting to the relevant Agency Directors for their review and approval at the July 6 meeting. The Directors need to know that the above people from their agencies have seen, commented and approved the document that is being sent to them.

As we discussed on the telephone, I am enclosing a draft letter to the Agency Directors and including a disc containing the draft letter, so that you can correct it and send it to the relevant people.

I will be in Geneva at a WHO meeting from this afternoon until Sunday June 26; I will be back in the office on June 27. My secretary, Sandy, will have telephone and fax numbers to reach me if you need to. Patsy also should be able to assist in answering questions.

Thank you very much for your assistance.

cc: Patsy Fleming

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DRAFT

TO: PHS Agency Directors

FROM: Lynne Mofenson, M.D.

DATE: June 21, 1994

RE: Review of draft PHS Document "Recommendations on the Use of Zidovudine to Reduce HIV Transmission From Mother to Child" for Dr. Lee's Agency Directors meeting on July 6, 1994

I was appointed by Dr. Lee to Chair the PHS/HHS Task Force on the Use of Zidovudine (ZDV) to Reduce Perinatal HIV Transmission. This Task Force was convened as a result of the findings of the National Institute of Health-sponsored AIDS Clinical Trial Group (ACTG) Protocol 076 that demonstrated a reduction in perinatal HIV transmission of 67% with a regimen of ZDV given to HIV-infected pregnant women and their newborns.

A two-day Workshop was held on June 6-7, 1994 to address the implications of ACTG 076 on treatment recommendations for use of ZDV in pregnancy and for counseling and HIV testing. The enclosed document is the summary of the treatment recommendations that emanated from that meeting.

This document has undergone review by Agency members of the PHS/HHS Task Force; the current document incorporates their comments and is in it's final stages of development. Agency members of the PHS/HHS Task Force include Dr. Patricia Salomon of HRSA; Dr. David Lanier of AHCPR; Dr. Steve Gitterman of FDA; Dr. Martha Rogers of CDC; and myself and Dr. Balsley of NIH.

Dr. Lee is planning to review this document with you at the July 6 meeting; please come prepared to provide your comments.

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 from mother to infant transmission. In the United States, serosurveys indicate that an estimated 7,000 HIV-infected pregnant women give birth annually; given a 20-30% transmission rate, it is estimated that 1,400 to 2,1 00 newly infected infants are born each year[1]. 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.[2]

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.[3] 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 a selected group of HIV-infected pregnant women (those with 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.[4] A regimen of ZDV begun between 14 and 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 HIVinfected pregnant women with advanced disease, prior antiretroviral therapy, or ZDV resistant virus is unknown. The long-term risk of ZDV exposure *in utero* 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 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, legal and HIV-infected communities and representatives from interested professional, community and advocacy organizations. The Workshop addressed two issues related to the results of ACTG 076: 1) what treatment 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. Recommendations regarding counseling and HIV testing will be published separately.

These recommendations are made for the United States. Although perinatal transmission of HIV infection is an international problem, alternative strategies may be appropriate in some other countries.[5] Policy and practice in other countries may differ from these recommendations and 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. Discussion of treatment options should be noncoercive, and the final decision to accept or reject recommended ZDV 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 and their newborns; 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.

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 200/μL or above; the mean CD4+ lymphocyte count was 586 cells/μL. Also, because this was a randomized 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 (1 9 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 occurs. The 34 week limit allowed most women to have several weeks of ZDV before delivery to allow time for reduction of 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 caregivers and institutions provide culturally-appropriate information and counseling to the HIV-infected woman to ensure that informed decisions are made.

Clinical Scenarios

1. **Pregnant women with CD4 + lymphocyte count $\geq$ 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. Little toxicity specifically attributable to ZDV was observed for the women in this study. 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. The presence of major or minor congenital abnormalities were approximately equal between the two groups, and no pattern in the type of abnormalities was observed. Similarly, in a recent report from the Antiretroviral Pregnancy Registry run by the Wdllcome Foundation in conjunction with the Centers for Disease Control and Prevention, no increase in the risk of congenital abnormalities 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.[6]

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 1 2 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.[7,8,9,10]

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. However, gamma DNA polymerase, required for mitochondrial replication, can be inhibited by ZDV at concentrations as low as 1μM, concentrations that can be achieved *in vivo*.

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*.[11] Rodent studies have demonstrated a small number of noninvasive squamous epithelial vaginal tumors after 1921 months of continuous high dosing (from 220 to 600 mg/kg/day). 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. It is not known if rodent carcinogenicity studies will be predictive of human experience. In humans, an increased incidence of non-Hodgkin's lymphoma has been reported in HIV infected men 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. [12] 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. it is often difficult to distinguish in an individual patient between effects secondary to ZDV itself or as 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.[13]

Reproductivity/fertility studies in animals have not shown adverse effects on male or female fertility in rats or the reproductive capacity of their progeny."' 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.[15,16]

ZDV (as well as zalcitabine and stavudine) 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. Other **FDA** Pregnancy categories are: **A,** in which adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters); **B,** in which animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women (didanosine is Category **B); D,** in which there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks; and **X,** in which studies in animals or adverse reaction reports have shown that the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit. Most animal studies of ZDV in pregnancy have not demonstrated teratogenicity; one study in which pregnant rats were given toxic doses of ZDV during organogenesis (equivalent to approximately 50 times the recommended daily clinical dose, based on relative body surface areas), found developmental malformations and skeletal variations in 12% of fetuses.[17] Data from ACTG 076 and from uncontrolled reports indicate that ZDV does not appear to be teratogenic in humans.[18,19,20,21,22] 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 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.[23] 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.[24,25] 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, stavudine).

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 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[26] near to or during delivery.[26] 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 viral load indicate that maximal effect is observed after 8 to 1 6 weeks of therapy.[27] 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 recommended for the woman for her own health benefit.[28] 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.[29,30] A variety of published studies document that HIV-infected pregnant women with lower CD4+ lymphocyte percent or absolute number have a greatly increased risk of HIV transmission to their infants, ranging between 22% to 60%[31,32,33,34,35,36,37] Viral load has been shown to increase as CD4+ lymphocyte count decreases thus, baseline maternal viral load would be expected to be high in this population.[38]

Although viral replication and therefore capacity for mutations is high, because these women have

limited (or no) prior exposure to ZDV, it is unlikely that preexisting ZDV-resistant viral strains would be present. Therefore, it is expected that ZDV will provide an acute reduction in 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.

However, it is unknown whether the magnitude of the effect of ZDV on reducing the transmission rate in this group would be the same as that demonstrated in ACTG 076 for women with higher CD4+ lymphocyte counts. 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. The regimen should be available to the woman following discussion with her health care provider, although the effectiveness of the full ACTG 076 ZDV regimen in this setting may vary depending on the clinical status of the woman. 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 transcriptasecoding 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 1 2 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 1 8 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 highlevel 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 preterm 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 circulating 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 predictable maternal 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; further studies are needed.

Infections that occur prior to labor (as much as 50% of transmission may occur *in utero)* 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 potential 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 mothers 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 complex,

administration of ZDV beginning as early as 1 0 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, any protection offered clearly 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 relatively few in number and approximately equal between women receiving ZDV and those receiving placebo. Drug dose was modified during pregnancy due to perceived toxicity in 60 women receiving ZDV and in 73 women receiving placebo. Six women discontinued study 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 $< 750/\mu L$, platelets $< 50,000/\mu L$) 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 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 31 60 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 1 1 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 $<$ 1 000 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. Coordination of care between gynecologic, pediatric, internal medicine, infectious disease and other health care specialists is essential to ensure that both mother and child receive appropriate medical follow-up. 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 neutrophil count $<$750 cells/μl.

CD4+ lymphocyte count should be monitored to determine 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/,PL: if CD4 + count is below 600 cells/iμl, evaluation should be repeated each trimester. CD4+ lymphocyte count should be assessed at 6 weeks and 6 months postpartum to evaluate if antiretroviral therapy is indicated.

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 1 2 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 *in utero* and early infancy treatment with ZDV. Consultation with a specialist in pediatric HIV infection may be considered if therapy is necessary in infected children whose mothers received ZDV during pregnancy. Further research is needed regarding response to therapy and disease progression in such infants.

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

General Issues:

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, 1 9 women who had received ZDV and 21 who had received placebo were receiving openlabel 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 *in utero* 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 progression 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) 3158465 for registrations from countries outside the United States. Written reports are available from Antiretrovirals in Pregnancy Registry, P.O. Box 1 2700, Research Triangle Park, NC 27709.

Continued follow-up of women who participated in ACTG 076 and their infants is planned. A women'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 *in utero* 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 address 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 and possible adverse outcomes of such ZDV treatment. 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 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 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.

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Table 1 -

Zidovudine Regimen from AIDS Clinical Trials Group Protocol O76

- Oral administration of 1 00 mg zidovudine (ZDV) five times daily, initiated at 1 4 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 1 2 hours after birth.

Table 2.

Eligibility Criteria for HIV-infected Pregnant Women

Participating in AIDS Clinical Trials Group Protocol 076

- Pregnancy between 14 weeks and 34 weeks gestation.
- No prior receipt of zidovudine (ZDV) during the current pregnancy for any indication.
- No clinical indications for maternal antiretroviral therapy in the judgement of her health care provider.
- CD4 + lymphocyte count $\geq$ 200 cells/μL at initial assessment.

Table 3.

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

I. **Women with CD4+ lymphocyte counts $\geq$ 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 health care provider should recommend the full ACTG 076 ZDV in the context of a risk/benefit discussion with the pregnant woman.

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

Recommendation:
The health care provider should recommend the full ACTG 076 ZDV 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. **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 recommended by the health care provider 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. **Women with significant prior ZDV (> 6 months of ZDV therapy) and/or other antiretroviral therapy prior to pregnancy.**

Recommendation:
There is 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. The regimen should be available to the woman following discussion with her health care provider, although the effectiveness of the full ACTG 076 ZDV regimen

in this setting may vary depending on the clinical status of the woman. Further clinical trials should evaluate alternative approaches for such women.

V. **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.

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ACTG PROTOCOL 076

COMPONENTS OF THERAPY

Rx ARM	INTRAUTERINE 14-34 wks gestation	INTRAPARTUM	POSTPARTUM Newborn
1	ZDV 100 mg po 5x/d	ZDV Loading dose 2mg/kg IV over 1 hr; Continuous infusion 1 mg/kg/hr until delivery	ZDV 2 mg/kg po q 6hr for 1st 6 wks life
2	Placebo (oral)	Placebo (intravenous)	Placebo (oral)

MAJOR ENTRY CRITERIA

- Between 14 and 34 weeks gestation
- CD4+ lymphocyte count $>200/mm^3$
- Has not received antiretroviral therapy during current pregnancy
  [Note: only 19 (4%) women had antiretroviral prior to pregnancy, for only short time period]
- Has no clinical indication for maternal antepartum antiretroviral therapy in judgement of health care provider

RESULTS

Transmission reduced from **25.5%** in Placebo to **8.3%** in ZDV recipients ($p=0.000056$)

RATIONALE FOR ACTG 076 REGIMEN

AZT during pregnancy:	■	Reduce viral load
	■	Interrupt transmission *in utero*
AZT infusion L&D:	■	Ensure adequate level AZT in infant during labor & passage through birth canal (time of intensive HIV exposure)
	■	Interrupt transmission during intrapartum period
AZT newborn x6 wk:	■	Ensure adequate level AZT in infant for limited period following birth

LIMITATIONS TO RESULTS OF ACTG 076

- Did not assess efficacy of AZT in HIV-infected pregnant women with:
  - gestational age over 34 weeks
  - CD4+ count $<200/mm^3$
  - Previous use of AZT
  - Late-stage disease who require antiretroviral for own health
- Cannot assess relative contribution of antepartum, intrapartum and postpartum therapy, therefore efficacy of regimens restricted to only 1 or 2 periods is unknown
- Did not evaluate risk/benefit of AZT given during the first trimester of pregnancy
- Long-term adverse effects for mothers and infants (infected and uninfected) of this regimen of AZT is unknown

PHS TASK FORCE ON USE OF ZDV TO REDUCE PERINATAL HIV TRANSMISSION: ISSUES/TIMELINES

PHS Task Force Members and Outside Consultants

NIH:	Lynne Mofenson MD (NICHD) Jim Balsley MD PhD (NIAID)
FDA:	David Feigal MD (Steve Gitterman MD alternate)
HRSA:	Pat Salomon MD
CDC:	Martha Rogers MD Helene Gayle MD (USAID)
ACHPR:	David Lanier MD
OASH:	Patsy Fleming
NAPO:	Frances Page RN MPH
Outside consultants:	Arlene Bardequez MD; Yvonne Bryson MD; Barabara DeBuono MD MPH; Ruth Faden PhD; Margaret Hamburg MD; Mary Jo O'Sullivan MD; Gwen Scott MD; Rhoda Sperling MD; Sallie Perryman; Patricia Whitley-Williams MD

POLICY ISSUES:

Treatment recommendations and testing/screening issues

These were the most time-urgent issues and immediate plans developed.

- NIH has responsibility for addressing treatment-related issues.

- CDC has responsibility for addressing issues regarding screening recommendations.

- HRSA has responsibility for implementing recommendations at the community health center level.

POLICY ISSUES Action Items & Timelines:

★ **APRIL Brief MMWR publication on trial results; interim recommendations** (published 4/29/94)

★ **APRIL-JUNE Outside consultant meeting**

★ **April** Task Force members assist NIH and CDC in developing agenda for meeting & selecting invitees.

★ **May** Task Force meeting mid-May to review documents & hear progress reports from other agencies.

★ **June 6-7** Two-day meeting of selected medical/community consultants.

Outline of meeting:

- First day - NIH responsible for organizing review scientific questions emanating from ACTG 076. Draft of consensus treatment recommendations agreed upon during evening working session by Executive Committee, composed of 15 outside consultants and NIH/CDC/HRSA staff.

- Second day - CDC responsible for organizing review of issues regarding counseling and HIV testing. Recommendation document from this meeting will be developed by CDC and sent to consultants for review and comment following the meeting.

★ **LATE JUNE Treatment Recommendations**
Review of draft Treatment Recommendations by Treatment Meeting Executive Committee followed by Task Force review of final document (completed 6/20); submit revised document to PHS for review & expedited approval.

★ **MID-JULY** PHS final approval; MMWR editing of Treatment document.

★ **AUGUST** Publication of Treatment Recommendation Document as MMWR supplement.

★ **JULY-SEPTEMBER Counseling & HIV Testing Recommendations**
Development of Counseling & Testing document by CDC; review by consultants; publication in Federal Register for open public comment.

★ **FALL 1994** Revision of Counseling & Testing document by CDC; possible open public forum for comment; finalization and publication of Counseling & HIV Testing Recommendation Document as MMWR supplement.

★ **APRIL-ONGOING Evaluation and long-term follow-up:**

- Long-term follow-up of infants with *in utero* exposure to antiretroviral therapy & effect of short term interrupted therapy of ♀ who receive therapy during pregnancy

  ★ **Ongoing** Prospective intensive long-term follow-up for ACTG 076 infants through ACTG 219.

  ★ **Ongoing** A similar protocol for ACTG 076 women is under design; adolescent enrollment into long-term follow-up protocol ACTG 220.

  ★ **April-ongoing** Coordination of ongoing cohort studies to collect relevant information regarding ♀ & infants receiving the ACTG 076 regimen outside of the protocol (eg., PSD, ASD, WITS, WIHS) with CDC, NIH collaboration.

- Plans need to be developed to evaluate the efficacy of the PHS recommendations.

  ★ **April-June** CDC and HRSA are jointly developing plans for evaluation of screening & health care recommendations.

RESOURCE ISSUES:

In parallel to planning for the above meeting

- Plans for implementation of the treatment and screening recommendations in community health programs
- Assessment of program funding needs
- Education of the health care provider network
- Plans for evaluation of the programs
- Drug availability
- Approval of labeling indications
- Reimbursement issues

RESOURCE ISSUES Action Items & Timelines:

- **Health care programs & provider issues:**

HRSA has lead in developing plans for these issues
in collaboration with other relevant agencies.

★ **APRIL-JULY Health care provider meeting:** In parallel to but separate from CDC/NIH meeting, meeting(s) of public health care providers (maternal and child health, family care, prenatal clinic) to address issues regarding implementation of PHS recommendations (initial meetings, May 23 & 25). Issues include provision of appropriate information and testing at publicly-funded health care sites.

★ **AUGUST-FALL Education issues:** Health care providers will need to be educated regarding the recommendations. HRSA HIV Education Branch, Division of Medicine, Bureau of Health Professions, could develop plans to address this.

★ **APRIL-ONGOING Evaluation:** Evaluation is necessary regarding implementation of screening programs and their success/non-success in identifying infected pregnant women, linkage of the women with health care, provision of appropriate preventive therapy with AZT, and linkage of their infant with health care. HRSA and CDC could plan for such evaluations; inter-agency collaborative funding of several demonstration projects might be considered.

- **Drug availability:**

FDA is responsible for information and timelines regarding availability of drug and labeling indications.

★ **JULY** Antiviral Advisory Committee review of modified AZT labeling indication application (July 28).

COMMUNICATION ISSUES:

- Information to health care providers, state and local health departments, HRSA demonstration projects, patients, and the lay public.

COMMUNICATION ISSUES Action Items & Timelines:

★ **APRIL**

- MMWR weekly article published.

★ **JUNE-JULY**

- Implementation Task Force emanating from Dr. Lee's office to have first meeting.

★ **AUGUST**

- MMWR supplement for treatment recommendations published.

★ **AUGUST-ongoing** Implementation Task Force works range of professional/community organizations to:

- Plan & coordinate the development of standardized and understandable information regarding PHS treatment recommendations.
- Develop and coordinate a process for communication and education of community health care providers, the affected community and the public regarding treatment and counseling/testing recommendations.
- Identify what resources will be necessary for implementation of the PHS recommendations.
- Plan how monitoring of implementation of the recommendations can best be accomplished.

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

General Principles of the Document:

- HIV-infected women should be informed of the known benefits and short-term safety of ZDV given during pregnancy and the newborn period.
- HIV-infected women should also be informed that long-term risks of such therapy to themselves or their children are unknown at this time.
- A decision by the woman regarding treatment involves a balance of the benefits and potential risks of the regimen to herself and her child.
- Discussion of treatment options should be non-coercive.
- The final decision to accept or reject recommended ZDV treatment to reduce perinatal transmission is the right and responsibility of the woman.
- A decision not to receive treatment should not result in punitive action or denial of care.
- ZDV should not be denied to a woman who decides to receive the regimen.

Components of the Document:

1. Treatment options for HIV-infected pregnant women and their newborns.
2. Recommendations on medical monitoring of pregnant women and neonates receiving ZDV.
3. Issues regarding long-term follow-up of women and children who have received ZDV.

SUMMARY: RECOMMENDATIONS FOR USE OF ZDV IN HIV-INFECTED PREGNANT WOMEN TO REDUCE PERINATAL HIV TRANSMISSION (CLINICAL SCENARIOS)

I. Women with CD4+ lymphocyte counts $\geq$ 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 health care provider should recommend the full ACTG 076 ZDV in the context of a risk/benefit discussion with the pregnant woman.

Rationale & Considerations:

- These women have characteristics most similar to women in the trial.
- ACTG 076 suggests ZDV regimen will result in about 2/3 reduction in risk of transmission of a fatal disease.
- ZDV appears safe in the short-term for the woman.
- ZDV did not cause adverse effect on the fetus or on fetal growth.
- ZDV appears safe in the short-term for infant; associated with mild, transient anemia in which resolved by 12 wks of age.
- The regimen did not completely prevent transmission.
- Long-term toxicity of ZDV for infant unknown: potential concerns regarding mutagenic, carcinogenic effects; potential for teratogenicity; potential effects on reproductive system.
- Long-term toxicity of ZDV for woman: potential issue of viral resistance.

II. 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 health care provider should recommend the full ACTG 076 ZDV 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.

Rationale & Considerations:

- This group of women have characteristics similar to ACTG 076; only difference is duration of antenatal therapy.
- Current estimates are that 50-70% of transmission occurs near to or during delivery.
- Maximal effect of ZDV on viral load is observed after 8-16 wks of therapy, but decrease in viral load is observed earlier.
- ZDV therefore may have some utility started >34 wks gestation, although utility likely to decrease as duration of antenatal therapy is reduced.
- Potential risks to woman and infant assumed to decrease the closer to delivery ZDV was started due to more limited length of ZDV exposure.
- Further studies are needed.

III. 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 recommended by the health care provider 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.

Rationale & Considerations:

- Meets current standard of care for ZDV treatment for woman's own health benefit, therefore ZDV provides direct benefit to the woman as well as potential benefit to her infant.
- Women with lower CD4+ count and/or high viral load have greatly ⇑ risk of perinatal transmission.
- Viral load ⇑ as CD4+ ⇓, therefore viral load in these woman is expected to be high.
- Due to limited prior ZDV exposure, unlikely that resistant virus present, therefore ZDV effect on viral load expected to be similar to that in women with higher CD4+.
- Maternal CD4+ count should not affect transplacental transfer of ZDV.
- The magnitude of a ZDV effect in this population is unknown.
- Since ZDV indicated for maternal health, additional risk of adding intra- & postpartum ZDV regimen is intravenous infusion in the woman and potential toxicity of 6 wks of ZDV in infant.
- Further studies are needed.

IV. 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. The regimen should be available to the woman following discussion with her health care provider, although the effectiveness of the full ACTG 076 ZDV regimen in this setting may vary depending on the clinical status of the woman. Further clinical trials should evaluate alternative approaches for such women.

Rationale & Considerations:

- These women may have viral strains with reduced susceptibility to HIV.
- Resistant virus emerges more quickly with later stage disease/lower CD4+ count.
- The prevalence of resistance will therefore be heterogeneous and vary depending on length of therapy and disease stage of the woman.
- ZDV administration might have decreased ability to reduce transmission if a significant burden of resistant virus exists.
- Further studies are needed.

V. 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.

Rationale & Considerations:

- No human data to bear on effectiveness of ZDV in this situation.
- Because maternal ZDV therapy is very limited, no effect on level of maternal virus expected.
- Administration of ZDV during labor results in infant being born with ZDV levels similar to that observed with the whole ACTG 076 regimen.
- To the extent that systemic ZDV in infant prior to exposure to HIV during passage through the birth canal plays a role in preventing intrapartum transmission, ZDV may have some utility.
- There is lack of data on oral ZDV during labor and concern regarding wide range bioavailability of oral preparations during labor, therefore no data support oral rather than IV administration.
- As much as 50% of transmission may not be prevented by an intrapartum/newborn regimen.
- If much of intrapartum transmission occurs during the last few weeks of pregnancy rather than during labor, this regimen may be ineffective.
- Risk to woman is minimal; risk to the infant is potential toxicity of 6 weeks of therapy, without *in utero* exposure.
- Further studies are needed.

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.

Rationale & Considerations:

- If mother had not received ZDV during pregnancy/labor, no circulating ZDV will be present in the infant during birth.
- Post-exposure prophylaxis studies in animals indicate that very early treatment (within hours) is necessary to prevent infection, if protection is observed.
- Relevance of animal models to perinatal transmission unknown.
- Failures of post-exposure prophylaxis have been reported; while not disproving potential efficacy, protection would clearly not be absolute.
- Further studies are needed.

SUMMARY: RECOMMENDED MONITORING OF ZDV REGIMEN FOR MOTHER AND INFANT

★ Ideally, follow-up should occur in family-centered setting, with mother/infant seen at same time in single site.

★ Comprehensive program of support services is necessary to assist maintenance of mother and child in health setting.

Maternal monitoring:

- Monitoring of HIV-infected pregnant women should be consistent with published guidelines (AHCPR).
- Monitoring of the woman should include assessment for ZDV-related hematologic and liver chemistry abnormalities.
- CD4+ monitoring consistent with published guidelines (AHCPR) is recommended.
- PCP prophylaxis should be administered if CD4+ count falls below 200.
- CD4+ count should be assessed at 6 wk and 6 mo postpartum to evaluate if antiretroviral therapy indicated after pregnancy is over.

Fetal Monitoring:

- Sonogram and non-stress testing performed as clinically indicated.

Infant Monitoring:

- CBC at birth for baseline, and at 6 and 12 wks of age.
- Administer ZDV with caution to infants born with severe anemia (< 8 gm/dl), and treatment of anemia and more intensive monitoring is warranted should drug be given.
- Evaluation for HIV infection, PCP prophylaxis and if infected, need for antiretroviral therapy should be consistent with published guidelines (AHCPR, Ped Resource Center guidelines).
- No data exist to address efficacy or lack of efficacy of ZDV therapy in infected children who require therapy and who have had *in utero* and early infancy ZDV treatment. Consultation with specialist may be considered in this situation.

SUMMARY: ISSUES REGARDING LONG-TERM EFFECTS ON WOMEN AND INFANT

- Issues of maternal concern: development of viral resistance and disease progression.
- Issues of infant concern: assessment of organ system toxicities, neurodevelopment, pubertal development, reproductive capacity and development of cancers.
- Special studies are needed, and innovative methods and support systems developed to assist in follow-up of these women and their children.
- Women enrolled in ACTG 076 should have long-term follow-up regarding disease progression and resistance in specific protocol (under development by ACTG).
- Infected and uninfected infants born to women enrolled in ACTG 076 should enroll in ACTG 219, designed to provide follow-up through age 21, with in-depth assessment of major organ functions and neuropsycholgic evaluations.
- Current and possibly new federally-funded cohort studies of HIV-infected women and their infants should be used to provide information regarding potential long-term consequences of the complete or partial ACTG 076 ZDV regimen.

~~CONFIDENTIAL~~

DRAFT ~~CONFIDENTIAL~~: 05.25.94 PLEASE DISCARD PRIOR VERSION

ACTG 076 Implications: Treatment & Screening Workshop, June 6 & 7, 1994
DRAFT Summary of Invited Consultants to PHS Task Force

CONSULTANT/OBSERVER LIST & AREA OF EXPERTISE

June 6 Treatment Workshop

E = Executive Committee [Writing Group] Consultant (responsible for writing draft recommendations)

C = Consultant

S = Speaker Consultant

O = Observer

*** = Co-Chair of June 6 Meeting**

June 7 Screening Workshop

P = Participant

O = Observer

NOTE: Those invited may stay for both days, although role may differ (eg., if "E" for 6/6 workshop, may stay as "O" for 6/7, unless invited in other role). Unless noted, attendance is confirmed.

Scientific expertise:

Obstetrics/gynecology [TOTAL 11]

E Mary Jo O'Sullivan, M.D. (Miami, FL): TASK FORCE CONSULTANT Principal Investigator on ACTG 082, the phase I trial of AZT in pregnancy that preceded ACTG 076. Obstetric Co-Chair of the ACTG Perinatal Working Group.

E Arlene Bardequez, M.D. (Newark, NJ): TASK FORCE CONSULTANT Chair of the ACTG Women's Health Committee. Protocol Chair of ACTG 255, a study to evaluate vertical transmission of AZT resistant virus from mother's on long-term AZT to their infants. Protocol Chair for protocol in development for follow-up of women from ACTG 076. Involved in perinatal HIV clinical trials of ACTG.

* E&P Howard Minkoff, M.D. (NYC, NY): Expert in HIV infection in women and in pregnancy, has written extensively on treatment options for women in pregnancy. Co-Principal Investigator for the SUNY Brooklyn site of the NICHD/NCI-funded Mother & Infants Transmission Study (MITS).

E Isaac Delke, M.D. (Jacksonville, FL): Obstetrician with experience in the care of HIV-infected women at a non-ACTG site with approximately 50 births to HIV-infected women annually.

E&P Michael Lindsey, M.D. (Atlanta, GA): Obstetrician at Grady Hospital, experienced in care of HIV-infected women. Emory NICHD ACTG site did not participate in ACTG 076.

E&P Carmen Zorilla, M.D. (Puerto Rico): Obstetric Co-Principal Investigator for Puerto Rico site of the NIAID/NICHD-funded Women & Infants Transmission Study (WITS); involved in perinatal HIV clinical trials of ACTG.

C Ruth Tuomala, M.D. (Boston, MA): Principal Investigator for the Massachusetts site of the NIAID/NICHD-funded WITS. Has developed interim guidelines for the use of AZT in pregnancy for her hospital in Boston. Involved in perinatal HIV clinical trials of ACTG.

C&P Patricia Loftman (NYC, NY): Midwife from Harlem Hospital in NYC, cares for large population of HIV-infected pregnant women.

S Rhoda Sperling, M.D. (NYC, NY): TASK FORCE CONSULTANT Obstetric Protocol Chair on ACTG 076. Obstetrician/Gynecologist Beth Israel Medical Center. Former Obstetric Co-Chair of ACTG Perinatal Transmission Scientific Committee. Expert in HIV in pregnancy, did survey of AZT use during pregnancy published in 1991 in *New England Journal of Medicine*.

P Janet Mitchell, M.D. (NYC, NY): Obstetrician from Harlem Hospital in NYC, cares for large population of HIV-infected pregnant women. Provided prior consultation to CDC and NIH on issues related to HIV-infected women.

P Maureen Shannon (San Francisco, CA): Co-Chair of HIV Committee of American College of Nurse Midwifery; from Bay Area Perinatal AIDS Center, University of California, San Francisco.

Pediatrics [TOTAL 12]

E Yvonne Bryson, M.D. (Los Angeles, CA): TASK FORCE CONSULTANT Principal Investigator for Pediatric ACTG, UCLA. Pediatric Co-Chair of the ACTG Perinatal Working Group; member of ACTG Pediatric Virology Committee. Principal Investigator on an RO-1 grant studying vertical transmission of HIV in a prospective cohort of HIV-infected women and their children; collaborating in the Ariel Project, a study evaluating factors associated with vertical transmission funded by the Pediatric AIDS Foundation.

E Gwen Scott, M.D. (Miami, FL): TASK FORCE CONSULTANT Principal Investigator for Pediatric ACTG, Miami. Expert in pediatric HIV infection. Chairperson of the Provisional Committee on Pediatric AIDS of the American Academy of Pediatrics (AAP), also representing AAP.

E Diane Wara, M.D. (San Francisco, CA): Former Chair of the Pediatric ACTG, Principal Investigator for Pediatric ACTG, UCSF. Current Chair of the Pediatric Vaccine Working Group. Principal Investigator on an RO-1 grant studying vertical transmission of HIV (BAYPAC) in a prospective cohort of HIV-infected women and their children; collaborating in the Ariel Project, a study evaluating factors associated with vertical transmission funded by the Pediatric AIDS Foundation.

* **E** Wade Parks, M.D. (NYC, NY): Chief of Pediatrics at Beth Israel Hospital, NYC. Experienced in care of HIV-infected children.

E&P Clemente Diaż, M.D. (Puerto Rico): Principal Investigator for Pediatric ACTG, Puerto Rico. Pediatric Co-Principal Investigator on Puerto Rico site of the NIAID/NICHD-funded WITS. Former Chair of Pediatric Working Group of WITS. Participated in Advisory Groups to CDC on pediatric HIV-related issues.

E Angus Nicoll, M.D. (London, England): Pediatrician. Head of Pediatric Subcommittee of MRC, PHLS Communicable Disease Surveillance Center.

C Patricia Whitley, M.D. (Atlanta, GA): TASK FORCE CONSULTANT Member of the ACTG Data Safety and Monitoring Board. Acting Chair of Pediatrics at Morehouse School of Medicine, Atlanta, GA.

S Ed Connor, M.D. (Gaithersburg, MD): Pediatric Co-Chair of ACTG 076, formerly Principal Investigator of Pediatric ACTG, Newark, NJ. Currently Clinical Director at MedImmune. Can only attend 6/6.

C&P Herman Mendez, M.D. (Brooklyn, NY): Pediatrician. Co-Principal Investigator for two prospective cohort studies of HIV-infected mothers and infants at SUNY Brooklyn (WITS and MITS) and for HRSA-funded pediatric demonstration project.

P Louis Cooper, M.D. (NYC, NY): Director, Dept. of Pediatrics at St. Luke's Roosevelt Hospital.

P Celine Hanson (Houston, TX): Pediatrician. Co-Principal Investigator at Baylor site for two prospective cohort study of HIV-infected mothers and infants (WITS and NHLBI-funded Pulmonary and Cardiac Complications of Pediatric HIV Infection [P2C2]).

P Robert Pantell (San Francisco, CA): Pediatrician at University of California, San Francisco. Member of AAP Provisional Committee on Pediatric AIDS. Developing cost:benefit evaluation of prenatal HIV testing.

Adult Infectious Disease [TOTAL 3]

E Mary Young, M.D. (Washington, D.C.): Internist at Georgetown University, expert in care of HIV-infected woman. Principal Investigator at Washington D.C. site for Women's Interagency HIV Study (WIHS).

C Charles Carpenter, M.D. (Providence, RI): Infectious disease specialist on issues of HIV in women. Participating investigator in the Women's Interagency HIV Study (WIHS), and in the HIV Epidemiology Research Study (HERS), both focusing on HIV infection in women. Can only attend 6/6.

S Robert Coombs, M.D. (Seattle, WA): Protocol Virologist for ACTG 076. Former Chair of ACTG Virology Committee. Extensively experienced in virology of HIV, including diagnostic methodology such as PCR as well as evaluation of antiretroviral resistance. Can only attend 6/6.

Pharmacokinetics [TOTAL 1]

S Stephen Weller, M.S. (Burroughs-Wellcome; NC): Senior pharmacokineticist, Division of Pharmacokinetics and Drug Metabolism, Burroughs-Wellcome Co. Participated in analysis of pharmacokinetic AZT studies in pregnant women and neonates. Can only attend 6/6.

Statistician [TOTAL 2]

E Paul Meier, Ph.D. (Chicago, IL): Statistician at Columbia University, expert in clinical trials. Member of FDA Antiviral Advisory Committee. Can only attend 6/6.

S Richard Gelber, Ph.D. (Boston, MA): Senior biostatistician, Harvard School of Public Health. Pediatric Head, Statistical Data and Safety Monitoring Board of ACTG; statistician for ACTG 076. Can only attend 6/6.

Public Health Agencies [TOTAL 2 - see also Organization list for additional P]

C&P Polly Thomas, M.D. (NYC, NY): Pediatrician. Heads NYC AIDS Surveillance for NYC Department of Public Health. Expert in pediatric HIV infection; prior consultant to CDC on screening and reporting issues.

P Laurene Mascola, M.D. (Los Angeles, CA): Pediatrician. Head Los Angeles AIDS Surveillance for Los Angeles Department of Public Health. Principal Investigator on Los Angeles Pediatric Spectrum of Disease Project, expert in pediatric HIV infection.

Law/Ethics [TOTAL 2]

P Ruth Faden, Ph.D. (Baltimore, MD): TASK FORCE CONSULTANT Behavioral scientist/ethicist, Professor at Johns Hopkins School of Public Health. Has written extensively regarding perinatal and prenatal HIV screening, with special emphasis on the impact of HIV screening on women. Can only attend 6/7.

P Marybeth Caschetta (NYC, NY): Will substitute for Theresa McGovern, J.D., Executive Director of HIV Law Project.

Behavioral Science [TOTAL 1]

P Jeanette Ickovics, Ph.D. (New Haven, CT): Behavioral scientist from Yale.

HIV-Infected Women/Community Advocates [TOTAL 9 - see also Organization list for additional P]

E&P Sallie Perryman (NYC, NY): TASK FORCE CONSULTANT Health Program Administrator, Criminal Justice Initiative, AIDS Institute, NY State Department of Health. Member of CDC HIV Advisory Committee.

C&P Lisa Hernandez (Cincinnati, OH): HIV-infected woman. Member of Community Constituency Group of ACTG and Pediatric Executive Committee of ACTG.

C&P Kelo Ammons Blenman (Boston, MA): HIV-infected woman. Works as Woman and Family Treatment Advocate for Multicultural AIDS Coalition in Boston, MA - works with HIV-infected persons interested in participating in clinical trials at adult and pediatric ACTG.

C&P Gloria Spears (Atlanta, GA): HIV-infected woman. Has participated as consultant for CDC Pediatric PCP Prophylaxis meeting. Mother of infected child.

C&P Mary Kay Whitaker (Pleasantville, NJ): HIV-infected woman and mother of infected child. Has participated in Nat Ped Res Ctr/HRSA family network meeting in NJ.

C&P Linda Horton (Baltimore, MD): HIV-infected woman, previous participant in meetings sponsored by Nat Ped Res Ctr/HRSA.

C&P Barbara Aranda-Naranjo, R.N. (San Antonio, TX): University of Texas Health Science Center. Project Coordinator for HRSA-funded Pediatric AIDS Demonstration Project. Community-based care for HIV-infected women and culture issues relating HIV-infected Hispanic women. (HRSA)

P Marian Banzhof (New Brunswick, NJ): Executive Director, New Jersey Women and AIDS Network.

P [O] Ana Dumois & Vickie Alexander (NYC, NY): Executive Director of Community Family Planning Council. Colleague Vickie Alexander will also attend as observer.

International [TOTAL 4, UK already listed under Pediatric E]

O France (ACTG 076-participating institutions: INSERM, ANRS): Dr. Delfraisy should select the person **To be contacted**

C WHO: Joep M.A. Lange, M.D. (Geneva, Switzerland): Chief, Clinical Research and Product Development, Division of Research and Intervention Development, Global Programme on AIDS.

O WHO: Michael Merson **To get letter**

O Canada: Gerry Bally: Member of Canadian Task Force on ACTG 076. **To get letter**

O United Kingdom: Angus Nicoll will represent UK (see **Pediatric: E**)

Other Invited Organization Representatives [TOTAL 27, AAP already listed under Pediatric E]

AIDS ORGANIZATIONS [9]

- National Association of Persons with AIDS
  P Gary Rose: Substitute for Cornelius Baker, Director.

- National Black Woman's Health Project
  P Cynthia Newbille: Executive Director. **Pending confirmation**

- National Coalition of Hispanic Health and Human Services Organization
  P Merlene Robb

- National Minority AIDS Council
  P Paul Kawata: Executive Director; possible alternate.

- Pediatric AIDS Foundation
  P Art Ammann, M.D. (Los Angeles, CA): Medical Director of Pediatric AIDS Foundation and Director of The Ariel Project. Expert in pediatric HIV infection. May only be able to attend 6/7.

- New York AIDS Institute
  C Bruce Agins, M.D.: Acting Director; infectious disease physician **Pending confirmation**

- AmFAR
  O Ellen Cooper, M.D. **To get letter**

- AIDS Action Council
  O Dan Bross **To get letter**

- National Pediatric Resource Center
  O Mary Boland, R.N. (Newark, NJ): Nurse, expert in pediatric HIV infection. Director AIDS Program, Children's Hospital of New Jersey. Principal Investigator for HRSA-funded National Pediatric HIV Resource Center.

MEDICAL [8]

- American Medical Association
  P James Allen, M.D.: Vice President, Science, Technology & Public Health.

- National Medical Association
  P Rosemary Davis: Executive Director **Pending confirmation**

- American College of Obstetricians/Gynecologists
  P Stanley Zinberg: Director, Practice Activities **To get letter**

- American Academy of Pediatrics
  E&P Gwen Scott, M.D. (see **Pediatric: E**)

- American Nurses Association
  O Virginia Belb **To get letter**

- Black Nurses Association
  O Sedako Holmes **To get letter**

- Council of Dept. Obstetric/Gynecology Chairman
  O Gerson Weiss, M.D.: Chairman of Ob/Gyn at UMDNJ, Newark. **To get letter**

- American Psychological Association
  O Jacquelyn Gentry: Director. Will send alternate.

PUBLIC HEALTH [6]

- Council on State and Territorial Epidemiologists
  P Richard Hoffman, M.D.: State Epidemiologist, Colorado Department of Public Health. **Pending confirmation**

- Association of State and Territorial Health Officers
  P Llyod Novick, M.D.: New York State Dept. of Health

- National Association of State and Territorial AIDS Directors
  P Kathleen Edwards

- U.S. Council of Mayors
  O Mara Patermaster: Senior staff.

- Association of Maternal and Child Health Directors
  O Catherine Hess: Executive Director. **Pending confirmation**

- Association of State and Territorial Public Health Laboratory Directors
  O David Carpenter **Pending confirmation**

OTHER ORGANIZATIONS [5]

- American Social Health Association
  O Linda Alexander

- American Public Health Association
  O Margaret Anderson

- Planned Parenthood
  O Pamela Maraldo: President; will send alternate.

- Burroughs-Wellcome
  O Mary Elkins, R.N., M.S.: Head, Antiviral Therapy Section, Clinical Research Division, Burroughs-Wellcome Co. Involved in design of ACTG 076. Can only attend 6/6.

- Institute of Medicine
  O Leslie Hardy: Director of AIDS Activities

PHS Agency Staff [TOTAL 37]

NIH [TOTAL 14]

* **[E facilitator]&P** Lynne Mofenson, M.D. (PAMA, NICHD): TASK FORCE MEMBER Pediatric infectious disease specialist, expert in pediatric and perinatal HIV infection. Directs NICHD Perinatal Clinical Trials Network and clinical trials in HIV-infected children and pregnant women, including ACTG 076. Medical Officer on ACTG 185 (HIVIG trial). Former State Epidemiologist, Massachusetts Dept. of Public Health.

[E facilitator]&S James Balsley, M.D., Ph.D. (DAIDS, NIAID): TASK FORCE MEMBER Branch Chief, Pediatric Medicine Branch, Division of AIDS, NIAID; directs scientific activities of Pediatric ACTG. NIAID Medical Officer for ACTG 076.

O Jack Moye, M.D. (PAMA, NICHD): Pediatrician, expert in pediatric HIV infection. PAMA Branch NICHD Medical Officer on ACTG 076.

S Mary Glenn Fowler, M.D. (DAIDS, NIAID): Pediatrician, DAIDS.

O Philip Pizzo, M.D. (NCI): Pediatrician, expert in pediatric HIV infection and therapies. **To get letter**

O Mary Culnane (DAIDS, NIAID): DAIDS staff participant on ACTG 076.

O Anne Willoughby, M.D., M.P.H. (PAMA, NICHD): Chief, Pediatric, Adolescent & Maternal AIDS Branch, NICHD. **To get letter**

O Senior Staff **To get letter**
William Paul, M.D. (OAR)
Jack Whitescarver, Ph.D. (OAR)
Lewellys Barker, M.D. (NIAID)
William Duncan, Ph.D. (NIAID)
Jack Killen, M.D. (NIAID)
Tony Fauci, M.D. (NIAID)
Duane Alexander, M.D. (NICHD)

CDC [TOTAL 3+]

[E facilitator]&P Martha Rogers, M.D. (Division HIV/AIDS): TASK FORCE MEMBER Chief, Epidemiology Branch, Division HIV/AIDS, expert in perinatal transmission of HIV, responsible for development of policy on screening for HIV infection in pregnant women and other policy issues related to pediatric/perinatal HIV.

O Helene Gayle, M.D.: TASK FORCE MEMBER Agency AIDS Coordinator, Office of Health, Bureau for Research and Development, USAID. Pediatrician, knowledgeable about perinatal HIV transmission; international expertise.

O Herbert Peterson, M.D.: Obstetrician/gynecologist. Chief of Women's Health and Fertility Branch, Division of Reproductive Health, CDC. **To get letter**

Additional staff TBN by Dr. Rogers

FDA [TOTAL 4]

S Steve Gitterman, M.D.: Medical Officer, Antiviral Division, FDA. Alternate for Dr. Feigal.

O Randolph Wykoff, M.D., M.P.H., T.M.: Associate Commissioner, Office of AIDS and Special Health Issues.

S James Farrelly, Ph.D.: Chief Pharmacologist/toxicologist, FDA.

O Sam Maldonato, M.D.: Medical Officer responsible for Burroughs-Wellcome AZT labeling indication review.

HRSA [TOTAL 4]

[E facilitator] Patricia Salomon, M.D.: TASK FORCE MEMBER Associate Bureau Director for Clinical Affairs, Bureau of Primary Health Care, HRSA.

O Steve Bowen, M.D.: Associate Director for HIV. Directs and coordinates AIDS activities at HRSA. Responsibilities include overseeing provider education and linkages with community health programs.

O Beth Roy: Chief, Hemophilia and AIDS Branch, Maternal and Child Health Bureau, HRSA.

O Elaine Daniels, M.D.: Chief, Health Professions/HIV Education Branch, HRSA. Responsible for coordinating HIV education activities for community health providers.

AHCPR [TOTAL 2]

O David Lanier, M.D.: TASK FORCE MEMBER Health Policy Analyst, AHCPR

O David Adkins, M.D., M.P.H.: Science Advisor to U.S. Preventive Services Task Force, Office of Disease Prevention and Health Promotion, expert in research and health policy related to HIV screening. Currently writing the U.S. Preventive Services Task Force recommendations for HIV screening.

SAMHSA [TOTAL 3]

O&P Wendell McConnell, M.D.: Center for Substance Abuse Treatment. **To get letter**

O Mel Haas, Ph.D.: Center for Mental Health Services. **To get letter**

O Lucille Perez, M.D.: Center for Substance Abuse Prevention. **To get letter**

Department of Health & Human Services, Office of the Secretary [TOTAL 3]

O Patsy Fleming: TASK FORCE MEMBER Special Assistant to the Secretary, DHHS.

O Kristine Gebbie, R.N.: Office of National AIDS Policy. **To get letter**

O Frances Page, R.N., M.P.H.: TASK FORCE MEMBER Office of National AIDS Policy.

Other Federal Agency Invitees [TOTAL 5]

- HCFA
  O Clarence Boone **Will send alternate**

- Office of Surgeon General
  O M. Joycelyn Elders, M.D. **To get letter**

- Department of Defense
  O Merlin Robb, M.D.

- Office of Population Affairs **To get letter**

- OPRR **To get letter**

ACTG 076 Workshop: Numbers of Consultants/Observers

	6/6 E (Exec. Committee)	6/6 C (Consultant)	6/6 S (Speaker)	6/7 P (Participant) [# overlap with 6/6 E or C]	O (Invited Observers)
Obstetrics [11]	6	2	1	6 [4]	
Pediatrics [12]	6	2	1	5 [2]	
Internal Med [3]	1	1	1		
Pharmacol. [1]			1		
Statistics [2]	1		1		
Public Health [2]		1		2 [1]	
Law/Ethics [2]				2	
Beh. Science [1]				1	
HIV + ♀/ Advocates [9]	1	8		9 [7]	1
International [5;1 overlap = 4]	[1] Nicolls Ped E	1			3
AIDS Organiz. [9]		1		5	3
Medical Organiz. [8;1 overlap = 7]				4 [1] Scott Ped E	4
Pub. Health Organiz. [6]				3	3
Other Organiz. [5]					5
PHS: NIH [14]	2 Mofenson/Balsley facilitator		2 [1]	1 [1]	11 [7 Sr Staff]
PHS: CDC [3+]	1 Rogers facilitator			1 [1]	2+
PHS: FDA [4]			2		2
PHS: HRSA [4]	1 Salomon facilitator			1 [1]	3
PHS: AHCPR [2]					2
PHS: SAMHSA [3]				1	2
PHS: OASH [3]					3
PHS: Other [5]					5
TOTAL: 111+ [130+ - 19 overlap]	16 [+4 facilitators]	16	9 [1 overlap]	41 [18 overlap]	49+

Public Health Service/Health and Human Services Task Force on Use of Zidovudine to Prevent Perinatal HIV Transmission

Minutes: April 14, 1994 meeting **FINAL VERSION - PLEASE REPLACE PRIOR VERSION**

PHS Members

Present: Lynne Mofenson MD (NIH), James Balsley MD (NIH), Martha Rogers MD (CDC), Steve Gitterman MD (FDA), Patricia Salomon MD (HRSA), David Lanier MD (AHCPR), Patsy Fleming (OASH)

Absent: Helene Gayle MD (CDC), David Feigal MD (FDA - Dr. Gitterman substituting)

Outside Consultants

Present: Arlene Bardequez MD, Mary Jo O'Sullivan MD, Gwen Scott MD, Sallie Perryman, Barbara DeBuono MD

Absent: Ruth Faden PhD, Margaret Hamburg MD, Patricia Whitley-Williams MD, Yvonne Bryson MD, Rhoda Sperling MD

Observers Steve Bowen MD (HRSA), Francis Page (NAPO), Wendy Wertheimer (OAR)

Dr. Kirschstein welcomed the Task Force members.

Dr. Mofenson reviewed the Task Force Goals. Treatment recommendations and prenatal testing recommendations are the highest priority for the Task Force. Dr. Mofenson proposed that the Task Force be the Executive Planning Committee for a two or three day meeting to specifically address treatment and testing issues that would involve a larger number of outside consultants and community members. The first day would be devoted to treatment recommendations, the second to testing recommendations, with a possible third day for wrap-up. There would be a core group of approximately 30 PHS staff and consultants that would be responsible for formulating recommendations, and a group of approximately 30 relevant observers to contribute to the discussion. While there may be overlap between the participants for the treatment and testing meetings, each day might have separate lists of participants/observers.

The meeting would be planned for early June. The major work of the Task Force will be to review and discuss the issues to be addressed at the meeting and recommend relevant persons to attend the meeting. In parallel, activities involving other agencies, such as HRSA and FDA, will be ongoing, with report to the Task Force on progress.

Dr. Balsley reviewed the design and results of ACTG 076 and answered questions. Pertinent materials were enclosed in the April 14 briefing book.

Dr. Mofenson then reviewed ongoing activities within the PHS and the planned MMWR publication (pertinent materials in the April 14 briefing book).

Dr. Mofenson distributed two documents, "Outline of ACTG 076 Implications and Task Force Issues" and "Proposed Timelines and Action Items for the 076 Task Force", which was used by the group as a basis for discussion. Task Force members agreed to the goals, plans and timelines. Ms. Wertheimer, OAR, indicated that OAR will coordinate finding an appropriate location and date for the planned meeting in early June.

Dr. Bowen noted that HRSA and CDC have begun discussion regarding potential funding of 1 to 3 demonstration projects that would evaluate methods of prenatal HIV counseling and testing as well as methods to provide long-term follow-up to mothers and infants receiving the ACTG 076 AZT regimen. He also noted Title 1 federal funding recipients could be requested to delineate their plans for follow-up to such mothers and children as part of their funding application.

Ms. Perryman and Ms. Fleming discussed the need to have community representation at the June meetings; some suggestions for representatives were then provided by Task Force members. Ms. Perryman provided the group with a copy of a press release from a New York City activist group, CURE AIDS, to illustrate some of the perceptions the community may have regarding ACTG 076 (copy enclosed). A copy of a memo from the ACTG Pediatric Executive Committee regarding the implications of the preliminary results of ACTG 076 was also provided to the Task Force by OAR (copy enclosed).

Dr. Gitterman briefly discussed the FDA regulatory process in reference to application from Burroughs-Wellcome for an AZT labeling indication for prevention of vertical transmission. He offered to present to the Task Force in more detail at the next meeting the FDA process of review and regulation and the responsibilities of the manufacturer regarding adverse events and long-term follow-up.

Dr. Mofenson distributed a draft outline of the "Proposed ACTG 076 Treatment Implications Meeting: Plan and Potential Invited Participants (NIH portion of the 2-day meeting)". The remainder of the meeting focused on a discussion of topics for this portion of the meeting and potential invitees. There was a consensus that there was a need for participants that were not directly involved in ACTG 076 to be part of the meeting, and suggestions were discussed. Dr. Mofenson requested that Task Force members provide her and Dr. Rogers recommendations for participants by Tuesday April 19.

Dr. Rogers then briefly outlined the approach that CDC plans for the prenatal screening meeting, which she will discuss in more detail at the next meeting. There was agreement by Task Force members that invitations to the June meeting should be sent out by NIH and CDC within the next 2 weeks and general planning be ongoing, due to the short timelines for preparation for this meeting.

The date for the next Task Force meeting will be **May 20, 1994**, approximately 10am to 5pm. The location and exact times will be announced in the near future.

2. Develop plans for Title 1 requirement for follow-up of patients receiving the ACTG 076 AZT regimen for discussion with Task Force at next meeting.

3. Share "responses" document prepared by the HRSA AIDS Advisory Committee regarding ACTG 076; provide document for distribution prior to next meeting.

4. Develop plans, outline and timelines for constituent meeting(s) regarding ACTG 076 results to present to Task Force at next meeting.

FDA

1. Review FDA process of labeling indication assessment for the Task Force at the next meeting.

OAR

1. Delineate location and dates for the June meeting (targeting June 8, 9, 10).

Enclosures:

Press release from CURE AIDS, NYC

Memo from ACTG Pediatric Executive Committee

ACTION ITEMS FOR NEXT MEETING

Task Force Members:

1. Fax names of suggested participants to Dr. Mofenson by close of business Tuesday, April 19 (format for recommendations attached on last page of meeting planning document).

NIH:

1. Following receipt of suggested participants from Task Force members, develop a list of participants for June meeting. This list will be shared with the Task Force members.

2. Begin process of inviting participants to June meeting.

3. Begin draft document of treatment issues and options for the consultants to review at June meeting; the draft will be shared with Task Force members for discussion at next meeting.

4. Begin evaluation of how ongoing NIH-funded natural history studies of HIV infection in women and children (WITS, P2C2, WIHS) could provide information regarding long-term effects of the ACTG 076 regimen of AZT in pregnant women and their infants who receive the regimen.

CDC:

1. Develop list of suggested participants for June meeting. This list will be shared with the Task Force members.

2. Begin process of inviting participants to June meeting.

3. Draft document of prenatal testing issues and options for the consultants to review at June meeting; the draft will be shared with Task Force members for discussion at next meeting.

4. Outline issues regarding development of a long-term follow-up registry for infants with *in utero* exposure to AZT for further discussion by Task Force at next meeting.

5. Begin evaluation of how ongoing CDC-funded natural history studies of HIV infection in women and children (WIHS, PSD, ASD) could provide information regarding long-term effects of the ACTG 076 regimen of AZT in pregnant women and their infants who receive the regimen.

HRSA

1. Share plans for demonstration project(s) delineating counseling/testing and follow-up with Task Force at next meeting.

Public Health Service/Health and Human Services Task Force on Use of Zidovudine to Prevent Perinatal HIV Transmission

Minutes: May 20, 1994 meeting

PHS Members

Present: Lynne Mofenson MD (NIH), James Balsley MD (NIH), Martha Rogers MD (CDC), Steve Gitterman MD (FDA), Patricia Salomon MD (HRSA), David Lanier MD (AHCPR), Patsy Fleming (OASH), Frances Page RN MPH (NAPO)

Absent: Helene Gayle MD (CDC), David Feigal MD (FDA - Dr. Gitterman substituting)

Outside Consultants

Present: Arlene Bardequez MD, Sallie Perryman, Barbara DeBuono MD, Patricia Whitley-Williams MD

Absent: Mary Jo O'Sullivan MD, Gwen Scott MD, Ruth Faden PhD, Margaret Hamburg MD, Yvonne Bryson MD, Rhoda Sperling MD

Observers Shelly Gordon (HRSA), Elizabeth Bishop

Dr. Mofenson reviewed minutes from the April 14 meeting; Ms. Perryman requested a correction of the text of her comments from that meeting to reflect the term "perception" rather than "misperception"; the minutes will be amended accordingly and the final version distributed to Task Force members (see enclosure; **please discard** prior April 14 minutes).

Dr. Mofenson then reviewed progress on the Action Items from the April 14 meeting, which were used as a basis for the subsequent discussion.

Dr. Mofenson reviewed discussions by investigators from the NIAID/NICHD-funded Women and Infants Transmission Study regarding evaluation of potential long-term AZT effects on mothers and infants. This evaluation was given high priority by the investigators.

Dr. Bardequez reviewed progress on the development of an ACTG protocol to provide follow-up for the women from ACTG 076. The primary objectives of the protocol will be to evaluate maternal viral load, conversion from non-syncytia-inducing to syncytia-inducing phenotype, and genotypic analysis for the development of mutations associated with resistance. Women would be followed every 6 months for 3 years, with overlap with the labor & delivery and 6 month follow-up visit of ACTG 076. Each visit will include physical exam, including gynecologic evaluation with a pap smear, and immunologic and virologic evaluations. Women who have completed the ACTG 076 protocol will be able to enroll and be evaluated as part of the analysis. The protocol is currently having the statistical analysis section developed, following which expedited approval by the various ACTG committees is anticipated.

Dr. Mofenson reviewed the meeting location (Bethesda Holiday Inn) and the available room. Following discussion, it was decided that a "U"-shape format would be most conducive for the meeting, given the shape of the reserved room - the consultants would be seated in a "U" shaped table, and the observers would have row seating available at the open portion of the "U".

Progress on invitations to participants for the combined June 6 and 7 Workshop was reviewed by Dr. Mofenson. Several Task Force members and consultants had provided Dr. Mofenson with suggested names, many of which are reflected in the current draft list of participants. A draft of the combined June 6 & 7 Workshop participant list was sent with the materials sent to the Task Force members and consultants for this meeting.

Dr. Mofenson reviewed the status of each participant; most outside consultants have been personally contacted by Dr. Mofenson and have agreed to participate. Several additional representatives from organizations were suggested by Task Force members; it was agreed that the American Nurses Association, Black Nurses Association, AIDS Action Council, and Council of Chairman of Obstetrics/Gynecology would be contacted to participate as observers. Dr. Mofenson will have letters sent to these organizations inviting them to both days of the Workshop as observers. A revised, updated draft participant list is enclosed; ; **please discard** prior participant list in May 20 meeting materials.

Dr. Mofenson discussed the draft agenda for the June 6 Treatment Workshop that was included in the mailed meeting materials. The morning agenda includes presentations with time for questions; presentations would include a brief update on regulatory issues from the FDA, a detailed review of the ACTG 076 results, discussion of potential long-term effects and plans for long-term follow-up of infants and women. The afternoon would be devoted entirely to discussion of therapy recommendations, including treatment monitoring and follow-up.

Co-chairs for the meeting are Dr. Mofenson and Drs. Howard Minkoff (obstetric) and Wade Parks (pediatric). The afternoon discussion section would be moderated by Drs. Minkoff and Parks. In the evening there will be a working dinner and meeting time, during which the writing group will summarize recommendations for the PHS. Drs. Mofenson, Balsley, Rogers and Salomon will be available to facilitate this process.

Discussion of the appropriate terminology for the writing group ensued, and it was decided that a better terminology would be "Executive Committee", as any recommendations developed by this group would be preliminary and need to go through appropriate clearance before being viewed as PHS policy.

There was discussion and delineation of the review process for the treatment recommendations. The suggested process for review was: following generation of the June 6 Executive Committee document, Dr. Mofenson would ensure rapid generation (within a week) of a document for the Executive Committee to review with a rapid turn-around (eg. 48 hours). Following the Committee's approval, the document would be circulated to the Task Force members for rapid comment (48 hours). Following comment, each PHS agency representative will ensure rapid review by their respective PHS agencies; it would be desirable to have this accomplished in approximately one weeks time. Following

agency review, the document would be sent by Dr. Mofenson to Dr. Lee's office for approval; Ms. Fleming volunteered to assist with rapid review at this level.

The goal would be to have the recommendations published as a supplement to the MMWR in August. Dr. Rogers will contact the MMWR office regarding approval for an August supplement publication. To meet this schedule, the document needs PHS approval by mid-July.

Dr. Balsley distributed a draft Treatment Workshop background document to Task Force members and consultants, which was then used as a basis for further discussion. It was advised that the document not provide current "straw-man" recommendations for the writing group, but rather outline the relevant issues and scientific data and potential risks in a briefer, bullet-like fashion. Dr. Balsley agreed to revise the draft Treatment Issues document accordingly.

Dr. Rogers described the planned format for the Screening meeting. Briefly, following a short summary of the prior day's deliberations by Drs. Minkoff and Parks, the focus will be on four major issues: 1) what are goals of counseling/testing of pregnant women; 2) should screening be universal or prevalence-based targeted; 3) what should be the content of pre-test counseling and the level of consent; 4) how to minimize any coercive appearance and adverse consequences of counseling/testing.

Similar to the June 6 Treatment Workshop, materials will be sent to the consultants and observers ahead of time. Following brief presentations, specific consultants will be called upon to offer specific comments during the meeting, followed by general discussion (5 minutes comment, 5 minutes discussion). Each of the sessions will be led by two co-chairs (one consultant and one CDC staff).

The materials will include a background document reviewing each of these four issues and relevant data, as well as relevant papers. These materials are currently being developed, and will be provided to Dr. Mofenson by May 31 to ensure the mailings are sent and received prior to the meeting.

The process for the Screening Workshop will differ somewhat from the Treatment Workshop. There will not be an Executive Committee/writing group for the Screening Workshop. Following the meeting, the CDC will develop/revise a document which would then be sent to the consultants for their comment. A period of public comment may also be desired prior to finalization of the screening recommendations. Thus, it is anticipated that the publication of the treatment recommendations would precede that for screening.

There was general discussion regarding what meeting documents would go to whom. There was consensus that copies of the ACTG 076 Clinical Trials Alert, Q & A, 3-page Summary of Results and MMWR should be sent to all those invited, including observers. Additionally, it was decided that the specific materials prepared by Dr. Balsley and the CDC should also be sent to all invited, including observers. A confidential copy of the ACTG 076 Executive Summary that includes detailed tables would be sent only to the June 6 Executive Committee/writing group consultants.

Dr. Salomon then updated the Task Force on activities undertaken by HRSA. The June State-of-the-Art HRSA HIV conference call (an expert panel discussion that is accessible to any provider via prior registration, with ability to send in questions) will focus on pediatric HIV infection and issues related to ACTG 076.

The National Pediatric HIV Resource Center [NPHRC] (funded by HRSA) is also sponsoring a Public Policy Conference May 23-24, 1994 at the Vista Hotel in Washington, D.C.. This meeting will include a panel discussion of ACTG 076 (Dr. Mofenson will participate, and Ms. Culnane from DAIDS, NIAID will represent Dr. Balsley), followed by several small workshops on clinical and policy implications of ACTG 076. Additionally, on May 21, NPHRC and HRSA will have a small focus group consisting of HIV-infected women discuss implications of ACTG 076. Several of the women participating in this focus group will also be invited to participate as consultants to the June 6-7 Workshops.

HRSA, in conjunction with SAMSA, will be having one, possibly two, meetings of working groups on prevention of perinatal transmission of HIV; the first meeting is May 25, 1994 at the Washington Vista Hotel. The working group is composed of HRSA grantees (providers, organizations, and patients) to offer the opportunity to articulate their thoughts regarding the implications of ACTG 076.

Following the development of PHS treatment recommendations, HRSA will have a open forum meeting (planned for August or September) to discuss plans for implementation.

HRSA is planning to fund, in conjunction with CDC, several demonstration projects that would assess the kinds of interventions and services that are needed to bridge the gap between recommendations and their implementation.

Dr. Salomon discussed the possibility of using HRSA-funded care sites to pursue practice-based research that could assist in long-term follow-up of infants with *in utero* AZT exposure; such research could be subsidized with additional funding by HRSA. Dr. Mofenson discussed the desirability of bringing together the relevant HRSA grantees with ACTG investigators involved in ACTG 219 to delineate what specific long-term follow-up might be done in the context of patient care. A meeting might be planned in late summer to fall.

Dr. Gitterman reviewed the current status of the FDA regulatory process. He delineated the extent of independent data review that is provided by the FDA Medical Officer, and the types of presentations that will occur at the Antiviral Advisory Committee review of the Burroughs-Wellcome application for new labeling indication. He also discussed that possible Phase IV monitoring of long-term effects on mothers and infants that can be required of the company by the FDA. Currently, the Antiviral Advisory Committee meeting on this indication is planned for July 29, 1994. Dr. Gitterman will provide a brief summary of this process at the June 6 Workshop. The chief pharmacologist at FDA, John Farrelly, will give a short discussion regarding potential long-term effects of nucleosides at the June 6 Workshop as well.

The Task Force discussed whether additional meetings of the Task Force would be necessary following the June 6-7 Workshop. It was decided by the members and consul-

tants that further on-site meetings were not viewed as necessary at present, as the primary goals of the Task Force will have been accomplished at the June 6-7 Workshop. If necessary, Dr. Mofenson could schedule a conference call if additional consultation following review of the treatment recommendations was necessary.

Ms. Fleming discussed the possible development of an "oversight" group, possibly centered at OASH, to ensure that the agencies responsible for implementing the recommendations from the Task Force that are adopted by the PHS are accountable for such implementation. She stated she would have further discussions at OASH regarding the future formation of such a PHS group.

Dr. Mofenson thanked the Task Force members and consultants for their assistance is development of the June 6-7 Workshop.

ACTION ITEMS

1. Observer invitations will be sent to American Nurses Association, Black Nurses Association, AIDS Action Council, and Council of Chairman of Obstetrics/Gynecology. Appropriate names and telephone numbers were provided to Dr. Mofenson. Dr. Mofenson will revise the draft participant to provide to the Task Force members and consultants.

2. Dr. DeBuono will contact ASTHO regarding provision of an alternative Health Officer for the meeting to Dr. Mofenson, as she will not be able to attend the June workshop.

3. Drs. Rogers and Balsley will provide the background materials under development for the June 6-7 Workshop to Dr. Mofenson by May 31 for distribution to those invited to the Workshop. Dr. Rogers also needs to provide Dr. Mofenson with the June 7 Workshop Agenda.

4. All participants, including observers, will receive the agenda, ACTG 076 Clinical Trials Alert, Q & A, ACTG 076 Executive Summary, the Treatment Background document (Dr. Balsley to finalize) and Screening Background document (Dr. Rogers to finalize). A confidential draft of the detailed ACTG 076 Fxecutive Summary will be provided to the Executive Committee of the Treatment Workshop. This mailing will be sent by federal express to participants on June 1 (assuming that materials are received by Dr. Mofenson on May 31).

5. Dr. Rogers will contact the MMWR Publication Office regarding the feasibility of publication of treatment recommendations as an August MMWR Supplement; she will let Dr. Mofenson know regarding her negotiations.

6. The Treatment Background document being developed by Dr. Balsley will remove any draft recommendations and be re-formatted to be more "bullet-like". It was recommended that specific risk:benefit information necessary to be provided to the woman for informed decision-making regarding treatment be included by the Executive Committee recommendations.

7. Dr. Mofenson will have further discussion of the role of Co-Chair and Moderator for the June 6 Workshop with Drs. Minkoff and Parks prior to the Workshop.

8. Drs. Rogers and Salomon will attend the June 6 Executive Committee evening working session in addition to Drs. Mofenson and Balsley to facilitate writing of draft recommendations.

9. Drs. Mofenson, Rogers and Salomon will have further discussion regarding a potential late summer-fall meeting of investigators regarding the potential for practice-based research on long-term effects of AZT on infants (and possibly mothers).

10. Following development and approval of draft Treatment Recommendations by the Executive Committee, Dr. Mofenson will circulate the recommendations to the Task Force members and consultants for rapid review. PHS Agency Task Force members will be responsible for ensuring timely review of the recommendations by their Agency Directors.

Enclosures:

Final April 14, 1994 Task Force minutes; PLEASE DISCARD prior minutes

Revised participant list for June 6-7 meeting; PLEASE DISCARD prior list

May 20 meeting materials (only for those not in attendance at the May 20 meeting)

May20.Min 05.25.94