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Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus

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Contents

Introduction 1
Background 2
General Principles Regarding Treatment Recommendations 6
Clinical Situations and Recommendations for Use of ZDV to Reduce Perinatal Transmission 7
Recommendations for Monitoring the ZDV Regimen for Mothers and Infants 13
Potential Long-Term Effects of ZDV Therapy for Mothers and Infants and Recommendations for Follow-Up 14
Conclusion 15

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Executive Committee and U.S. Public Health Service Task Force

On June 6, 1994, the U.S. Public Health Service convened a workshop in Bethesda, Maryland, to develop recommendations for the use of zidovudine to reduce the risk for perinatal transmission of human immunodeficiency virus (HIV). The recent results of AIDS Clinical Trials Group Protocol 076, a controlled clinical trial sponsored by the National Institutes of Health in collaboration with the National Institute of Health and Medical Research and the National Agency of Research on AIDS in France, indicate that zidovudine administered to a selected group of HIV-infected women and their infants can reduce the risk for perinatal transmission of HIV by approximately two-thirds. The implications of these results for use of zidovudine in HIV-infected pregnant women and neonates were discussed at the workshop. The following persons participated in the workshop and either served as the Executive Committee writing group that developed the recommendations or were members of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal HIV Transmission.

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Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus

Summary

*These recommendations update the interim guidelines (*1*) developed by the U.S. Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal transmission of human immunodeficiency virus (HIV) infection. The recently reported results of AIDS Clinical Trials Group Protocol 076 demonstrated that ZDV administered to a selected group of HIV-infected pregnant women and their infants can reduce the risk for perinatal HIV transmission by approximately two-thirds. The regimen used in this trial included antenatal oral administration of ZDV beginning at 14–34 weeks of gestation and continuing throughout pregnancy, followed by intrapartum intravenous ZDV and postnatal oral administration of ZDV to the infant for 6 weeks after delivery.*

This document summarizes the results of the trial, discusses limitations in the interpretation of the results, reviews the potential long-term adverse effects of this ZDV regimen for infants and women, and provides recommendations for the use of ZDV to reduce perinatal transmission and for medical monitoring of pregnant women and infants receiving this therapy. Because the clinical status of many HIV-infected women may differ from that of the women in this trial, the recommendations should be tailored to each woman's clinical situation. The potential benefits, unknown long-term effects, and gaps in knowledge about her specific clinical situation must be discussed with the woman. This information is intended to provide a basis for discussion between the woman and her health-care provider so that the woman can weigh the risks and benefits of such therapy and make informed decisions about her treatment.

INTRODUCTION

Worldwide, perinatal (i.e., mother-to-infant) transmission accounts for most human immunodeficiency virus (HIV) infections among children. In the United States, approximately 7,000 infants, 1,000–2,000 of whom are HIV infected, are born to HIV-infected women each year (*2*). In the United States, HIV is currently the seventh leading cause of death in children 1–4 years of age (*3*) and the fourth among women 25–44 years of age (*4*).

The ideal approach to reducing perinatal transmission is to prevent HIV infection among women. However, despite ongoing efforts to provide education about HIV prevention, the incidence of infections among women of reproductive age in the United States is increasing in some areas (*2*). In the United States, where safe alternatives to breast milk are available, HIV-infected women are advised to refrain from breastfeeding to avoid postnatal transmission of HIV to their infants (*5*). However, refraining

from breastfeeding will not prevent transmission occurring in utero or intrapartum, and strategies to reduce transmission during these periods are being evaluated.

The recently reported interim results of the Acquired Immunodeficiency Syndrome (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 and the National Agency of Research on AIDS in France, indicate that zidovudine (ZDV) administered to a selected group of HIV-infected pregnant women and their infants can reduce the risk for perinatal HIV transmission by approximately two-thirds (*1,6*). This use of ZDV has the potential to substantially reduce the rate of perinatal transmission, which would reduce overall child mortality. However, the results of this study are directly applicable only to HIV-infected women with characteristics similar to those of the women who entered the study, and the long-term risks of ZDV used in this manner are not known.

On June 6–7, 1994, the U.S. Public Health Service convened a workshop, "Use of ZDV to Prevent Perinatal HIV Transmission (ACTG Protocol 076): Workshop on Implications for Treatment, Counseling, and HIV Testing." The medical, scientific, public health, and legal communities and interested professional, community, and advocacy organizations were represented. The workshop addressed two issues related to the results of ACTG Protocol 076: a) treatment recommendations for the use of ZDV to reduce perinatal transmission of HIV and b) the implications of the trial results for HIV counseling and testing.

This report summarizes the conclusions of the workshop with regard to the use of ZDV to reduce perinatal transmission, provides recommendations for treatment options for HIV-infected pregnant women and their newborns and medical monitoring for pregnant women and neonates receiving ZDV, and discusses issues related to long-term follow-up of women and their children who have received ZDV.

BACKGROUND

Summary of Results of ACTG Protocol 076

On February 21, 1994, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health and Human Development announced the interim results of a randomized, multicenter, double-blind, placebo-controlled clinical trial, ACTG Protocol 076. Eligible participants were HIV-infected pregnant women at 14–34 weeks of gestation who had received no antiretroviral therapy during their current pregnancy, had no clinical indications for antepartum antiretroviral therapy, and had CD4+ T-lymphocyte counts ≥200/μL at the time of entry into the study (Box 1). The study began in April 1991; as of December 20, 1993, the time of the interim analysis, 477 women had been enrolled and 421 infants born. The racial/ethnic distribution of the HIV-infected women enrolled in the trial was similar to that of the total population of HIV-infected women in the United States.

Enrolled women were assigned randomly to receive a regimen of either ZDV or placebo. The ZDV regimen included oral ZDV initiated at 14–34 weeks of gestation and continued throughout the pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for 6 weeks after delivery (Box 2). The placebo regimen was administered identically. Blood specimens were obtained for HIV culture

BOX 1. Eligibility criteria for HIV-infected pregnant women participating in AIDS Clinical Trials Group Protocol 076

- Pregnancy at 14–34 weeks of gestation.
- No antiretroviral therapy during the current pregnancy.
- No clinical indications for antenatal antiretroviral therapy.
- CD4+ T-lymphocyte count ≥200 cells/μL at the time of entry into the study.

BOX 2. Zidovudine regimen from AIDS Clinical Trials Group Protocol 076

- Oral administration of 100 mg of zidovudine (ZDV) five times daily, initiated at 14–34 weeks of gestation and continued throughout the pregnancy.
- During labor, intravenous administration of ZDV in a 1-hour loading dose of 2 mg per kg of body weight, followed by a continuous infusion of 1 mg per kg of body weight per hour until delivery.
- Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg of body weight per dose every 6 hours) for the first 6 weeks of life, beginning 8–12 hours after birth.

from all infants at birth and at 12, 24, and 78 weeks of age. A positive viral culture was considered indicative of HIV infection. Sera from the infants at 15 and 18 months of age also were tested for HIV antibody.

The Kaplan-Meier method (*7*) was used to estimate the rate of perinatal transmission at 18 months of age among the 364 children whose HIV infection status was known on the basis of culture and who therefore were included in the interim analysis. The estimated transmission rate was 25.5% among the 184 children in the placebo group (95% confidence interval [CI]=18.4%–32.5%), compared with 8.3% among the 180 children in the ZDV group (95% CI=3.9%–12.8%). The difference in the estimated transmission rate between the two groups was statistically significant (p=0.00006). ZDV treatment did not appear to delay the diagnosis of HIV infection.

Observed toxicity specifically attributable to ZDV was minimal among the women in this study. Adverse effects such as anemia, neutropenia, thrombocytopenia, and liver chemistry abnormalities were reported as frequently among women receiving placebo as among women receiving ZDV. Six women—three in each treatment group—discontinued therapy because of toxicity attributed to the study drug. The women were evaluated at 6 weeks and 6 months postpartum. A statistically significant increase in CD4+ T-lymphocyte 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, the CD4+ T-lymphocyte counts for both groups had decreased to similar levels. CD4+ T-lymphocyte counts decreased to <200/μL in only four women, including one receiving ZDV and three receiving placebo. No women died during the study.

Serial sonographic evaluations for fetal growth and amniotic fluid volume as conducted in the study (at entry and every 4 weeks from 28 weeks of gestation until delivery) demonstrated no differences between pregnancies in women who had received placebo or ZDV. Birth parameters (gestational age; birth weight, length, and head circumference; and Apgar scores) were similar among infants born to women in either group. The median birth weight was 3,160 g (range: 1,040–5,267 g), and the median gestational age at birth was 39 weeks (range: 27–43 weeks). No statistically significant difference was observed between the ZDV and placebo groups in the number of infants with birth weight <2,500 g, who were small or large for gestational age, or who were born prematurely. The occurrence of major or minor congenital abnormalities was approximately equal between the two groups, and no pattern in the type of abnormalities was observed.

The infants in the study tolerated the ZDV therapy well. The only adverse effect observed more frequently among infants in the ZDV treatment group was mild, transient anemia. Hemoglobin values for infants in the group receiving ZDV were lower than for the group receiving placebo, with a maximum mean difference of 1 gm/dL occurring at 3 weeks of age. The lowest mean hemoglobin value in infants receiving ZDV occurred at 6 weeks of age and resolved without therapy for anemia after the infants had completed the ZDV treatment. The hemoglobin values of infants receiving ZDV were similar to those of placebo recipients by 12 weeks of age. The incidence of neutropenia and serum chemistry abnormalities was similar between ZDV and placebo groups of infants, and no difference in the pattern of chemistry abnormalities was observed.

Based on these interim findings, NIAID accepted the recommendation of its independent data and safety monitoring board to terminate enrollment into the trial and to offer ZDV to women in the placebo group who had not yet delivered and to their infants up to 6 weeks of age.* Follow-up of patients enrolled in the study is ongoing.

Limitations in Interpretation and Extrapolation of ACTG Protocol 076 Results

This clinical trial demonstrated that the ACTG Protocol 076 ZDV regimen can substantially reduce perinatal HIV transmission. However, several important limitations should be noted. First, perinatal HIV transmission was still observed despite drug therapy. Second, the efficacy of this therapy is unknown for HIV-infected pregnant women who have advanced disease, who have received prior antiretroviral therapy, or who have ZDV-resistant virus strains. Third, although the ZDV regimen used in this trial was not associated with serious short-term adverse effects, such effects may be observed when this use of ZDV becomes more widespread. Fourth, the long-term risks for the child associated with exposure to ZDV in utero and early infancy have not been determined. Fifth, it is not known if use of ZDV during pregnancy will affect the drug's efficacy for the woman when it becomes clinically indicated for her own health.

Further complicating the incorporation of this ZDV regimen into clinical practice is the fact that some HIV-infected women seek medical care late in pregnancy or when

* A summary of the study's findings is available from the AIDS Clinical Trials Information Service at 1(800)TRIALS-A (1[800]874-2572).

they are already in labor, when the full ZDV regimen used in ACTG Protocol 076 cannot be administered. Moreover, many pregnant women are not aware that they are HIV infected, are not tested before or during pregnancy, and remain undiagnosed. As a result, they do not receive information about therapy that could reduce the risk for HIV transmission to their infants.

Potential Long-Term Adverse Effects of ZDV Administered During Pregnancy

The long-term effects of ZDV treatment during pregnancy solely to reduce perinatal transmission or of fetal and neonatal exposure to ZDV are not known. ZDV is a nucleoside analog 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 much higher than those required to inhibit HIV polymerase. However, gamma DNA polymerase, which is required for mitochondrial replication, may be inhibited by ZDV at concentrations nearer to those that can be achieved in vivo.

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

ZDV has been shown to be a mutagen in vitro, and, in a mammalian in vitro cell transformation assay, ZDV was positive at concentrations of ≥0.5 μg/mL (*8*). Noninvasive squamous epithelial vaginal tumors were produced after 19–21 months of continuous dosing in 12% of mice administered a dosage equivalent to three times the estimated human exposure at the recommended therapeutic dosage. Similar findings were observed in 3% of rats that received 24 times the recommended therapeutic dosage. Carcinogenicity studies in rodents, however, may not 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 this increase probably reflects longer survival despite severe immunodeficiency rather than a direct effect of ZDV (*9*). The potential for carcinogenesis should be further assessed through continued follow-up of children who were exposed to ZDV in utero.

Myopathy and cardiomyopathy have been associated with ZDV therapy. In an individual patient, the effects secondary to ZDV are often difficult to distinguish from those of HIV infection. A prospective study of HIV-infected children demonstrated no effect of ZDV therapy on cardiac function (*10*).

Reproductivity/fertility studies in animals have demonstrated no adverse effects of ZDV on either the fertility of male or female rats or the reproductive capacity of their offspring (*11*). ZDV administered to mice early in gestation was associated with an embryotoxic effect and fetal resorptions; however, ZDV administered at or beyond midgestation had no detectable effect on the fetus (*12,13*).

ZDV is assigned pregnancy category C status by the Food and Drug Administration (FDA).* Most studies of ZDV administered to pregnant animals have not demonstrated teratogenicity. In one study, pregnant rats were administered toxic doses of ZDV during organogenesis (i.e., equivalent to approximately 50 times the recommended daily clinical dose, based on relative body surface areas); developmental malformations and skeletal abnormalities were observed in 12% of fetuses (*14*).

In humans, observational studies involving small numbers of subjects have demonstrated no apparent association of fetal malformations with antenatal ZDV use (*15–19*). In ACTG Protocol 076, the incidence of congenital malformations was similar for ZDV and placebo recipients. However, because ZDV was not administered until after 14 weeks of gestation in this study, the potential teratogenicity of ZDV administered during the first trimester cannot be assessed. Similarly, in a recent report from the Antiretroviral Pregnancy Registry maintained by the Wellcome Foundation and Hoffman LaRoche in conjunction with CDC, no increase in the risk of congenital abnormalities above that expected for all pregnancies was observed among infants born to 121 prospectively registered HIV-infected women who received ZDV during pregnancy, nor was there any unusual pattern of birth defects (*20*).

Use of ZDV during pregnancy could be associated with the development of ZDV-resistant virus, which may lessen the drug's therapeutic benefit for the woman when it is needed for her own health. However, patients with early-stage HIV disease rarely develop ZDV-resistant strains before they have received 18–24 months of continuous therapy (*21*). After discontinuation of ZDV therapy, an increase in ZDV-susceptible isolates has been observed in some patients who had ZDV-resistant isolates while they were receiving ZDV, although resistance to ZDV has been reported to persist for more than a year after therapy was discontinued (*22,23*). Because the development of ZDV-resistant viral strains secondary to transient ZDV use during pregnancy is a theoretical concern, considerations for the woman's future health care should include the availability of alternative drugs for treatment of HIV infection.

GENERAL PRINCIPLES REGARDING TREATMENT RECOMMENDATIONS

The following treatment recommendations have been formulated to provide a basis for discussion between the woman and her health-care provider about the use of ZDV to reduce perinatal transmission. HIV-infected women should be informed of the substantial benefit and short-term safety of ZDV administered during pregnancy and the neonatal period observed in ACTG Protocol 076. However, they also must be

*FDA pregnancy categories are: A, in which adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk during later trimesters); B, in which animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted; C, in which safety in human pregnancies has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus; 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 reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

informed that the long-term risks of ZDV therapy to themselves and their children are unknown. A woman's decision to use ZDV to reduce the risk for HIV transmission to her infant should be based on a balance of the benefits and potential risks of the regimen to herself and to her child.

Discussion of treatment options should be noncoercive, and the final decision to accept or reject ZDV treatment recommended for herself and her child is the right and responsibility of the woman. A decision not to accept 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.

Various circumstances that commonly occur in clinical practice are described and the factors influencing treatment considerations are highlighted in the following discussion (Box 3). All potential clinical situations cannot be enumerated, and, in many cases, definitive evidence upon which to base a recommendation is not currently available. Therefore, each pregnant woman and her health-care provider must consider the potential benefits, unknown long-term effects, and gaps in knowledge relating to her clinical situation. Furthermore, health-caregivers and institutions should provide culturally, linguistically, and educationally appropriate information and counseling to the HIV-infected woman so that she can make informed decisions.

CLINICAL SITUATIONS AND RECOMMENDATIONS FOR USE OF ZDV TO REDUCE PERINATAL TRANSMISSION

Clinical Situation Meeting the Entry Criteria for ACTG Protocol 076

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/μL who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Discussion:

The results of ACTG Protocol 076 are directly applicable only to women who meet the entry criteria for the study (Table 1). The data from that study indicate that the complete ACTG Protocol 076 ZDV regimen will likely reduce the risk for perinatal transmission by about two-thirds.

Because this study was randomized and placebo controlled, entry was restricted to women who had no clinical indications for ZDV use for their own health and who had CD4+ T-lymphocyte counts ≥200/μL. Prior ZDV use during the current pregnancy resulted in exclusion from the study. Few women (4%) had received ZDV before the current pregnancy, and most of that therapy was of limited duration.

Women were not enrolled either before the 14th week or after the 34th week of gestation. The rationale for exclusion before 14 weeks of gestation was to preclude ZDV exposure during fetal organogenesis. The 34-week limit allowed most women to receive several weeks of ZDV before delivery to allow time for a decrease in maternal viral load (a presumed important determinant of transmission risk).

Although ZDV was successful in reducing perinatal transmission, the study regimen did not completely prevent it. The possible reasons for transmission to

these infected infants are being evaluated but have not yet been identified. Several case reports also have described perinatal transmission despite the initiation of ZDV therapy during pregnancy (*24–27*).

Although long-term toxicity to infants is unknown, this risk must be weighed against the decreased risk for transmission of an infection associated with substantial risk of death. Currently, there is no way to predict if an individual pregnancy will be associated with HIV transmission; therefore, each fetus must be considered to have an estimated 25% risk of a life-threatening infection. Because ZDV therapy reduced the rate of transmission by two-thirds (from 25.5% to 8.3%), any long-term toxicity related to ZDV would have to be severe (e.g., malignancy or profound developmental delay) and relatively common among ZDV-exposed infants to outweigh the substantial benefit.

Recommendation:

The health-care provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category. This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known. The decision about this regimen should be made by the woman after discussion with her health-care provider.

Clinical Situations Not Meeting the Study Entry Criteria

Information about the benefit and short-term risks of ZDV therapy is applicable from this trial only for women who meet the entry criteria of the study. Recommendations about 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.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Discussion:

This patient population has clinical characteristics similar to those of women enrolled in ACTG Protocol 076; the major difference is gestational age at which ZDV therapy would begin. Therefore, the ZDV regimen for these women would differ from the ACTG Protocol 076 regimen only in duration of antenatal therapy. As much as 50%–70% of perinatal transmission may occur close to or during delivery (28). Therefore, the ACTG Protocol 076 ZDV regimen may have some benefit when initiated at >34 weeks of gestation, although the intervention is likely to decrease in effectiveness as the duration of antenatal ZDV administration is reduced. A study evaluating the effect of ZDV on quantitative p24 antigen levels indicates that maximal effect is observed after 8–16 weeks of therapy (*29*). A shorter duration of ZDV therapy may thus be associated with an effect on maternal viral load that is less than can be anticipated when ZDV is initiated before 34 weeks of gestation. Both potential risks and benefits for the woman and her infant may decrease the closer to delivery that the ZDV regimen is initiated.

Further clinical trials should be designed to assess the efficacy of interventions that are initiated late in the third trimester for preventing perinatal transmission.

Recommendation:

The health-care provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200/μL who are at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Discussion:

Women in this group meet the current standard of care for ZDV treatment of HIV infection for their own benefit (*30,31*); therefore, administration of ZDV during pregnancy for these women provides direct benefit to them as well as potential benefit to their infants. The risk for HIV transmission to the infants of HIV-infected pregnant women with low CD4+ T-lymphocytes or percent of total lymphocytes ranges from 22% to 60% (*32–38*).Viral load has been shown to increase as CD4+ T-lymphocyte count decreases (*39*); thus, baseline viral loads can be expected to be high among the women in this group.

Although viral replication and resultant capacity for mutations in this group are high, preexisting ZDV-resistant viral strains are unlikely to be present because these women have had little or no exposure to ZDV. Therefore, ZDV therapy can be expected to result in an acute reduction in maternal viral load analogous to that observed in women who have CD4+ T-lymphocyte counts ≥200/μL. Additionally, the mother's CD4+ T-lymphocyte count would not be expected to affect ZDV levels or toxicity in the infant after administration of ZDV during labor and the first 6 weeks of life. Hence, maternal CD4+ T-lymphocyte count should not affect the potential utility of neonatal levels of systemic ZDV for reducing intrapartum transmission.

Although this population of pregnant women was not studied in ACTG Protocol 076, addition of the intrapartum and neonatal components of the ACTG Protocol 076 ZDV regimen to antenatal maternal therapy may reduce the risk for HIV transmission. However, the magnitude of the effect of ZDV on reducing the transmission rate in this group may not be the same as that demonstrated in ACTG Protocol 076 for women with CD4+ T-lymphocyte counts ≥200. Further clinical trials should assess the utility of interventions in this group of women. Because ZDV therapy is clinically indicated for these women for their own health, the additional risk of the remainder of the ACTG Protocol 076 regimen is the discomfort to the woman of another intravenous infusion during labor and the possible effects of the additional 6 weeks of ZDV exposure for the infant.

Recommendation:

The health-care provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit (*31*). The intrapartum and neonatal

components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Discussion:

Women who have received extensive prior ZDV therapy may be infected with viral strains with reduced susceptibility to ZDV. These resistant strains of HIV can be transmitted from mother to fetus; however, the frequency with which such transmission occurs is unknown.

Resistant virus appears to emerge more quickly if therapy is initiated at later stages of HIV disease (*21*). The appearance of mutations associated with ZDV resistance follows a temporal pattern, and the level of in vitro resistance is proportional to the number of mutations in the reverse transcriptase-coding region of HIV (*40*). Phenotypically and genotypically diverse HIV populations can coexist in patients who are receiving ZDV therapy.

In one study, ZDV-resistant strains appeared earlier during ZDV therapy in patients with advanced HIV disease than in patients whose ZDV therapy was initiated at an early stage of the disease. After 12 months of ZDV therapy, viral isolates from 89% of patients with late-stage disease and 31% of those with early-stage disease were resistant (*21*). However, isolates from only 33% of late-stage patients demonstrate high-level resistance (defined as a 100-fold decrease in susceptibility [*41*]). Resistant virus also was more likely to be isolated from patients who had low CD4+ T-lymphocyte counts when therapy was initiated: 1-year estimated rates of resistance in patients with baseline CD4+ T-lymphocyte 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 6–18 months of therapy. However, in patients with early-stage disease, high-level resistance appears to be delayed until after 24 months of therapy (*22*). Therefore, ZDV-resistant strains are likely to be more common in women with advanced disease who have received prolonged therapy.

ZDV-resistant viral strains also may be more common in persons receiving alternative antiretroviral agents because their disease progressed while they were receiving ZDV therapy. There is controversy regarding the association of clinical disease progression during ZDV therapy with the development of ZDV resistance and regarding whether resistance persists when therapy is changed to an alternative antiretroviral agent (*41*). Some studies involving small numbers of children have indicated that in vitro susceptibility to ZDV is correlated with clinical outcome, suggesting that ZDV-resistant isolates are associated with diminished efficacy of ZDV and more rapid clinical progression (*42,43*). However, at least one study indicated that disease progression may be associated more closely with the development of syncytia-inducing viral phenotype than with resistance to ZDV (*44*). Change to alternative antiretroviral therapy has been associated with reversal of ZDV resistance in some studies, but resistance has been reported to persist for considerable periods of time after discontinuation of ZDV (*23,45*). The prevalence of ZDV-resistant viral strains in women

who are receiving alternative antiretroviral agents because of disease progression has not been defined.

The capability of ZDV to reduce HIV transmission may be decreased for mothers in whom ZDV-resistant strains predominate, particularly if the strains have high-level resistance; however, this assumption is not yet supported by data. Further clinical trials to evaluate alternative approaches for such women are needed.

Recommendation:

Because data are insufficient to extrapolate the potential efficacy of the ACTG Protocol 076 regimen for this population of women, the health-care provider should consider recommending the ACTG Protocol 076 regimen on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed include her clinical and immunologic stability on ZDV therapy, the likelihood that she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g., lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The health-care provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Discussion:

Data from studies in humans are insufficient to evaluate the potential effectiveness of ZDV in this situation. Because the mother's exposure to ZDV would be brief, such therapy can be expected to have no effect on the level of maternal virus in blood or genital secretions. However, because of the intravenous loading dose and continuous infusion of ZDV during labor, the infant will be born with circulating levels of ZDV similar to those of infants whose mothers have received antenatal as well as intrapartum ZDV. ZDV may have some utility for this group of patients—regardless of whether the pregnancy is at term or preterm—because the presence of systemic levels of ZDV in the infant before or shortly after HIV exposure through contact with the mother's blood and genital secretions during delivery may help prevent intrapartum transmission.

The intravenous route was chosen for drug dosing during labor in ACTG Protocol 076 because continuous intravenous infusion of drug after an initial loading dose results in predictable levels of ZDV in the mother. Under optimal circumstances, these maternal levels provide a substantial fetal blood level during birth, when the infant is presumed to be exposed extensively to HIV through contact with the mother's blood and genital secretions. Because gastric emptying is delayed during labor, the absorption of orally administered drugs is unpredictable (*46*). Therefore, oral administration of ZDV during labor might produce widely variable systemic levels in the mother and infant. Oral ZDV administered intrapartum cannot be assumed to be equivalent to the intravenous intrapartum ZDV component used in ACTG Protocol 076. Further studies are needed to characterize the pharmacokinetics of oral ZDV during labor.

Intrapartum ZDV cannot prevent the substantial number of infections that occur before labor (*26*). Therefore, ZDV administered only during labor and to the newborn may not be effective.

Because the mother would receive ZDV only during labor, her risk for developing resistant virus or ZDV toxicity would be minimal. The primary risk is that associated with an intravenous catheter. The risk to the infant would be limited to the potential toxicity associated with transfer of drug from the maternal intrapartum infusion and with 6 weeks of oral ZDV therapy, without in utero exposure to the drug. The effect of neonatal ZDV treatment in ameliorating disease progression in infected infants is unknown. Clinical trials should be designed to address the efficacy of antiretroviral therapy in this situation.

Recommendation:

For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the health-care provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

VI. Infants who are born to HIV-infected women who have received no intrapartum ZDV therapy.

Discussion:

Infants whose mothers have not received ZDV during late pregnancy and/or labor will not have circulating ZDV levels during birth, a period of presumed viral exposure. Data are insufficient to allow assessment of the potential efficacy of postexposure prophylaxis with ZDV in this situation. Studies of postexposure prophylaxis of retroviral infection with ZDV in animal models have yielded inconclusive results. Additionally, studies involving animal models should be interpreted with caution: many of these studies have involved nonhuman retroviruses that may have different pathogenic mechanisms from those of HIV, used methods of viral inoculation that are not relevant to perinatal transmission (e.g., intrathymic injection), and/or used a massive inoculum of virus (*47*).

The limited data from animal studies indicate that if ZDV is to have any effect as postexposure prophylaxis, prompt administration (within hours) is important, and that even with early initiation of ZDV, such prophylaxis may not be protective. In a SCID-hu mouse model of HIV infection (an immune-deficient model reconstituted with human cells), a time-dependent suppression of HIV replication was observed with ZDV prophylaxis (*48*). When ZDV was administered within 2 hours of viral inoculation, viral replication was not detectable at 2 weeks after inoculation in all treated animals; when ZDV was administered 2–36 hours after inoculation, rates of viral detection at 2 weeks increased in proportion to increasing time since ZDV was administered; and when ZDV was administered 48 hours after inoculation, virus was detectable in all animals (*48*). Therefore, whether the effect of ZDV therapy is prevention or suppression of infection cannot be established. In several animal model systems, ZDV administration was observed only to suppress or ameliorate retroviral infection (*49–51*).

At least 13 reports have described the failure of prophylactic ZDV to prevent HIV infection in humans following exposure to HIV-infected blood, even though the drug was administered promptly after exposure (*52*). Although these anecdotal reports do not establish that ZDV therapy is ineffective as postexposure prophylaxis, its efficacy can be expected to be lower in this situation than with the full regimen. Further studies are needed to evaluate whether a therapy administered only during the neonatal period can effectively prevent perinatal transmission.

Recommendation:

If the clinical situation permits and if ZDV therapy can be initiated within 24 hours of birth, the health-care provider should offer the ACTG Protocol 076 postpartum component of 6 weeks of neonatal ZDV therapy for the infant in the context of a risk-benefit discussion with the mother. Data from animal prophylaxis studies indicate that, if ZDV is administered, therapy should be initiated as soon as possible (within hours) after delivery. If therapy cannot begin until the infant is >24 hours of age and the mother did not receive therapy during labor, no data support offering therapy to the infant.

RECOMMENDATIONS FOR MONITORING THE ZDV REGIMEN FOR MOTHERS AND INFANTS

Women and their children should receive care together in a family-centered setting. Care should be coordinated between gynecologic, pediatric, internal medicine, infectious disease, and other health-care specialists to ensure that both mother and child receive appropriate medical follow-up. A comprehensive program of support services is necessary to ensure that both mother and child continue to receive health care.

Maternal Monitoring

HIV-infected pregnant women should be monitored in accordance with previously published guidelines (*31,53*). Monitoring during pregnancy should include monthly assessment for ZDV-associated hematologic and liver chemistry abnormalities. Indications of toxicity that might require interrupting or stopping the dose of ZDV include a) hemoglobin <8 gm/dL, b) absolute neutrophil count <750 cells/μL, or c) AST (SGOT) or ALT (SGPT) greater than five times the upper limit of normal.

CD4+ T-lymphocyte counts should be monitored to determine if prophylaxis for opportunistic infections, such as *Pneumocystis carinii* pneumonia (PCP), should be initiated. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200 cells/μL should receive appropriate PCP prophylaxis. If the CD4+ T-lymphocyte count is <600 cells/μL, the evaluation should be repeated each trimester. CD4+ T-lymphocyte counts should be measured at 6 weeks and 6 months postpartum to evaluate if antiretroviral therapy is indicated.

Fetal Monitoring

Antepartum testing, including sonographic and nonstress testing and intrapartum fetal monitoring, should be performed only as clinically indicated, not specifically because the patient is being treated with ZDV during pregnancy.

Infant Monitoring

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

Previously published guidelines contain recommendations for diagnosing HIV infection in infants and for initiating PCP prophylaxis and antiretroviral therapy for those who are infected (*53–55*). The potential efficacy of ZDV therapy for HIV-infected children who require antiretroviral therapy and who received ZDV in utero and during early infancy has not been determined. A specialist in pediatric HIV infection may be consulted if therapy is necessary for infected children whose mothers received ZDV during pregnancy. Further research is needed to describe the response to therapy and progression of disease in such infants.

POTENTIAL LONG-TERM EFFECTS OF ZDV THERAPY FOR MOTHERS AND INFANTS AND RECOMMENDATIONS FOR FOLLOW-UP

Discussion

Observational data about the pregnancy outcomes of women who receive ZDV during pregnancy are being collected through the Antiretroviral Pregnancy Registry. The purpose of the registry is to provide surveillance for possible teratogenicity among infants born to women who received ZDV during pregnancy. Health-care providers can register such patients by calling the registry at (800) 722-9292, extension 8465, in the United States or (919) 315-8465 outside the United States. Written reports are available from Antiretroviral Pregnancy Registry, P.O. Box 12700, Research Triangle Park, NC 27709.

Concerns about the potential long-term adverse effects among women include development of ZDV-resistant virus when ZDV therapy is used intermittently to reduce perinatal transmission, particularly during more than one pregnancy, and the potential effect such resistance could have on disease progression for the woman. Although results of studies have demonstrated an association between emergence of ZDV resistance and total duration of ZDV exposure, none of the study designs has specifically addressed the effect of intermittent therapy on development of resistance.

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

Data are insufficient to address any effect that exposure to ZDV in utero might have on risk for neoplasia or organ system toxicities. ACTG Protocol 219 is an ongoing study designed to provide prospective evaluation for children who have been exposed through ACTG protocols to antiretroviral agents in utero or to HIV vaccines until they are 21 years of age. This protocol will provide intensive evaluation of multiple organ

system functions, neuropsychologic testing, and quality of life. Information about the potential long-term effects of the complete or partial ACTG Protocol 076 ZDV regimen on women and children receiving the regimen outside a clinical trial protocol also may be provided from evaluation of federally funded and other prospective studies of HIV-infected women and their infants.

Recommendation:

Additional efforts are required to characterize the long-term effects of the ACTG Protocol 076 ZDV regimen on women and children. The specific issues of viral resistance and disease progression should be addressed among women who receive ZDV during pregnancy solely to reduce perinatal HIV transmission. Monitoring for these HIV-infected women should include Pap smears and gynecologic examinations as recommended in previously published guidelines (*56*), as well as an assessment of the patient's future needs for family planning consultation and services.

Long-term follow-up of both uninfected and infected infants born to mothers receiving ZDV during pregnancy is important. Assessment of organ system toxicities, neurodevelopment, pubertal development, reproductive capacity, and development of neoplasms should be emphasized. Special studies will need to be developed to address these specific concerns, and innovative methods and support systems should be designed to assist in follow-up of these women and their children.

CONCLUSION

The decision by an HIV-infected pregnant woman to use ZDV to reduce the risk for perinatal transmission requires a complex balance of individual benefits and risks that is best accomplished through discussions with her health-care provider. Such discussions should be noncoercive, linguistically and culturally appropriate, and tailored to the patient's educational level.

The recommendations in this report have been developed for use in the United States. Although perinatal transmission of HIV infection is an international problem, alternative strategies may be appropriate in other countries (*57*). The policy and practice in other countries may differ from these recommendations and 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.

These recommendations have been developed in response to the urgent need to provide guidance to women and health-care providers in the United States about the use of ZDV to reduce the risk for perinatal HIV transmission and about the possible adverse outcomes of such ZDV treatment. They have been formulated on the basis of the available data from ACTG Protocol 076 and current information regarding factors associated with transmission. The information on 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 Protocol 076 regimen for preventing perinatal transmission of HIV requires weighing the benefits and potential risks to the HIV-infected woman and her child despite numerous uncertainties. Further research is a high priority and should include a) clarification of long-term risks of the ZDV regimen to the woman and/or her child, b) elucidation of the reasons for transmission despite use of

the ZDV regimen, c) delineation of the relative efficacy of the various components of the ACTG Protocol 076 ZDV regimen for reducing transmission, d) evaluation of the efficacy of the regimen in women whose characteristics differ from those enrolled in ACTG Protocol 076, and e) evaluation of other interventions for preventing perinatal transmission. As further information becomes available, these recommendations may need to be modified. In addition, appropriate methods and materials should be developed for communicating treatment options, risks, and benefits to women and health-care providers so that they can make informed decisions about treatment.

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BOX 3. Summary: Clinical situations and recommendations for use of zidovudine* to reduce perinatal HIV transmission

I. Pregnant HIV-infected women with CD4+ T-lymphocyte counts ≥200/μL who are at 14–34 weeks of gestation and who have no clinical indications for ZDV and no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation:
The health-care provider should recommend the full ACTG Protocol 076 regimen to all HIV-infected pregnant women in this category. This recommendation should be presented to the pregnant woman in the context of a risk-benefit discussion: a reduced risk of transmission can be expected, but the long-term adverse consequences of the regimen are not known. The decision about this regimen should be made by the woman after discussion with her health-care provider.

II. Pregnant HIV-infected women who are at >34 weeks of gestation, who have no history of extensive (>6 months) prior antiretroviral therapy, and who do not require ZDV for their own health.

Recommendation:
The health-care provider should recommend the full ACTG Protocol 076 regimen in the context of a risk-benefit discussion with the pregnant woman. The woman should be informed that ZDV therapy may be less effective than that observed in ACTG Protocol 076, because the regimen is being initiated late in the third trimester.

III. Pregnant HIV-infected women with CD4+ T-lymphocyte counts <200/μL who are at 14–34 weeks of gestation, who have no other clinical indications for ZDV, and who have no history of extensive (>6 months) prior antiretroviral therapy.

Recommendation:
The health-care provider should recommend initiation of antenatal ZDV therapy to the woman for her own health benefit. The intrapartum and neonatal components of the ACTG Protocol 076 regimen should be recommended until further information becomes available. This recommendation should be presented in the context of a risk-benefit discussion with the pregnant woman.

IV. Pregnant HIV-infected women who have a history of extensive (>6 months) ZDV therapy and/or other antiretroviral therapy before pregnancy.

Recommendation:
Because data are insufficient to extrapolate the potential efficacy of the ACTG Protocol 076 regimen for this population of women, the health-care provider should consider recommending the ACTG Protocol 076 regimen

*These recommendations do not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question.

BOX 3. Summary: Clinical situations and recommendations for use of zidovudine to reduce perinatal HIV transmission (Continued)

on a case-by-case basis after a discussion of the risks and benefits with the pregnant woman. Issues to be discussed include her clinical and immunologic stability on ZDV therapy, the likelihood she is infected with a ZDV-resistant HIV strain, and, if relevant, the reasons for her current use of an alternative antiretroviral agent (e.g., lack of response to or intolerance of ZDV therapy). Consultation with experts in HIV infection may be warranted. The health-care provider should make the ACTG Protocol 076 regimen available to the woman, although its effectiveness may vary depending on her clinical status.

V. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor.

Recommendation:
For women with HIV infection who are in labor and who have not received the antepartum component of the ACTG Protocol 076 regimen (either because of lack of prenatal care or because they did not wish to receive antepartum therapy), the health-care provider should discuss the benefits and potential risks of the intrapartum and neonatal components of the ACTG Protocol 076 regimen and offer ZDV therapy when the clinical situation permits.

VI. Infants who are born to HIV-infected women who have received no intrapartum ZDV therapy.

Recommendation:
If the clinical situation permits and if ZDV therapy can be initiated within 24 hours of birth, the health-care provider should offer the ACTG Protocol 076 postpartum component of 6 weeks of neonatal ZDV therapy for the infant in the context of a risk-benefit discussion with the mother. Data from animal prophylaxis studies indicate that, if ZDV is administered, therapy should be initiated as soon as possible (within hours) after delivery. If therapy cannot begin until the infant is >24 hours of age and the mother did not receive therapy during labor, no data support offering therapy to the infant.

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