

**Prevention of Perinatal HIV
Transmission Clinical
Guidelines**

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PREFACE

The first edition of this booklet, *Clinical Guidelines for the Use of Zidovudine Therapy in Pregnancy to Reduce Perinatal Transmission of HIV*, was published in fall 1994 soon after the landmark announcement from the Pediatrics AIDS Clinical Trial Group (PACTG) 076 study that zidovudine (ZDV, also known as AZT) could clearly and substantially reduce perinatal HIV transmission.

Since the implementation of those guidelines, clinical management of HIV/AIDS has evolved at a rapid pace. Direct measures of viral burden are now routinely used in conjunction with CD4 monitoring to guide clinical management. In the treatment arena, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have considerably improved the prognosis for many patients, resulting in the routine use of combination antiretroviral therapy as the standard of care. A second edition of this booklet incorporating these advances was published in 1998.

Mounting epidemiologic evidence and clinical trials support the success of perinatal ZDV therapy. The benefit of cesarean section delivery for some HIV-infected women and the efficacy of antiretroviral prophylaxis late in pregnancy and in the newborn period have been recently determined by clinical trials and observational data. Nationwide, the number of pediatric AIDS cases and the number of HIV-exposed newborns reported to the Centers for Disease Control and Prevention (CDC) have fallen dramatically.

In order to integrate the body of knowledge amassed since publication of the first and second editions of these guidelines, the New York State Department of Health/AIDS Institute (NYSDOH/AI) convened a distinguished committee of 22 New York State health care providers and public health experts to reexamine the guidelines in the context of this new information. The committee investigated and debated a range of new issues and topics, including potential benefits and risks of combination therapy for both mother and child; delivery via cesarean section; efficacy of abbreviated antiretroviral regimens; epidemiology of HIV in children; new data on other strategies that might prevent transmission, and the long-term effects of these treatments on the mother and the infant. The committee grappled with the complex decisions that a pregnant woman and her treating clinician must face in weighing the benefits and risks of aggressive therapy directed against maternal HIV infection during pregnancy while also considering its efficacy as prophylaxis of perinatal HIV transmission and the potential effects on the unborn fetus. The committee agreed that ZDV has proven to be efficacious for use as prophylaxis. The group acknowledged that preliminary data suggest that combinations of antiretroviral therapy, with or without ZDV, are effective in preventing transmission and need to be further studied. For women who have received no antiretroviral drugs antenatally, reasonable options for prevention of transmission include: 1) intrapartum intravenous ZDV followed by 6 weeks of ZDV to the newborn; 2) single dose nevirapine at the onset of labor followed by a single dose of nevirapine to the newborn at age 48 hours; 3) oral ZDV/3TC during labor followed by 1 week of oral ZDV/3TC to the newborn; or 4) the 2-dose nevirapine regimen combined with intra-

partum intravenous ZDV and 6 weeks of ZDV to the newborn. At the same time, the committee emphasized the need to use combination regimens to treat maternal HIV infection as dictated by the clinical and immunologic status of the woman as well as by her previous antiretroviral history. In crafting these recommendations, the group has attempted to delineate the various factors that must be contemplated by the patient and her physician in making a treatment decision, such as the potential of drug resistance developing with monotherapy and the potential transplacental toxicity of combination regimens, especially during early pregnancy. The ultimate decision rests with the individual woman who must weigh how the decision will affect her own health as well as that of her child.

As publication of these guidelines nears the final stages, we realize that important information remains unknown. Many issues remain to be explored in clinical trials, clinical practice, and through the longitudinal accumulation of data about the experience of individuals who have chosen to receive these regimens. The committee wishes to acknowledge the expert presentations of Lynne Mofenson, M.D. and Jennifer Read, M.D., of the National Institute of Child Health and Human Development, National Institutes of Health. We also wish to thank Dr. Mofenson for her very careful and thoughtful peer review of this document. We call upon providers and family members to make every effort to work with public health agencies to ensure that information concerning exposure to antiretroviral agents during pregnancy be captured in order to provide much needed information about both the long-term benefits and toxicities of such agents.

Clinicians should prospectively report cases of pregnant women receiving antiretroviral therapies to the Antiretroviral Pregnancy Registry:

Registrar
Antiretroviral Pregnancy Registry
1410 Commonwealth Drive
Wilmington, NC 28403
Telephone: 1-800-258-4263

Clinicians may also fax completed data collection forms to 1-800-800-1052.

We hope that you will find this publication useful in your practice. We look forward to feedback on these guidelines from all providers of care to women and children with HIV infection. Please address any comments or suggestions to:

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INTRODUCTION

The purpose of this document is to provide clinicians with updated information about available treatments for reducing mother-to-child HIV-1 transmission while maintaining optimal health for a pregnant woman with HIV. These guidelines are intended to assist the clinician in both carrying out a discussion about the benefits and risks of treatment with his/her patient and then formulating an individualized treatment plan.

New York State regulations require HIV counseling with a clinical recommendation to test in all regulated prenatal care settings; NYSDOH recommends this as a standard of care in all other prenatal settings.

All maternal testing must be done with consent. In the past year, the Institute of Medicine recommended a "national policy of universal HIV testing with patient notification as a routine component of prenatal care."¹ The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists published a joint statement in July 1999 strongly supporting this recommendation.²

Because of the complexity of care, consultation with an HIV Specialist is strongly encouraged for all HIV-infected pregnant women (see Appendix V).

This booklet, divided into four sections, covers:

1. Recommendations

2. Scientific Updates

Updates about the efficacy and safety of zidovudine (ZDV) and other antiretroviral agents for the prevention of mother-to-child HIV-1 transmission as well as other co-factors which may affect transmission.

3. Management of HIV-Infected Pregnant Women

Antepartum and intrapartum management to prevent HIV transmission and maintain maternal health, including recommendations.

4. Pediatric Management to Prevent Perinatal Transmission

Pediatric management of infants born to HIV-infected women, including recommendations.

RECOMMENDATIONS

MANAGEMENT OF HIV-INFECTED PREGNANT WOMEN

A. Immunologic Monitoring

Consultation with an HIV Specialist is strongly encouraged for all HIV-infected pregnant women.

If a pregnant woman is diagnosed with HIV infection during her current pregnancy, her baseline immunologic function should be assessed with a CD4 cell count that is repeated every 3 months. For patients known to be HIV-infected prior to pregnancy, the CD4 cell count does not need to be repeated if it has been obtained within the prior 3 months.

Prevention of opportunistic infections (OI) should be part of the obstetrical care plan. Some evidence now suggests that individuals who have CD4 counts that are persistently above 200 cells/mm³ for at least 6 months may be able to safely discontinue primary prophylaxis against certain OIs, such as *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV). However, with the exception of CMV, insufficient data exist to evaluate the safety of discontinuing secondary prophylaxis in such patients. Pneumococcal vaccination (once every 5 years) and influenza vaccination (once every year) are recommended for all patients.

B. Viral Load Monitoring

Once a pregnant woman is identified as HIV-1 seropositive, maternal plasma viral burden should be assessed with a plasma RNA determination.

During pregnancy, plasma RNA levels should be repeated 4-6 weeks after antiretroviral treatment is initiated and every 3 months after the patient is on a stable antiretroviral regimen to monitor response to therapy.

In order to best assess changes in plasma RNA level, determinations should be made using the same assay system and preferably the same laboratory.

At least one plasma HIV RNA level should be obtained in the third trimester to assist in discussing and offering different delivery options because there is a direct relation between plasma HIV RNA level and risk of transmission.

C. Maternal Antiretroviral Therapy

Clinicians should discuss the use of antiretroviral agents both to prevent mother-to-child transmission and to optimize maternal health with all patients.

The success of ZDV regimens for the prevention of mother-to-child transmission should be discussed with all patients.

For the prevention of mother-to-child transmission, the three-part (antepartum, intrapartum, and newborn) regimen studied in PACTG 076 remains the recommended treatment (see Appendix I).

For the treatment of maternal health, recommendations for initiating highly active antiretroviral therapy (HAART) should be based on plasma viral load, CD4 cell count, and clinical history.

For those pregnant women already known to be seropositive, formulation of an appropriate treatment regimen requires knowledge of prior use of ZDV and other antiretrovirals as well as consideration of previous drug toxicities, other concomitant medications, clinical conditions, and adherence to the regimen.

For those patients who become pregnant while receiving antiretroviral therapy, the decision to continue or interrupt the current regimen is complex and should be consistent with practice guidelines for adults and decided on an individualized basis with consideration of potential toxicity to the fetus.

The choice of HAART should be made in consultation with an HIV Specialist.

Whenever a HAART regimen is either initiated or changed during pregnancy, incorporation of ZDV is recommended unless otherwise contraindicated.

Only three drugs/drug combinations have been proven in clinical trials to be effective in reducing maternal-infant transmission: ZDV; short course ZDV/3TC or nevirapine (NVP). However, the full three-part antepartum, intrapartum, and newborn PACTG 076 ZDV regimen is the best studied effective regimen. Studies have demonstrated that antenatal duration of ZDV as short as 2-4 weeks prior to delivery is still beneficial.

D. Labor and Newborn Management When There Is No Antenatal Antiretroviral Treatment

For women who have received no antenatal antiretroviral therapy, reasonable options for prevention of transmission include:

1) intrapartum intravenous ZDV followed by 6 weeks of ZDV to the newborn; 2) single-dose nevirapine at the onset of labor followed by a single dose of nevirapine to the newborn at 48 hours; 3) oral ZDV/3TC during labor followed by 1 week of oral ZDV/3TC to the newborn; or 4) the 2-dose nevirapine regimen combined with intrapartum intravenous ZDV and 6 weeks of ZDV to the newborn.

If the mother has not received antiretroviral therapy during labor, 6 weeks of newborn therapy with ZDV is still recommended because epidemiologic data indicate some protection may be seen. In such situations, ZDV should be started as soon as possible after birth (preferably within 12 hours). In this circumstance, clinicians may consider the addition of a single dose of nevirapine given to the newborn as soon as possible after birth in addition to the 6-week newborn ZDV regimen. This is based on theoretical considerations, however, because no data currently exist to address the additional benefits of nevirapine in such situations.

When maternal therapy has not been given, the efficacy and safety of HAART given to the newborn to prevent transmission have not been studied and are unknown.

In the absence of data regarding efficacy of other regimens, ZDV alone, ZDV/3TC, nevirapine alone or in combination with ZDV are acceptable regimens in the intrapartum/newborn setting when the mother has received no antenatal antiretroviral therapy.

E. Transfer of HIV Information from Obstetrical Care Provider to the Labor and Delivery Unit

Antepartum medical records must be transferred to the labor and delivery unit preferably early in the third trimester.

In New York State, transfer of HIV information does not require a special HIV consent form. HIV information should be transferred with all other prenatal information with the usual protection of patient confidentiality. The general medical consent signed to transfer all prenatal records is adequate to include HIV information.

F. Mode of Delivery

Cesarean section with intact membranes and before the onset of labor offers an additional protective effect. Cesarean section prior to onset of labor or ruptured membranes is recommended for women with no antenatal antiretroviral therapy or with an elevated viral load at the time of delivery. The protective effect of cesarean section delivery has not been confirmed for women with suppressed viral load (<1,000 copies/mL). Although the risk of cesarean section delivery is significantly higher than vaginal delivery, the added risk of cesarean delivery among HIV-infected pregnant women compared with non-HIV-infected women is small or negligible in most instances. A woman's autonomy in deciding which mode of delivery is best for her should be respected.

G. Maternal Safety Monitoring

Clinicians monitoring pregnant women on ZDV or combination antiretroviral therapy should order complete blood counts and liver function tests at the start of therapy as well as other tests appropriate for treatment regimen. These tests should be repeated every 4-6 weeks or as indicated.

For pregnant women on ZDV therapy, dose interruption or dose modification should be considered when serum hemoglobin levels fall below 8.5 g/dL and/or there is an elevation in liver function tests that is three times higher than baseline and that cannot be attributed to any other medical or obstetrical condition. Use of stimulating factors such as erythropoietin may be considered to support hematologic abnormalities. Dose interruptions/modifications of other antiretrovirals should be done in consultation with an HIV Specialist.

Monitoring of HAART during pregnancy should be consistent with recommendations for non-pregnant adults.

H. Management of the Woman with Unknown HIV Status at Labor and Delivery

In New York, HIV counseling and consented expedited testing are required if a woman presents in labor with no prenatal HIV test result and is not known to be HIV-infected.

If the woman declines testing during labor, the infant must be tested immediately after birth. In this setting, written informed consent for testing the newborn is not required.

HIV test results must be returned as soon as possible but no later than 48 hours after the test is drawn.

The meaning of a positive preliminary test result should be discussed with the mother, and based on this discussion, the mother and the physician must decide whether or not to initiate antiretroviral prophylaxis.

Antiretroviral prophylaxis should be initiated as soon as possible in labor or after birth. It is unlikely to be beneficial if initiated beyond 48 hours after birth.

I. Transfer of Information from Obstetrical Care Provider to Pediatric Care Provider

In New York State, labor and delivery records must document maternal HIV counseling and testing history. Ideally, this information should be available prior to labor.

For seropositive women, labor and delivery records should document maternal antiretroviral treatments during the current pregnancy, including specific medications, weeks of gestation at initiation of treatment, duration of treatment, and, if possible, a note about adherence.

Information should be routinely transferred to the newborn's pediatric record and the child's primary care provider.

Emphasis should be placed on the need for the child's guardian to share responsibility for transmitting information about the child's history of antiretroviral exposure with future primary care providers.

An appointment with a pediatric HIV Specialist should be made before the infant is discharged from the nursery. Precautions for confidentiality of patient information must be ensured.

A. Antiretroviral Therapy and Monitoring

All HIV-exposed newborns should be treated with ZDV for 6 weeks as part of the three-part regimen to prevent transmission.

Premature infants will require ZDV dose modification. Consultation with an HIV Specialist is recommended.

For newborns exposed to ZDV, a complete blood count should be obtained at birth and at the completion of the 6-week course of therapy. Some clinicians recommend an additional monitoring visit at 3-4 weeks of life to assess the need for dose interruption or modification based on weight gain of the infant.

Uninfected infants and children exposed to ZDV and other antiretroviral drugs *in utero* and in early infancy may be at risk for potential late onset drug-related toxicities. If future screening is required to assess for this potential, it is important to ensure that the prenatal antiretroviral drug exposure information is in the child's medical record.

Clinicians who care for HIV-exposed infants in the newborn period should inform families that this information needs to be shared with the child's future health care providers, guardians, and caretakers.

For infants born to mothers whose HIV-infection status is unknown, NYSDOH regulations now require that HIV testing be completed within 48 hours after the test is drawn. If the mother's HIV status is unknown, the infant's preliminary HIV-antibody status must be determined as soon as possible after birth. If this preliminary test is positive, the clinician should discuss with the mother the likelihood that the test result is a true positive, assess her risk for being HIV-infected, and discuss the risks and benefits of initiating antiretroviral prophylaxis with ZDV, or ZDV and NVP. Administration of ZDV or other antiretroviral treatment is included in the general medical consent permitting treatment with other medications and does not require a separate written consent.

Identification of an infant's HIV exposure may not take place until after the immediate newborn period due to factors such as receipt of results of newborn testing by the state laboratory or the infant's birth outside of New York State. If breastfeeding has been initiated, some experts would consider initiating prophylaxis of the infant at the time the maternal HIV status becomes known. The mother should be counseled to discontinue breastfeeding. The infant should undergo HIV DNA PCR testing. If the infant is infected, prophylaxis should be discontinued and combination antiretroviral treatment for HIV infection is recommended. If the infant is uninfected, the 6-week ZDV prophylaxis course should be completed.

Although anatomical abnormalities have not been reported to date, all infants exposed to antiretroviral agents *in utero* should be examined for congenital abnormalities.

B. Newborn/Infant Testing for HIV Infection Status

Routine evaluations should be performed for the early diagnosis of newborn HIV infection. There are many different acceptable testing schedules. One acceptable schedule includes an HIV DNA PCR within 1 week, at 2 weeks, at 4-6 weeks, at 6-12 weeks, and at 4-6 months.

For initial HIV testing, clinicians may either use the New York State Department of Health's Wadsworth Center in Albany which provides testing at no cost (telephone: 518-474-2160) or submit documentation of HIV diagnostic test results (HIV DNA PCR or HIV culture) from a laboratory with an appropriate New York State permit. Plasma HIV RNA PCR testing is not appropriate as the sole diagnostic assay.

C. Clinical Management of HIV-Exposed Infants

Infants should be tested for HIV infection (see section B).

Infants identified as HIV-infected should receive comprehensive medical and psychosocial care in accordance with the updated NYSDOH/AI guidelines.¹² Consultation with an HIV Specialist is strongly recommended.

Antiretroviral prophylaxis should be discontinued once a diagnosis of HIV infection has been made. An antiretroviral treatment regimen should be initiated in consultation with a pediatric HIV Specialist.

At 4-6 weeks of age, prophylaxis to prevent PCP should be initiated for HIV-exposed as well as HIV-infected infants.

Breastfeeding by HIV-infected women is not recommended in the United States; if the mother has been breastfeeding, she should be counseled to discontinue.

D. Pediatric Follow-up of Antiretroviral-Exposed Infants

The pediatric medical record should document all antiretroviral exposures during gestation and early infancy. Vital information includes the names of the antiretroviral agent(s), dosage, duration of exposure, and, if possible, a note about adherence.

Clinicians need to develop confidential systems to track and, if necessary, contact antiretroviral-exposed, HIV-uninfected individuals if long-term toxicities are suspected or identified.

The New York State Department of Health is developing methods to look at long-term follow-up of antiretroviral-exposed infants.

Clinicians should emphasize the need for the child's guardian to share responsibility for transmitting the child's history of antiretroviral exposure to future primary care providers.

SCIENTIFIC UPDATES

A. ANTIRETROVIRAL REGIMENS TO PREVENT MOTHER-TO-CHILD HIV TRANSMISSION

In February 1994, an interim analysis of the National Institutes of Health (NIH)-sponsored Pediatrics AIDS Clinical Trial Group (PACTG) 076 study demonstrated that a regimen which combined maternal and newborn zidovudine (ZDV) could dramatically reduce the risk of mother-to-infant HIV-1 transmission.³ The availability of a regimen which could reduce the transmission of a fatal pediatric disease led the United States Public Health Service⁴ and many state and local health departments, including the New York State Department of Health/AIDS Institute,⁵ to develop consensus guidelines for clinicians endorsing the use of ZDV during pregnancy.

Since implementation of these guidelines, additional information supporting the efficacy of ZDV for the prevention of perinatal transmission has become available.

In November 1996, an efficacy update from the PACTG 076 study confirmed the interim findings. The study included 402 mother-infant pairs, all of whom had completed the 18-month infant follow-up. The rate of HIV-1 transmission was 7.6% with ZDV treatment and 22.6% with placebo ($p < 0.001$).⁶

In March 1997, enrollment in another pediatric study, PACTG 185, was stopped prematurely due to an unexpectedly low transmission rate in both study arms.⁷ PACTG 185 was a randomized, controlled clinical trial that compared HIVIG (an immunoglobulin preparation containing high levels of antibodies to HIV) with IVIG (standard immunoglobulin) to evaluate whether passive immunotherapy could further reduce the risk of mother-to-child transmission if added to the maternal/child ZDV regimen successfully used in PACTG 076. The PACTG 185 study was designed for women with more advanced immunosuppression than in the 076 study. In PACTG 076, all women had CD4 cell counts exceeding 200 cells/mm³ and only 5% had received any prior ZDV while in PACTG 185, 23% had baseline CD4 cell counts less than 200 cells/mm³ and 24% of women had received prior ZDV. After analyzing outcomes in 379 infants, the overall rate of mother-to-infant HIV transmission was 4.8% with no difference between treatment arms.⁷ The utility of prophylactic ZDV in pregnant women with advanced immunosuppression that was demonstrated in PACTG 185 is consistent with other reports.^{8,9}

B. ALTERNATE REGIMENS OF ANTIRETROVIRAL PROPHYLAXIS

Recently, results of studies on the efficacy of other antiretroviral regimens have been reported.

In a CDC-sponsored study in Thailand, pregnant, infected women were given either zidovudine 300 mg orally b.i.d. starting at 36 weeks gestation and during labor 300 mg orally every 3 hours until delivery, or placebo. Infants did not receive zidovudine and were not breastfed. The median maternal CD4 count was 424 cells/ μ L, and the cesarean section rate was approximately 14%. The transmission rate was 9.4% (95% confidence interval (CI) 5.2-13.5%) in the ZDV group and 18.9% (95% CI 13.2-24.2%) in the placebo group.¹⁰

The UNAIDS PETRA study involving several African countries examined zidovudine and lamivudine administration in the prenatal (ZDV 300 mg twice a day and 3TC 150 mg twice a day from week 36), intrapartum (ZDV 300 mg and 3TC 150 mg every 3 hours), and postnatal periods (newborn ZDV 4 mg/kg twice a day and 3TC 2 mg/kg twice a day for 7 days) compared with placebo. Transmission at age 6 months was 9.2% (95% CI 5.0-13.5%) in the treatment group and 18.6% (95% CI 13-24%) in the control group, a 51% decrease in transmission. Women breastfed their infants. Median maternal CD4 count was 450 cells/ mm^3 ; cesarean sections accounted for 33% of deliveries. When ZDV/3TC was initiated during the intrapartum period and continued for 1 week postpartum for both the mother and baby, the transmission rate was 10.8% compared with 17.2% in the placebo group, a 37% reduction in transmission.¹¹ However, intrapartum ZDV/3TC alone was not effective in reducing transmission.

The NIH-sponsored HIVNET 012 study performed in Uganda compared intrapartum and newborn administration of nevirapine with a very short course of oral intrapartum and newborn ZDV (administered for 1 week). In one group, women received a single 200 mg dose of nevirapine at the onset of labor and the newborns received a single nevirapine dose of 2 mg/kg within 72 hours after birth. The comparison group received 600 mg ZDV orally at the start of labor followed by 300 mg every 3 hours until birth. Infants were treated with zidovudine 4mg/kg/dose b.i.d. for 7 days. Median CD4 count of the women was 448 cells/ μ L. Cesarean sections accounted for 11% of births. Breastfeeding occurred in 95% of the women delivering. The transmission rate was 13.1% in the nevirapine group versus 25.1% in the zidovudine group when evaluating the infant's infection status at 14-16 weeks of age.¹²

An observational study in New York State examined 939 HIV-exposed infants whose blood specimens were submitted for PCR testing between 1995 and January 1997. When ZDV was initiated in the prenatal period, 26/423 (6.1%) infants were infected. Five infants out of 50 (10%) were infected when ZDV was initiated in the intrapartum period; 8 infants out of 86 (9.3%) when ZDV was initiated within 48 hours of birth, and 7 out of 38 (18.4%) when ZDV was initiated more than 48 hours after birth. No ZDV prophylaxis resulted in a 26.6% transmission rate.¹³ A further analysis of timing of newborn ZDV administration in a subset of 21 infants

demonstrated that 17 received ZDV within 12 hours after birth and 4 within 24 hours after birth.¹⁴ A New York City study found that most ZDV administered to newborns was given within the first 12 hours.¹⁵

Results of these clinical trials as well as multiple observations demonstrate that antiretroviral regimens during pregnancy, labor, and the newborn period significantly reduce mother-to-child HIV-1 transmission.

Nationwide, the number of pediatric AIDS cases reported to the CDC declined 67% between 1992 and 1997.^{16, 17}

In North Carolina, mother-to-child transmission rates decreased from 25% in 1993 to 3% in 1997 following the use of ZDV.¹⁸

In New York City, in a cohort of 1080 children followed between 1996 and 1997, the transmission rate was 7% in those mother-infant pairs who received any ZDV compared with 21% in mother-infant pairs who received no ZDV.^{19, 20}

Studies using ZDV in combination with other antiretroviral agents for the prevention of mother-to-child transmission are ongoing. Although definitive data have not been published, some small studies and a NYC observational study have reported that effective maternal HAART therapy coupled with 6 weeks of newborn ZDV prophylaxis is associated with extremely low rates of vertical transmission.^{21, 22, 23} Until additional efficacy and safety information are available from clinical trials, the three-part maternal/newborn ZDV regimen studied in PACTG 076 remains the recommended regimen in the United States.

C. ANTIRETROVIRAL RESISTANCE

HIV is more likely to develop drug resistance with increasing duration of suboptimal therapy associated with incomplete viral suppression and advanced immunosuppression. Suboptimal therapies, including therapy with a single antiretroviral agent or treatment with two nucleoside analogues, have been associated with the more rapid emergence of drug resistance.²⁴ In the PACTG 076 study, however, short-term maternal ZDV therapy was *not* associated with the development of high-level ZDV resistance.²⁵ In many situations, a significant factor influencing the development of resistance is inadequate adherence to complex treatment regimens.

D. TREATMENT ADHERENCE

Studies indicate that difficulties in adhering to complex medical regimens in chronic disease states may be as high as 50%.²⁶ Medication side effects, complicated dosing regimens, and absence of significant disease symptoms as well as medication benefits that may not be immediately realized by the infected individual contribute to incomplete adherence.^{27, 28, 29, 30} While concerns about medication effects on the pregnancy and lack of information or misinformation regarding drug efficacy are factors in treatment adherence, family and peer pressure also play important roles. The stresses of mother-

hood, her own treatment, her newborn's treatment as well as responsibilities toward other family members may serve as barriers to treatment adherence for the newly postpartum woman.

Many approaches such as educational programs coupled with individualized counseling have been used to enhance HIV medication adherence.⁴⁰ A combined approach that simplifies the regimen, minimizes the side effects, provides patient education, and uses the patient's own support network may provide the best opportunity to improve adherence.

The utility of zidovudine in the reduction of perinatal transmission lies in adherence to therapy. While ZDV and, in some instances, NVP or ZDV/3TC are the only antiretroviral medications recommended for the reduction of perinatal transmission,^{3, 12, 13} many providers treat pregnant patients with HAART for their HIV disease. As a result, the issues of adherence to therapy are complex, especially in the peripartum period. Adherence to therapy should be encouraged and monitored at all antepartum and postpartum visits.

E. FACTORS ASSOCIATED WITH THE RISK OF TRANSMISSION

1. Maternal plasma viral load

A high maternal plasma viral burden (plasma HIV RNA level measured by either reverse transcriptase polymerase chain reaction (RT-PCR), branched deoxyribonucleic acid (bDNA), or the nucleic acid sequence based amplification assay (NASBA)) has been shown to significantly increase the risk for transmission.⁴¹⁻⁴⁶ In the PACTG 076 study, although the risk of transmission was decreased in those with the lowest maternal plasma RNA levels, transmission occurred across the entire measurable range of maternal plasma RNA levels.⁶ In two recent reports, the lowest risk of transmission was associated with a viral load <1,000 copies/mL (0 of 57)³⁷ or <500 copies/mL (0 of 84 at baseline and 0 of 107 at delivery).³⁸

2. CD4 cell count

In the PACTG 076 study, the risk of transmission in the placebo group was highest in those who had the lowest CD4 cell counts at study entry.⁶ This is consistent with other reports.^{39, 40} In the PACTG 076 study, however, ZDV was effective regardless of the maternal CD4 cell count at entry.⁶

3. Maternal co-infections

In a cohort study from Zaire, both funisitis (inflammation of the umbilical cord) and chorioamnionitis were associated with an increased risk of mother-to-child HIV transmission.⁴¹ Similar findings have been reported by the Ariel Project.⁴² Maternal co-infections with syphilis⁴³ and hepatitis C virus⁴⁴ may also be associated with an increased risk of transmission.

4. Duration of rupture of membranes

Several vertical transmission studies have reported an association between transmission risk and rupture of membranes prior to delivery when the duration of rupture of membranes exceeded 4 hours.^{45, 46}

5. Mode of delivery

Several studies have reported that delivery by cesarean section with intact membranes that occurs prior to the onset of labor is associated with a significantly decreased risk of mother-to-child HIV-1 transmission.¹⁷⁻²⁰ In an individual patient data meta-analysis from 15 cohort studies in the United States and Europe,¹⁷ cesarean section with intact membranes and before the onset of labor was associated with an approximately 50% decrease in transmission, even among women on the PACTG 076 regimen. One randomized clinical trial in Europe of cesarean section with intact membranes and before the onset of labor has replicated these findings.⁴⁸ In this study, women were randomized at 34-36 weeks to either a scheduled cesarean section or vaginal delivery. The transmission rate was 1.8% (3/170) in the cesarean-section group and 10.5% (21/200) in the vaginal delivery group. A cesarean section performed as an emergency procedure did not appear to be protective. These significant reductions in transmission are encouraging although it is not known whether the benefit of a planned cesarean section would persist if a pregnant woman was on an aggressive antiretroviral regimen with or without complete suppression of HIV production. A recent report described transmission rates of less than 2% in women with very low viral load and on combination retroviral therapy independent of the mode of delivery.⁵¹ Cesarean section would be unlikely to provide an incremental protective benefit in women with such low transmission risk.

6. Vaginal washing

Vaginal washing in labor had been considered as a potentially simple, low-cost strategy which could be used worldwide. However, results from a large clinical trial reported from Malawi showed that chlorhexidine vaginal cleansing during labor was unsuccessful in reducing mother-to-child HIV transmission.⁵²

7. Vitamin A

Poor nutritional status of pregnant women might contribute to mother-to-child transmission. Particular attention has been focused on vitamin A because of its stimulatory effect on the immune system and its role in maintaining the integrity of mucosal surfaces.⁵³ However, two trials, one in South Africa and the other in Malawi, found that vitamin A supplementation during pregnancy did not lower the risk of perinatal transmission although there was a lower rate of adverse pregnancy outcome (e.g., preterm delivery, low birth weight).^{54, 55}

Although vitamin A deficiency is a serious worldwide problem, severe vitamin A deficiency among HIV-infected pregnant women in the United States is uncommon (<11%).^{56,57} When prenatal vitamins are routinely administered, additional supplementation is not recommended because of the association of high doses of vitamin A with congenital birth defects.⁵⁸

8. Breastfeeding

Since HIV can be transmitted by breastfeeding, the longer an infant breastfeeds, the greater the risk of contracting HIV from an infected mother. HIV transmission from breastfeeding is estimated at 0.7% incidence per month at age 2-6 months and 0.3% incidence per month at 12-18 months. The estimated added risk of transmission in an infant who breastfed for 24 months was 10.3%.⁵⁹ In a clinical trial in Africa, women were randomized to either formula feed or breastfeed their infants. At 24 months, the transmission rate was 36.7% among the breastfed infants and 20.5% among the formula-fed infants. The added risk of transmission from breastfeeding was estimated at 16.7%.⁶⁰

F. SAFETY INFORMATION

Specific questions have been raised regarding adverse effects of ZDV and other antiretroviral therapies on the short-term and long-term health of uninfected infants and on maternal disease progression.

1. Short-term safety of ZDV

The only short-term infant toxicity associated with the PACTG 076 regimen was a mild, reversible anemia with a nadir at 6 weeks of age that resolved by 12 weeks of age.³ The severity and duration of the anemia were not associated with the duration of maternal ZDV treatment. Among uninfected children aged 0-18 months in the PACTG 076 study, there were no differences between the ZDV-exposed group and the placebo group in growth patterns, immunologic parameters (lymphocyte subsets), or the occurrence of childhood neoplasias.⁶¹ Among cases reported to the Antiretroviral Pregnancy Registry, a voluntary, collaborative prospective registry supported by pharmaceutical manufacturers, there has not been any reported association between ZDV exposure and congenital anomalies.⁶²

2. Animal models and carcinogenic potential of ZDV

Although animal testing is frequently performed to assess safety in pregnancy, animal data may be difficult to interpret and may not accurately predict risks to human pregnancy. Nucleoside analogues such as ZDV can interfere with DNA synthesis and may be potential carcinogens. One safety concern with ZDV use during pregnancy is the potential risk of cancer to children following transplacental exposure. In one rodent model, extremely high doses of ZDV administered during pregnancy were associated with an increased risk of multi-organ

tumors in offspring.⁶³ Other studies on rodents have not reported similar risks.⁶⁴

In February 1997, an NIH expert panel comprised of clinicians, scientists, and patient advocates reviewed all available animal data and unanimously concluded that the benefits of ZDV in reducing perinatal HIV infection far outweighed the potential risks.⁶⁵ This panel also emphasized the importance of informing women of these data and recommended long-term follow-up of all children exposed *in utero* as well as increased clinical and basic research on the topic.

3. Long-term safety

Data concerning the long-term safety of zidovudine and other antiretroviral agents continue to be collected. In PACTG 219, 234 uninfected children born to women participating in PACTG 076 (122 in the zidovudine group, 112 in the placebo group) have been followed for a median of 4.2 years. No differences have been seen between these two groups when comparing lymphocyte subsets, growth parameters, and cognitive development. There have been no deaths or malignancies. Two zidovudine-exposed children had unexplained but clinically asymptomatic ophthalmic abnormalities; one ZDV-exposed child had a mild cardiomyopathy detected by echocardiogram but was clinically asymptomatic.⁶⁶ Long-term follow-up of this cohort and others continues. A report from France described eight infants with mitochondrial dysfunction who were HIV-uninfected, exposed *in utero* and/or newborn period to ZDV/3TC or ZDV alone.⁶⁷ Two infants died from neurologic disorders. Three infants were symptomatic; three were asymptomatic but had laboratory abnormalities suggestive of mitochondrial abnormalities. In an evaluation of over 20,000 HIV-exposed infants in the United States, there were 353 deaths, none similar to those reported in France.⁶⁸ Data have also been reviewed regarding neurologic adverse events in 1,798 children who participated in the ZDV/3TC PETRA trial; no increased risk of neurologic events was observed among children treated with ZDV/3TC compared with placebo, regardless of intensity of the ZDV/3TC exposure.⁶⁹

4. Effects of ZDV monotherapy on infant disease progression

Children who become HIV-infected despite ZDV perinatal prophylaxis may be at higher risk for rapid disease progression during the first years of life. In a natural history study of HIV-infected children in Italy, investigators reported that compared with children born to untreated mothers, HIV-infected children with mothers treated with ZDV during pregnancy were significantly more likely to develop severe immune suppression, severe disease manifestations and/or to die.⁷⁰ A similar investigation is on-going in several large cohorts of HIV-exposed infants in the United States. Early and aggressive combination antiretroviral therapy may be beneficial for this population of children. In contrast, however, an observational study of 57 mother/infant pairs in

PACTG 076 did not demonstrate a more rapid disease progression among ZDV-treated infants.⁷¹

5. Effects on maternal disease progression

In PACTG 076, at 6 months postpartum, there were no differences in clinical, immunologic, or virologic disease progression between those women who received the PACTG 076 ZDV regimen and those who received placebo.⁶¹ Data from an analysis of PACTG 288, a study that followed women from PACTG 076 postpartum (median follow-up 4.2 years), indicates no differences in CD4 count or time to progression to AIDS or death in women who received ZDV compared with those who received placebo.⁷² Although a retrospective Swiss report found that 10 of 30 infants born to women receiving combination antiretroviral therapy (with and without protease inhibitors) were born preterm,⁷³ data from a meta-analysis of United States PACTG perinatal trials and cohort studies did not find an elevated risk of preterm delivery among infants born to women who received combination therapy (with and without protease inhibitors) compared with those who received single drug or no therapy. Some data indicate that HIV-infected women who have received no antiretroviral therapy may have higher rates of preterm delivery than HIV-uninfected women.⁷⁴ HIV-infected women who have additional risk factors for preterm delivery should be followed in an appropriate high risk protocol whether or not they are receiving combination antiretroviral therapy (with or without protease inhibitors).

MANAGEMENT OF HIV-INFECTED PREGNANT WOMEN

A. IMMUNOLOGIC MONITORING

RECOMMENDATIONS:

Consultation with an HIV Specialist is strongly encouraged for all HIV-infected pregnant women.

If a pregnant woman is diagnosed with HIV infection during her current pregnancy, her baseline immunologic function should be assessed with a CD4 cell count that is repeated every 3 months. For patients known to be HIV-infected prior to pregnancy, the CD4 cell count does not need to be repeated if it has been obtained within the prior 3 months.

Prevention of opportunistic infections (OI) should be part of the obstetrical care plan. Some evidence now suggests that individuals who have CD4 counts that are persistently above 200 cells/mm³ for at least 6 months may be able to safely discontinue primary prophylaxis against certain OIs, such as *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV). However, with the exception of CMV, insufficient data exist to evaluate the safety of discontinuing secondary prophylaxis in such patients.

Pneumococcal vaccination (once every 5 years) and influenza vaccination (once every year) are recommended for all patients.

CD4 cell counts are routinely used as surrogate markers to assess the risk of HIV-related disease progression and/or death. Those individuals who have absolute CD4 cell counts less than 200 cells/mm³ are at high risk for development of the opportunistic infections that define AIDS. Clinically, CD4 cell counts are used to determine when prophylactic therapies should be initiated. In non-pregnant women, routine primary prophylaxis is recommended for *Pneumocystis carinii* when the CD4 cell counts fall below 200 cells/mm³, for *Toxoplasma gondii* when toxoplasma IgG seropositive adults have CD4 cell counts <100 cells/mm³, and for *Mycobacterium avium* complex (MAC) when a CD4 cell count of <50 cells/mm³ is observed.^{75,76} In addition, because of the morbidity associated with respiratory infections in HIV-infected individuals, pneumococcal vaccination and influenza vaccination should be given. However, deferring immunization with these vaccines until after pregnancy is an acceptable option. CDC recommends influenza vaccine for all HIV-positive pregnant women after the first trimester. Pregnancy considerations are included in recently published guidelines.^{75,76}

B. VIRAL LOAD MONITORING

RECOMMENDATIONS:

Once a pregnant woman is identified as HIV-1 seropositive, maternal plasma viral burden should be assessed with a plasma RNA determination.

During pregnancy, plasma RNA levels should be repeated 4-6 weeks after antiretroviral treatment is initiated and every 3 months after the patient is on a stable antiretroviral regimen to monitor response to therapy.

In order to best assess changes in plasma RNA level, determinations should be made using the same assay system and preferably the same laboratory.

At least one plasma HIV RNA level should be obtained in the third trimester to assist in discussing and offering different delivery options because there is a direct relation between plasma HIV RNA level and risk of transmission.

Studies have demonstrated that plasma viral load can predict progression to AIDS. Similarly, the level of maternal HIV RNA is the best predictor of perinatal transmission. Treatment with highly active antiretroviral therapies (HAART) can result in a reduction in plasma HIV RNA and an increase in CD4 cell counts.⁷ The most commonly used tests for viral load determinations are reverse transcriptase polymerase chain reaction (RT-PCR) assay, branch chain deoxyribonucleic acid (bDNA), and nucleic acid sequence based amplifications assay (NASBA). The results of these tests are reported as plasma RNA copy number per milliliter.

Changes in plasma viral burden are best compared by a log scale (see Appendix IV). Less than a 0.5 log change (threefold change) may represent assay variability and/or differences in specimen handling and, therefore, may not represent true biologic change. It is difficult to compare results from different assays as absolute copy numbers will differ with different assays.

C. MATERNAL ANTIRETROVIRAL THERAPY

RECOMMENDATIONS:

Clinicians should discuss the use of antiretroviral agents both to prevent mother-to-child transmission and to optimize maternal health with all patients.

The success of ZDV regimens for the prevention of mother-to-child transmission should be discussed with all patients.

For the prevention of mother-to-child transmission, the three-part (antepartum, intrapartum, and newborn) regimen studied in PACTG 076 remains the recommended treatment (see Appendix I).

As with any therapy initiated during pregnancy, a risk/benefit discussion should weigh the known benefits to either the fetus or the mother against the possible short-term and long-term risks to both the exposed infant and the woman.

A shorter course of ZDV started later in pregnancy also has proven efficacy in reducing the risk for mother-to-child transmission. Current data demonstrate that short antenatal/newborn regimens are significantly less effective than the full antenatal/newborn regimen.¹⁰ The impact of most other antiretroviral agents used either singly or in combination on prevention of perinatal transmission remains unknown and is the subject of current clinical studies. When ZDV is used for the prevention of transmission, treatment should be initiated after the first trimester in order to avoid exposure during the period of major human organogenesis.

For the treatment of maternal health, recommendations for initiating highly active antiretroviral therapy (HAART) should be based on plasma viral load, CD4 cell count, and clinical history.

For those pregnant women already known to be seropositive, formulation of an appropriate treatment regimen requires knowledge of prior use of ZDV and other antiretrovirals, as well as consideration of previous drug toxicities, other medications, clinical conditions, and adherence to the regimen.

For those patients who become pregnant while receiving antiretroviral therapy, the decision to continue or interrupt the current regimen is complex and should be consistent with practice guidelines for adults and decided on an individualized basis with consideration of potential toxicity to the fetus.

Both the success and toxicity of the current regimen should be evaluated. Factors to consider include first trimester safety during the period of major human organogenesis and other potential maternal or fetal toxicities. Discontinuation of maternal treatment is likely to be associated with rebound viremia and may have potentially adverse effects on maternal health and/or mother-to-child transmission. Discontinuation of a single drug from a successful combination regimen may result in selection of resistant virus. For patients who have had good virologic and clinical responses to their current antiretroviral regimen, the benefits of continuing therapy may outweigh the risks even during the first trimester.

The choice of HAART should be made in consultation with an HIV Specialist.

The choice of HAART is often complex and involves an understanding of the pharmacokinetics, toxicities, and drug interactions (see Appendix III). Therapeutic choices should be made to reduce selection of strains of resistant viruses that would diminish future treatment options. **Efavirenz is not recommended during pregnancy because of teratogenicity in animal studies.**

Whenever a HAART regimen is either initiated or changed during pregnancy, incorporation of ZDV is recommended unless otherwise contraindicated.

Only three drugs/drug combinations have been proven in clinical trials to be effective in reducing maternal-infant transmission: ZDV, short course ZDV/3TC or nevirapine (NVP). However, the full three-part antepartum, intrapartum, and newborn PACTG.076 ZDV regimen is the best studied effective regimen. Studies have demonstrated that antenatal duration of ZDV as short as 2-4 weeks prior to delivery is still beneficial.

The goal of therapy for treatment of maternal health is to control viral replication. Antiretroviral regimens that reduce viral loads are associated with better outcomes and fewer opportunistic infections or death.^{76, 79} The likelihood of long-term successful viral suppression and immune reconstitution is still unknown. The appropriate treatment for patients with low circulating viral loads is currently under investigation.

Therapeutic agents inhibiting different parts of the HIV-1 replications cycle are typically combined in a treatment regimen. It is possible to achieve undetectable plasma viral levels in many patients, as measured by current assays, although the duration of therapeutic response is not known. Highly active antiretroviral combination therapies (HAART) utilizing three or more drugs in combination have been recommended for initial therapy.^{76, 77, 79}

The three-drug combinations most commonly used during pregnancy include two nucleoside reverse transcriptase inhibitors (NRTIs) with a protease inhibitor. Other three-drug combinations seen in clinical practice but not well studied include combinations of an NRTI and nonnucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor, as well as combinations of two protease inhibitors and an NRTI. Salvage regimens (treatment regimens for those failing the usual HAART therapies) generally consist of more than three-drug combination regimens, frequently employing 4-6 drugs. **The NNRTI, efavirenz, is not recommended during pregnancy because of teratogenicity in animals.**

The indications for changing an antiretroviral regimen include treatment failure, toxicity, non-adherence, and current use of a suboptimal treatment regimen. Treatment failures are indicated by a significant increase in the HIV RNA levels, failure to achieve the desired reduction in plasma viral load, a declining CD4 cell count, treatment intolerance, or clinical disease progression.

For more specific information regarding antiretroviral therapy, see the NYSDOH/AIDS Institute document *Criteria for the Medical Care of Adults with HIV Infection*.⁷⁶

Factors to consider in selecting the appropriate HAART regimen in all HIV-infected patients include:

Relative ability of available regimens to inhibit HIV-1 replication for prolonged periods of time (potency and durability of the response);

Relative ability of available agents to delay or prevent the emergence of drug-resistant HIV variants;

Relation between the emergence of drug resistance and future treatment failures;

Toxicities associated with prolonged therapy;

The patient's ability to adhere to complex treatment regimens; and

Development of cross-resistance resulting in limitation of future treatment options.

Pregnancy presents unique treatment considerations including:

Concerns about the infant's drug exposures during the first trimester (the critical time for human organogenesis);

Both short- and long-term safety for both uninfected infants and infected infants following in utero exposures;

Impact of maternal antiretroviral therapy to optimize maternal health and prevent mother-to-child HIV-1 transmission;

Impact of antiretroviral regimens utilized during pregnancy on the ability to control maternal viremia in the future;

Impact of antiretroviral regimen utilized during pregnancy on selection of resistant virus that may or may not be transmitted to the newborn; and

Pregnancy-associated symptoms (emesis, heartburn, depression) that may limit adherence and potentially increase the risk of drug resistance during pregnancy and in the postpartum period.

D. LABOR AND NEWBORN MANAGEMENT WHEN THERE IS NO ANTENATAL ANTIRETROVIRAL TREATMENT

RECOMMENDATIONS:

For women who have received no antenatal antiretroviral therapy, reasonable options for prevention of transmission include: 1) intrapartum intravenous ZDV followed by 6 weeks of ZDV to the newborn; 2) single-dose nevirapine at the onset of labor followed by a single dose of nevirapine to the newborn at 48 hours; 3) oral ZDV/3TC during labor followed by 1 week of oral ZDV/3TC to the newborn; or 4) the 2-dose nevirapine regimen combined with intrapartum intravenous ZDV and 6 weeks of ZDV to the newborn.

If the mother has not received antiretroviral therapy during labor, 6 weeks of newborn therapy with ZDV is still recommended because epidemiologic data indicate some protection may be seen. In such situations, ZDV should be started as soon as possible after birth (preferably within 12 hours). In this circumstance, clinicians

may consider the addition of a single dose of nevirapine given to the newborn as soon as possible after birth in addition to the 6-week newborn ZDV regimen. This is based on theoretical considerations, however, because no data currently exist to address the additional benefits of nevirapine in such situations.

When maternal therapy has not been given, the efficacy and safety of HAART given to the newborn to prevent transmission have not been studied and are unknown.

In the absence of data regarding efficacy of other regimens, ZDV alone, ZDV/3TC, nevirapine alone or in combination with ZDV are acceptable regimens in the intrapartum/newborn setting when the mother has received no antenatal antiretroviral therapy.

Current scientific data show a significant risk of HIV-1 transmission at the time of labor and delivery. Observational data from New York State support the efficacy of intrapartum/newborn therapy and even limited efficacy for newborn treatment when initiated soon after birth.¹⁰ Data from HIVNET 012 also support the efficacy of single-dose oral NVP in labor and within 72 hours of life in reducing transmission.¹¹ Data from the PETRA study also support the efficacy of ZDV/3TC administered in labor and for 1 week to the newborn.¹¹ There are no data on safety or efficacy of combining ZDV and NVP for preventing perinatal transmission.

E. TRANSFER OF HIV INFORMATION FROM OBSTETRICAL CARE PROVIDER TO THE LABOR AND DELIVERY UNIT

RECOMMENDATIONS:

Antepartum medical records must be transferred to the labor and delivery unit preferably early in the third trimester.

In New York State, transfer of HIV information does not require a special HIV consent form. HIV information should be transferred with all other prenatal information with the usual protection of patient confidentiality. The general medical consent signed to transfer all prenatal records is adequate to include HIV information.

F. MODE OF DELIVERY

RECOMMENDATIONS:

Cesarean section with intact membranes and before the onset of labor offers an additional protective effect. Cesarean section prior to onset of labor or ruptured membranes is recommended for women with no antenatal antiretroviral therapy or with an elevated viral load at the time of delivery. The protective effect of cesarean section delivery has not been confirmed for women with suppressed viral load (<1,000 copies/mL). Although the risk of cesarean section delivery is significantly higher than vaginal delivery, the added risk of cesarean delivery among HIV-infected pregnant women compared with non-HIV-infected women is small or negligible in most instances.

The benefit of cesarean delivery for HIV-infected pregnant women is described for women whose cesarean delivery took place prior to the onset of labor and prior to rupture of membranes. After onset of labor or rupture of membranes, transmission rates were not statistically different from vaginal delivery. Emergency cesarean delivery was not associated with decreased transmission. When maternal HIV RNA level is less than 1,000 copies/mL, transmission rates approach zero, with cesarean delivery offering no added benefit.

A woman's autonomy in deciding which mode of delivery is best for her should be respected.

G. MATERNAL SAFETY MONITORING

RECOMMENDATIONS:

Clinicians monitoring pregnant women on ZDV or combination antiretroviral therapy should order complete blood counts and liver function tests at the start of therapy as well as other tests appropriate for the treatment regimen. These tests should be repeated every 4-6 weeks or as indicated.

For pregnant women on ZDV therapy, dose interruption or dose modification should be considered when serum hemoglobin levels fall below 8.5 g/dL and/or there is an elevation in liver function tests that is three times higher than baseline and that cannot be attributed to any other medical or obstetrical condition. Use of stimulating factors such as erythropoietin may be considered to support hematologic abnormalities. Dose interruptions/modifications of other antiretrovirals should be done in consultation with an HIV Specialist.

Monitoring of HAART during pregnancy should be consistent with recommendations for non-pregnant adults.⁷

Dosing and toxicities of currently available antiretroviral agents are included in Appendix III.

H. MANAGEMENT OF THE WOMAN WITH UNKNOWN HIV STATUS AT LABOR AND DELIVERY

RECOMMENDATIONS:

In New York State, HIV counseling and consented expedited testing are required if a woman presents in labor with no prenatal HIV test result and is not known to be HIV-infected.

If the mother declines testing during labor, the infant must be tested immediately after birth. In this setting, written informed consent for testing the newborn is not required.

HIV test results must be returned as soon as possible but no later than 48 hours after the specimen is drawn.

The meaning of a positive preliminary test result should be discussed with the mother, and based on this discussion, the mother and the physician must decide whether or not to initiate antiretroviral prophylaxis.

Antiretroviral prophylaxis should be initiated as soon as possible in labor or after birth. It is unlikely to be beneficial if initiated beyond 48 hours after birth.

I. TRANSFER OF INFORMATION FROM OBSTETRICAL CARE PROVIDER TO PEDIATRIC CARE PROVIDER

RECOMMENDATIONS:

In New York State, labor and delivery records must document maternal HIV counseling and testing history. Ideally, this information should be available prior to labor.

For seropositive women, labor and delivery records should document maternal antiretroviral treatments during the current pregnancy, including specific medications, weeks of gestation at initiation of treatment, duration of treatment, and, if possible, a note about adherence.

Information should be routinely transferred to the newborn's pediatric record and the child's primary care provider.

Emphasis should be placed on the need for the child's guardian to share responsibility for transmitting information about the child's history of antiretroviral exposure with future primary care providers.

An appointment with a pediatric HIV Specialist should be made before the infant is discharged from the nursery. Precautions for confidentiality of patient information should be ensured.

PEDIATRIC MANAGEMENT TO REDUCE PERINATAL TRANSMISSION

A. ANTIRETROVIRAL THERAPY OF THE NEWBORN AND MONITORING

RECOMMENDATIONS:

All HIV-exposed newborns should be treated with ZDV for 6 weeks as part of the three-part regimen to prevent transmission.

Premature infants will require ZDV dose modification. Consultation with an HIV Specialist is recommended.

For newborns exposed to ZDV, a complete blood count should be obtained at birth and at the completion of the 6-week course of therapy. Some clinicians recommend an additional monitoring visit at 3-4 weeks of life to assess the need for dose interruption or modification based on weight gain of the infant.

Uninfected infants and children exposed to ZDV and other antiretroviral drugs *in utero* and in early infancy may be at risk for potential late onset drug-related toxicities. If future screening is required to assess for this possibility, it is important to ensure that the prenatal antiretroviral drug exposure information is in the child's medical record. Clinicians who care for HIV-exposed infants in the newborn period should inform families that this information needs to be shared with the child's future health care providers, guardians, and caretakers.

For infants born to mothers whose HIV-infection status is unknown, NYSDOH regulations now require that HIV testing be completed within 48 hours after the test is drawn. If the mother's HIV status is unknown, the infant's preliminary HIV-antibody status must be determined as soon as possible after birth. If this preliminary test is positive, the clinician should discuss with the mother the likelihood that the test result is a true positive, assess her risk for being HIV-infected, and discuss the risks and benefits of initiating antiretroviral prophylaxis with ZDV, or ZDV and NVP. Administration of ZDV or other antiretroviral treatment is included in the general medical consent permitting treatment with other medications and does not require a separate written consent.

Identification of an infant's HIV exposure may not take place until after the immediate newborn period due to factors such as receipt of results of newborn testing by the state laboratory or the infant's birth outside of New York State. If breastfeeding has been initiated, some experts would consider initiating prophylaxis of the infant at the time the maternal HIV status becomes known. The mother should be counseled to discontinue breastfeeding. The infant should undergo HIV DNA PCR testing. If the infant is infected, the prophylaxis should be continued.

laxis should be discontinued and combination antiretroviral treatment for HIV infection is recommended. If the infant is uninfected, the 6-week ZDV prophylaxis course should be completed.

Although anatomical abnormalities have not been reported to date, all infants exposed to antiretroviral agents *in utero* should be examined for congenital abnormalities.

This cautious approach is especially important if exposures to any antiretroviral agents have occurred during the first trimester, the period of major human organogenesis.

Zidovudine is the primary agent currently recommended for the prevention of maternal-infant transmission. A significant reduction in maternal-infant transmission has been demonstrated in clinical trials (PACTG 076,⁴ PACTG 185,⁷ and the short-course ZDV study in Thailand¹⁰), by observational data and extensive experience with the pharmacokinetic profile of ZDV, and through the clinical finding that this therapy is well tolerated by both the mother and infant.

In a population of infected women who breastfed and who received no antenatal antiretroviral therapy in Uganda,¹² NVP was shown to be effective in reducing maternal-infant transmission when given as a single dose in labor and to the newborn within 72 hours after birth. In this study, NVP showed superior efficacy compared with short-course maternal ZDV during labor, and for 7 days in the newborn.

Effective August 1, 1999, NYSDOH regulations require that, in situations where the HIV-serostatus of a woman at the time of labor and/or delivery is not known, HIV counseling and expedited HIV-antibody testing be performed. These changes will lead to the additional identification of many seropositive infants born to women who did not receive antiretroviral therapy. In such cases, antiretroviral prophylaxis should be instituted as soon as possible. Epidemiologic data indicate that some protection may be seen if the 6-week regimen is initiated soon after birth (preferably within 12 hours).¹³ The antiretroviral prophylaxis regimen should include at least the 6-week ZDV regimen. Additionally, in this circumstance, the clinician may consider the addition of a single dose of nevirapine given to the newborn as soon as possible after birth in addition to the 6-week ZDV regimen. This recommendation is based on extrapolations from the HIVNET 012 trial,¹² where NVP given once to the mother intrapartum and once to the newborn significantly reduced transmission risk. However, there are currently no data to address whether NVP would have any benefit in the absence of intrapartum maternal NVP treatment. Similar data from the PETRA trial indicate that ZDV/3TC given to the mother intrapartum and the mother and newborn for 1 week reduces transmission by 37% compared with placebo.¹¹ However, the use of ZDV/3TC in the newborn alone was not studied; and the addition of 1 week of 3TC to the 6-week ZDV regimen is of unproven benefit. The safety of other antiretroviral drugs or combinations of drugs (e.g., HAART) given to the newborn has

not been studied. Their use is not currently recommended.

The use of HAART as chemoprophylaxis in the newborn has been advocated by some clinicians. Currently, there are no data that demonstrate equivalent or greater efficacy in preventing transmission by substituting or adding other antiretroviral agents to the ZDV component of the PACTG 076 chemoprophylaxis regimen for newborns. A thorough discussion of the potential risks and benefits must ensue in situations where more aggressive treatment is used. Factors to be considered include:

Availability of pediatric formulations;

Pharmacokinetics data which suggest a rational dosing regimen for newborns 0-6 weeks of age;

Potential associated carcinogenicity; and

Laboratory and/or clinical toxicities which may be further complicated by drug-drug interactions.

RECOMMENDATIONS:

Consultation with an HIV Specialist is strongly advised for the premature infant, for whom additional caution in utilizing these agents is warranted.

The ZDV dose for full-term infants is 2.0 mg/kg PO every 6 hours or 1.5 mg/kg intravenously every 6 hours if the infant is not able to tolerate oral feedings. The hepatic glucuronidation enzymatic system, the major route of ZDV metabolism, is relatively immature in newborns and especially in preterm infants. This phenomenon results in delayed ZDV clearance, resulting in the increased half-life of ZDV observed in a study of premature infants (26-32 weeks of gestation).¹⁴ A regimen of oral or intravenous ZDV dose of 1.5 mg/kg every 12 hours during the first 2 weeks of life followed by a regimen of 2.0 mg/kg every 8 hours until 6 weeks of age is now being evaluated in a phase I trial of preterm infants.

Following exposure to the PACTG 076 ZDV regimen, the only observed short-term toxicity has been a mild, reversible anemia within the first 6 weeks of life. With greater utilization of HAART during pregnancy, *in utero* exposures to agents other than ZDV will be more common. At the present time, insufficient data exist that address newborn toxicities following *in utero* exposures to other antiretroviral agents, either singly or in combination.

B. NEWBORN/INFANT TESTING FOR HIV-INFECTION STATUS

RECOMMENDATIONS:

Routine evaluations should be performed for the early diagnosis of newborn HIV infection. There are many different acceptable testing schedules. One acceptable schedule includes an HIV DNA PCR within 1 week, at 2 weeks, at 4-6 weeks, at 6-12 weeks, and at 4-6 months.

For initial HIV testing, clinicians may either use the New York State Department of Health's Wadsworth Center in Albany which provides testing at no cost (telephone no. 518-474-2160) or submit documentation of HIV diagnostic test results (HIV DNA PCR or HIV culture) from a laboratory with an appropriate New York State permit.

Plasma HIV RNA PCR is not appropriate as the sole diagnostic assay.

Definitive diagnosis of HIV-1 infection can be made in most infants by 6 months of age using the HIV-DNA polymerase chain reaction (DNA-PCR) assay.⁸¹ HIV infection can be reasonably excluded in HIV-exposed infants with two or more negative HIV DNA PCR tests, one performed at or after age 1 month and one at or after age 4 months. An infected child is one at any age who has tested positive by PCR on two separate determinations. In PACTG 076, infants who received ZDV prophylaxis had no delay in the time to establish or exclude definitive diagnosis of their HIV-infection status. The length of time to establish HIV status has not been studied in infants born to women receiving other antiretroviral therapy.

C. CLINICAL MANAGEMENT OF HIV-EXPOSED INFANTS

RECOMMENDATIONS:

Infants should be tested for HIV-infection (see section B).

Infants identified as HIV-infected should receive comprehensive medical and psychosocial care in accordance with the updated NYSDOH/AI guidelines.⁸² Consultation with an HIV Specialist is strongly recommended.

Antiretroviral prophylaxis should be discontinued once a diagnosis of HIV infection has been made. An antiretroviral treatment regimen should be initiated in consultation with a pediatric HIV Specialist.

At 4-6 weeks of age, prophylaxis to prevent PCP should be initiated for HIV-exposed as well as HIV-infected infants.

Breastfeeding by HIV-infected women is not recommended in the United States; if the infant has been breastfeeding, the mother should be counseled to discontinue.

D. PEDIATRIC FOLLOW-UP

RECOMMENDATIONS:

The pediatric medical record should document all antiretroviral exposures during gestation and early infancy. Vital information includes the names of the antiretroviral agent(s), dosage, duration of exposure, and, if possible, a note about adherence.

Clinicians need to develop confidential systems to track and, if necessary, contact antiretroviral-exposed, HIV-uninfected individuals if long-term toxicities are suspected or identified.

The New York State Department of Health is developing methods to look at long-term follow-up of antiretroviral-exposed infants.

Clinicians should emphasize the need for the child's guardian to share responsibility for transmitting the child's history of antiretroviral exposure to future primary care providers.

Adherence to public health guidelines to prevent mother-to-child HIV transmission and the treatment of maternal HIV disease during pregnancy will result in a large number of uninfected children with exposures to antiretroviral agents both *in utero* and in early infancy. It is also likely that in the future, a greater number of infants born to HIV-infected mothers will have multiple *in utero* antiretroviral exposures earlier in gestation. The possibility of unanticipated, long-term toxicities remains a concern. For these reasons, as these children age, it is critical that information concerning their antiretroviral exposures not be lost.