Antiretroviral Therapy During Pregnancy and Early Neonatal Life: Consequences for HIV-Exposed, Uninfected Children

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Women have emerged as the fastest growing human immunodeficiency virus (HIV) infected population worldwide, mainly because of the increasing occurrence of heterosexual transmission. Most infected women are of reproductive age and one of the greatest concerns for both women and their physicians is that more than 1,600 infants become infected with HIV each day. Almost all infections are a result of mother-to-child transmission of HIV. With the advent of combination antiretroviral therapies, transmission rates lower than 2% have been achieved in clinical studies. Antiretroviral compounds differ from most other new pharmaceutical agents in that they have become widely prescribed in pregnancy in the absence of proof of safety. We reviewed antiretroviral agents used in pregnant women infected with human immunodeficiency virus, mother-to-child transmission, and their consequences for infants.

Key Words: HIV-1, exposed, infant, consequences, antiretroviral.

At the end of 2000, it was estimated that over 36 million people were living with the human immunodeficiency virus (HIV). This includes 1.4 million children less than 15 years of age; more than 1,600 infants become infected with HIV each day [1]. Almost all infections are a result of mother-to-child transmission of HIV [2].

Significant progress has been made in the battle against transmission of HIV from mother to infant. Antiretroviral (ARV) regimens covering the latter part of gestation, labour and the first few weeks of neonatal life have shown great efficacy in reducing such transmission. With the advent of combination antiretroviral therapies, transmission rates lower than 2% have been achieved in clinical studies. Elective caesarean delivery has been shown to enhance the benefit of antiretroviral regimens, however the risks associated with this approach in many resource-poor settings in developing countries limit its role worldwide. Abbreviated antiretroviral regimens covering labour and the first few days of neonatal life have shown considerable promise in the developing world, resulting in a 50% reduction in transmission [3].

Antiretroviral compounds differ from most other new pharmaceutical agents in that they have become widely prescribed in pregnancy in the absence of proof of safety. Combinations of three or more compounds are recommended when treatment of the mother is deemed necessary because of advanced HIV infection. Though many thousands of women have undertaken antiretroviral therapy to reduce the risk of transmission, documented experience in human pregnancy unfortunately is lacking, with the possible exception of

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zidovudine (ZDV), which has been prescribed in clinical trials to several hundred mother-infant pairs [4]. Although there is no evidence of teratogenicity caused by antiretroviral drugs (ARV) given alone during the first trimester, exposure to a combination of ARV and folate antagonists was associated with a significantly higher risk of congenital abnormalities in a study of 195 mother-infant pairs [5]. We examined the safety of antiretroviral regimens currently used and most frequently tested in clinical trials on HIV-exposed, uninfected children to interrupt HIV mother-to-child transmission.

Use of antiretroviral drugs in pregnant HIV-1 infected women and interventions to reduce perinatal HIV-1 transmission

It is a consensus that pregnancy is not a reason to defer standard therapy. The use of antiretroviral drugs in pregnancy requires unique considerations, including the potential need to alter dosing as a result of physiological changes associated with pregnancy, the potential for adverse short or long-term effects on the fetus and newborn, and the effectiveness in reducing the risk for perinatal transmission [6]. Health care providers consider that the use of antiretrovirals in HIV infected women during pregnancy must take into account two issues: antiretroviral treatment of the woman’s HIV infection and antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV transmission [7].

The potential harm to the fetus from maternal ingestion of a specific drug not only depends on the drug itself, but on the dose used, the gestational age at exposure, the duration of exposure, the interaction with other agents to which the fetus is exposed, and to an unknown extent, the genetic makeup of the mother and fetus [6].

The benefits of antiretroviral therapy in a pregnant woman must be weighed against the risk for adverse events to the woman, fetus and newborn. Although ZDV chemoprophylaxis alone has substantially reduced the risk of perinatal transmission, when considering treatment of pregnant women with HIV infection, antiretroviral monotherapy is now considered suboptimal for treatment and combination drug therapy; two nucleoside analogues and one protease inhibitor is the current standard of care [7].

Zidovudine

Mother-to-child transmission

In 1996, final results were reported for all 419 infants enrolled in PROTOCOL AIDS CLINICAL TRIAL GROUP (PACTG) 076. It consisted of an antenatal treatment starting at 14 or 28 weeks gestation, continuing with intravenous intrapartum and then treatment of the neonate for six weeks. The results are similar to those initially reported in 1994; the estimated HIV transmission rate for infants who received the placebo was 22.6%, compared with 7.6% for those who received ZDV, giving a 66% reduction in risk of transmission [8].

In a short–course antenatal and intrapartum ZDV perinatal transmission prophylaxis trial in non-breast-feeding women in Thailand, administration of ZDV 300 mg twice daily for four weeks antenatally and 300 mg every three hours orally during labor reduced perinatal transmission by approximately 50%, compared to the placebo. Transmission decreased from 19% in the placebo group to 9% in the ZDV group [9].

In contrast, a second trial in breast-feeding women in Thailand compared administration of ZDV antenatally starting at 28 or 36 weeks gestation, orally intrapartum and in the neonate for three days or six weeks. The transmission rate was similar to that observed in infants who received no ZDV chemoprophylaxis [10].

Another epidemiological study found that administration of ZDV to the neonate for six weeks was associated with a significant reduction in transmission if the drug treatment was initiated within 12-24 hours of birth. This was consistent with a possible preventive effect of rapid postexposure prophylaxis [11,12].

The PACTG 185 enrolled pregnant women with advanced HIV disease and low CD4 T-lymphocyte counts who were receiving antiretroviral therapy; 24% had received ZDV before the pregnancy at the time of the study. Since advanced maternal HIV disease has
been associated with increased risk for perinatal transmission, the transmission rate in the control group was hypothesized to be 11%-15%, despite the administration of ZDV. The results of this trial confirm the efficacy of ZDV observed in PACTG 076, and extend this efficacy to women with advanced disease, low CD4 count, and prior ZDV therapy [13]. Rates of perinatal transmission have been documented to be as low as 3%-4% among women with HIV infection who receive all three components of the ZDV regimen, including women with advanced HIV disease [10,13].

The risk of transmission using a “short-short” course of ZDV, from 35 weeks in pregnancy for the mother and for the newborn until 3 days old; was higher than the risk using a “long-long” course; from 28 weeks in pregnancy for the mother and for the newborn until 6 weeks old (odds ratio (OR) 2.33, 95% confidence interval (CI) 1.16 to 4.68). However, the effectiveness of the long-short course (from 28 weeks in pregnancy for the mother and for the baby until 3 days old) and the short-long course (from 35 weeks in pregnancy for the mother and for the baby until 6 weeks old) did not differ from that of the long-long course [6].

Epidemiological data from a New York State study suggest a decline in transmission when infants were given ZDV during the first 6 weeks of life, compared to no prophylaxis [11,12]. Transmission rates were 9% (95% CI, 4.1%-17.5%) for newborn only prophylaxis (initiated within 48 hours after birth), compared to 18% (CI 7.7%-34.3%) when initiated after 48 hours, and 27% (CI 21%-33%), with no ZDV prophylaxis [11]. In contrast, epidemiological data from North Carolina did not demonstrate a benefit of newborn only ZDV, compared to no prophylaxis. In this study, transmission rates were 27% (CI 8%-55%) for newborn only prophylaxis and 31% (CI 24-39%) for no prophylaxis; however the timing of infant prophylaxis initiation was not defined in this study [10]. In most studies of animals, antiretroviral prophylaxis initiated 24-36 hours after exposure normally is not effective for preventing infection, although later administrations have been associated with decreased viremia [14-16].

In an international randomized trial of mode of delivery, transmission was 1.8% in women who had elective cesarean delivery; many of these women received ZDV [17].

**HIV mother-to-child transmission reducing mechanisms**

The mechanism by which ZDV reduced transmission in PACTG 076 has not been fully defined. The effect of ZDV on maternal HIV-1 RNA does not fully account for the observed efficacy of ZDV in reducing transmission. Preexposure prophylaxis of the fetus or infant may be a substantial component of protection. If so, transplacental passage of antiretroviral drugs would be crucial for the prevention of transmission. Additionally, in placental perfusion studies, ZDV has been found to be metabolized into the active triphosphate within the placenta, which could provide additional protection against intrauterine transmission [18,19]. This phenomenon may be unique to ZDV, because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogues that have been evaluated. This is consistent with a possible preventive effect of rapid postexposure prophylaxis [20,21].

Serum ZDV levels, and its metabolite in umbilical cord blood after continuous intravenous administration, appeared to be similar to maternal concentrations, with a significant positive correlation. Zidovudine was observed to have placental passage, with a newborn: mother drug ratio of about 0.85. On the other hand, maintenance of optimal virustatic ZDV concentrations with oral antenatal and oral intermittent intrapartum ZDV dosage regimens has been achieved in only 53%-83% of cases [22,23].

**Congenital abnormalities**

Similar rates of congenital abnormalities has been found in infants with and without intrauterine ZDV exposure. No increased risk was found for newborn structural abnormalities among infants born to women who receive ZDV antenatally, when compared with the general population [8,24].

No significant differences in ventricular function were observed between infants exposed versus unexposed to ZDV [25].
Neurodevelopment

Zidovudine prophylaxis has been implicated, although this is unproven, in developmental, neurological and cognitive problems [26]. Data for uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years (range 3.2-5.6 years) have not indicated any differences in cognitive and neurodevelopment status among infants born to mothers who received ZDV, compared with those born to mothers who received a placebo [27]. An investigation performed in Venezuela with 77 singleton pregnancies demonstrated in follow-up until three years old, failure to thrive in five children, gross motor development delays in two, and hyperactivity disorder in a toddler with recurrent urinary tract infections whose mother received prenatal ZDV for 24 weeks [26]. In infants followed through age 18 months in PACTG 076, the occurrence of neurological events was rare; seizures occurred in one child exposed to ZDV, in two exposed to a placebo, and one child in each group reported spasticity [27].

Immunological status

Data from follow-up of PACTG 076 uninfected infants through age six years did not indicate any differences in lymphocyte subsets or immune functions compared with uninfected children who had received ZDV and those who had received a placebo [27].

Growth parameters

Maternal ZDV prophylaxis did not result in growth differences (weight, height, head circumference) compared with unexposed counterparts. Similar data were found in another study [27,28].

Mitochondrial dysfunction

An alert was published during 1999 by the French Perinatal Cohort: eight cases of mitochondrial dysfunction were reported among 1,754 infants exposed to nucleoside analogues in utero and during the neonatal period. It was observed that ZDV induced mitochondrial DNA dysfunction in monkeys and neurobehavioral effects in mice at a dose similar to the human dose [29]. Nucleoside analogue drugs are known to induce mitochondrial dysfunction, as the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction [30]. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine (ddC), lamivudine, zidovudine and abacavir [31]. Toxicity related to mitochondrial dysfunction has been reported in infected patients receiving long-term treatment with nucleoside analogues, and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested [30]. Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance. Emerging complications, such as mitochondrial toxicity and transplacental carcinogenesis, make it necessary to monitor infants born to antiretroviral-exposed mothers until they reach reproductive age [30]. These syndromes have similarities to the HELLP syndrome that occurs during the third trimester of pregnancy. A number of investigators have correlated these pregnancy-related disorders with a recessively inherited mitochondrial abnormality in the fetus/infant that results in an inability to oxidize fatty acids [32]. Since the mother would be a heterozygotic carrier of the abnormal gene, there may be an increased risk of liver toxicity due to an inability to properly oxidize both maternal and accumulating fetal fatty acids [33]. Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to nucleoside analogue drugs, which is thought to be related to mitochondrial toxicity; it has been reported in infected individuals treated with nucleoside analogue drugs for long periods of time (>6 months). It is unclear if pregnancy augments the incidence of lactic acidosis and hepatic steatosis syndromes in non-pregnant individuals receiving nucleoside analogue treatment [6]. ZDV alone (in four infants) resulted in indications of mitochondrial dysfunction after the first few months of life [34]. No deaths attributable
to mitochondrial dysfunction were found in this evaluation of 9067 perinatally exposed, uninfected or indeterminate children born from 1993 through 1998 [35].

In a large database that included 223 deaths in over 20,000 children, with and without antiretroviral drug exposure, who were born to HIV-infected women, followed prospectively in several large cohorts in the United States, no deaths similar to those reported from France were identified [36]. Children with intrauterine antiretroviral exposure who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction [34].

Rapid disease progression (RDP)

Brocklehurst and Volmink [1] found that ZDV appears to decrease the risk of infant death during the first year of birth (OR 0.57, 95% CI 0.38-0.85). In PACTG 076 exposed infants, observed mortality at 18 months was 1.4% in ZDV-exposed, compared to 3.5% in placebo infants [8]. In contrast, another clinical study made with 291 infants, 139 of which used ZDV, the rapid disease progression rate was 29.4% in the no ZDV group compared with 70.6% in the ZDV group (p=0.012). In this study, prematurity was significantly associated with a higher risk of rapid disease progression (p=0.027). The rate of RDP was significantly higher among perinatally infected infants born to HIV-infected mothers treated with ZDV, than among infected infants born to untreated mothers. This could be due to the ability of ZDV to block intrapartum transmission preferentially and also to a lack of rapid disease progression resulting from intrapartum transmission [37].

Hepatic and hematological parameters

Mild anemia is to be expected in ZDV exposed infants, probably secondary to decreased maturation of the ZDV-compromised erythroid progenitor cells [38]. A study performed in Venezuela demonstrated no anemia at birth in babies of HIV-seropositive ZDV-treated women, but it was found in 90 per cent of newborns after six weeks of ZDV treatment, with resolution after stopping treatment. Anemia has been the primary complication of the six-week ZDV regimen in the neonate [39]. Infants who have anemia at birth, or who are born prematurely, warrant more intensive monitoring. Hematological parameters and serum alanine aminotransferase (ALT) levels associated with short-term neonatal antiretrovirals during one week did not differ between groups exposed to ZDV and the control group at birth. At six weeks of age, ALT levels were higher among the treated groups, compared with the control group (geometric mean 11.5 U/L for controls and 16.2-19.1 for treated groups; p=0.0001) and levels of hemoglobin, hematocrit, granulocytes and platelets were significantly lower. These changes were consistent with mild grade toxicity and were more noticeable among HIV-infected infants [40].

Pregnancy outcome

The birth outcome of children born of mothers who received ZDV as part of the PACTG trial was not compromised. There is no evidence that zidovudine influences the incidence of premature delivery (OR 0.86, 95% CI 0.57 to 1.29) or low birth weight (OR 0.74, 95% CI 0.53 to 1.04) [1]. Among 497 HIV-infected pregnant women enrolled in PACTG 185, 86% received antenatal monotherapy, predominantly zidovudine; the observed risk factors for adverse pregnancy outcomes in antiretroviral treated HIV-infected women were similar to those reported for uninfected women, independent of antiretroviral use, prior preterm birth, multiple gestation, antenatal alcohol use, antenatal diagnosis of genital herpes or pre-eclampsia, and antenatal cigarette use [13].

Antepartum fetal monitoring for women who receive only ZDV chemoprophylaxis should be performed, as clinically indicated, because data do not indicate that ZDV use in pregnancy is associated with increased risk for fetal complications [6].

Short-term malignancies

Data that demonstrate the short-term safety of the ZDV regimen are now available as a result of follow-
up of infants and women enrolled in PACTG 076. No malignancies were observed in short-term (up to six years of age) follow-up of more than 727 infants from PACTG 076 and from a prospective cohort study involving infants who have had intrauterine ZDV exposure [41].

Long-term malignancies
Follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Recent data from studies of animals concerning the potential for transplacental carcinogenicity of ZDV have demonstrated noninvasive vaginal epithelial tumors in rodents, showing the need for long-term follow-up of children exposed to antiretrovirals in the uterus [42].

Combination antiretroviral without protease inhibitors
Data suggest that antenatal use of combination antiretroviral regimens may further reduce transmission. Less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. A few years ago, a combination drug therapy with two nucleoside analogues, without protease inhibitors, was utilized. The most common scheme was association between zidovudine and lamivudine.

Lamivudine (3TC)

Mother-to-child transmission
Serum lamivudine (3TC) levels in umbilical cord blood after administration appeared similar to maternal concentrations, with a significant positive correlation. lamivudine was observed to undergo placental passage, with a newborn: mother drug ratio of about 1.0 [6].

An open-label, non-randomized study in 445 women with HIV infection in France evaluated the addition of 3TC at 32 weeks gestation to standard ZDV prophylaxis; 3TC was also given to the infant for six weeks in addition to ZDV. The transmission rate in the ZDV/3TC group was 1.6% (95% confidence interval, 0.7-3.3%); in comparison the transmission rate in an historical control group of women receiving only ZDV was 6.8% (95% CI 5.1-8.7%) [43].

Hepatic and haematological parameters
Treatment with ZDV and lamivudine during pregnancy of 39 women resulted in neonatal anaemia in 62% of the newborns, with no children needing transfusion; mild elevations of liver function tests, primarily aspartate aminotransferase, were noted in 58% of the newborns tested, though none were clinically jaundiced and the overall rate of neonatal HIV infection was 2.5% [44].

A case of severe anaemia, with 11% haematocrit, was reported in an infant whose mother received ZDV, 3TC and ddc, as part of an antiretroviral regimen during pregnancy [39].

Mitochondrial dysfunctions
A French group reported that in a cohort of 1,754 uninfected infants born to HIV-infected women who received antiretroviral drugs during pregnancy, four uninfected infants with intrauterine and/or neonatal exposure to ZDV/3TC developed indications of mitochondrial dysfunction after the first few months of life. Two of these infants developed severe neurological disease and died (both of whom had been exposed to ZDV/3TC), three had no symptoms, but had transient laboratory abnormalities. An association between these findings and intrauterine exposure to antiretroviral drugs has not been established [34].

Pregnancy outcome
In a French open-label study of 445 HIV-infected women receiving ZDV who had lamivudine added to their therapy at 32 weeks gestation, the rate of preterm delivery was 6%, similar to the 9% rate in a historical control group of women receiving only ZDV [43]. Less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. Thus, more intensive fetal monitoring should be considered for mothers receiving such therapy, including assessment of fetal anatomy with level II ultrasound, and continued assessment of fetal growth and well being during the third trimester [6].
Neurodevelopment

No increased risk of neurological events was observed among children treated with ZDV/3TC, compared to a placebo, regardless of the intensity of treatment in 1,798 children that participated in PETRA, an African Perinatal Trial [45]. In a prospective cohort of 4,426 uninfected French children born to HIV-1-infected mothers, the risk of first febrile seizure was found to be higher for children perinatally exposed to nucleoside analogue antiretrovirals than for those who were not exposed (p = 0.0198) [46].

Congenital abnormality

No increased risk was found for newborn structural abnormalities among infants (6% of who had been exposed to ZDV/3TC antenatally), when compared with the general population. No significant differences in ventricular function were observed between infants exposed and unexposed to ZDV/3TC [25].

Malignancies

Follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. No tumors have been described in rodents [6].

Nevirapine

Mother-to-child transmission

Serum levels of nevirapine, a nucleoside non-analogue, measured in umbilical cord blood after administration, appeared similar to maternal concentrations, with a significant positive correlation. Nevirapine was observed to have placental passage, with a newborn: mother drug ratio of about 1.0 [6].

A large randomized controlled trial demonstrated that nevirapine given to mothers as a single dose at the onset of labour and to babies as a single dose within 72 hours of birth is more effective than intrapartum and postpartum regimens of ZDV (OR 0.51, 95% CI 0.33 to 0.79). In contrast, when nevirapine was given to mothers already receiving standard antiretroviral therapy, there appeared to be no additional advantage (OR 1.10, 95% CI 0.42 to 2.86) [1].

The frequency of resistance mutations in the reverse transcriptase gene was over 10% in most studies, and it reached as high as 23% [6].

Congenital abnormality

Follow-up has been too limited to provide a definitive assessment of congenital abnormality. A ventricular septal defect has been described in rodents [6].

Hepatic and hematological parameters

Hematological parameters and serum alanine aminotransferase (ALT) levels associated with short-term neonatal antiretrovirals during one week did not differ between the nevirapine plus ZDV and control groups [40].

Combination therapy with protease inhibitor

Little is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. Nowadays, combination drug therapy usually includes two nucleoside analogues and one protease inhibitor. Nelfinavir has been frequently chosen because it is FDA Pregnancy Category class B [6].

Nelfinavir

Mother-to-child transmission

In a longitudinal epidemiological study conducted in the U.S. since 1990, transmission was observed in 205 women with HIV infection who received no antiretroviral treatment during pregnancy; HIV was transmitted by 10.4% of the mothers who received ZDV alone, in 3.8% who received combination therapy without protease inhibitor, and in 1.2% who received combination therapy with protease inhibitor [47]. The effect of combination antiretroviral therapy in the mother and/or newborn on the sensitivity of infant virological diagnostic testing is unknown. Infants with negative virological tests during the first six weeks of life should have their diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen [6].
It is unlikely that scheduled cesarean delivery would further reduce this low transmission rate among treated women who have undetectable viral loads, and it would not be expected to prevent intrauterine transmission [6].

**HIV mother-to-child transmission reducing mechanism**

HIV-protease inhibitors prevent cleavage of gag and gal-pol protein precursors in acutely and chronically infected cells, arresting maturation and thereby blocking the infectivity of nascent virions. The main antiviral action of HIV-protease inhibitors is thus to prevent subsequent waves of infection. They have no effect on cells already harboring integrated proviral DNA. These agents are active against clinical isolates of HIV types 1 and 2. The absorption of the drugs is maximal within four hours after ingestion. Their elimination half-lives range from 1.8 to 5 hours; they have a high rate of placental penetration. Nelfinavir and ritonavir also reduce the plasma concentrations of other drugs, presumably because of hepatic enzyme induction. They reduce the area under the plasma-concentration-time curve of zidovudine by 35 percent and 25 percent, respectively, presumably because of the induction of glucuronyl transferases. However, the intracellular concentration of ZDV triphosphate (the active drug) is not normally affected by such a reduction in the plasma concentration of ZDV, and therefore no adjustment of the dose of ZDV is recommended when it is given with nelfinavir or ritonavir. The pharmacokinetics of other nucleoside analogues, which are mainly eliminated by the kidneys, are not affected by protease inhibitors [48,49]. HIV-protease inhibitors rapidly and profoundly reduce the viral load, as indicated by a decline in plasma HIV RNA concentrations within a few days after the start of treatment [50,51]. This causes plasma HIV RNA concentrations to be reduced by a factor of 100 to 1000 in 4 to 12 weeks. The frequency of primary resistance mutations in the protease gene ranges from 1-16% [6].

**Toxicity**

Data concerning potential toxicities in infants of mothers who have received combination antiretroviral therapy are limited. More intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life is advised in these infants. The clinical relevance of lactate levels in the neonatal period to assess the potential for mitochondrial toxicity has not been adequately evaluated [6].

**Pregnancy outcome**

Data are conflicting as to whether a combination of antiretroviral therapies during pregnancy is associated with adverse pregnancy outcomes, such as preterm delivery. A retrospective Swiss report evaluated the pregnancy outcome in 37 women treated with combination therapy. A possible association of combination antiretroviral therapy with pre-term births was noted, as 10 of 30 babies were born prematurely. The pre-term birth rate did not differ between women receiving combination therapy with or without protease inhibitors. In this study, the contribution of maternal HIV disease stage and other co-variates that might be associated with a risk for prematurity were not assessed [52]. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study reported data on 3,920 mother-child pairs. Adjusting for CD4 cell count and intravenous drug use, they found a 2.6 fold (95% CI, 1.4-4.8) increased chance of pre-term delivery in infants exposed to combination therapy, with or without protease inhibitors. In this study, the contribution of maternal HIV disease stage and other co-variates that might be associated with a risk for prematurity were not assessed [52]. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study reported data on 3,920 mother-child pairs. Adjusting for CD4 cell count and intravenous drug use, they found a 2.6 fold (95% CI, 1.4-4.8) increased chance of pre-term delivery in infants exposed to combination therapy, with or without protease inhibitors, compared to no treatment; women on combination therapy from before pregnancy who had initiated it prior to pregnancy were twice as likely to deliver prematurely as those starting therapy in the third trimester [53].

In contrast, in an observational study of pregnant women with HIV infection in the U.S. (PACTG 367), in which 1,150 of 1,472 women received combination therapy, no association was found between application of combination therapy and pre-term birth [6]. The highest rate of pre-term delivery was among women who had not received any antiretroviral therapy, consistent with several other reports that show elevated pre-term birth rates in untreated women with HIV infection [54-56]. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-infected pregnant women who delivered infants from 1990 through 1998, and who had received antenatal antiretroviral therapy,
and 1,143 women who did not receive antenatal antiretroviral therapy during pregnancy (monotherapy in 1,590, combination therapy without protease inhibitors in 396, and combination therapy with protease inhibitors in 137); use of multiple antiretroviral drugs as compared to no treatment or treatment with one drug was not associated with increased rates of preterm labor (OR, 1.08; 95% CI, 0.71-1.62), low birth weight (OR, 1.03; 95% CI, 0.64-1.63), low Apgar scores, or stillbirth [57]. In an observational study of pregnant women with HIV infection in Ribeirão Preto, Brazil, in which 25 of 55 women received combination therapy since 14 weeks pregnancy, 20 women received ZDV alone, and 10 women were the control group, no association was found between combination therapy and low umbilical cord blood pH or differences in base excess (P. El Beitune & G. Duarte, unpublished data). It is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia and its repercussion on the fetus/newborn [6].

In PACTG, 185 patients, 14% of whom received combination antiretrovirals, the observed risk factors for adverse pregnancy outcomes in antiretroviral treated HIV-infected women were similar to those reported for uninfected women, independent of antiretroviral use, prior preterm birth, multiple gestation, antenatal alcohol use, antenatal diagnosis of genital herpes or pre-eclampsia, and antenatal cigarette use [13].

Malignancies

Data remain insufficient to address the effect that exposure to antiretroviral agents in utero might have on long-term risk for neoplasia or organ-system toxicities in children. No tumor has been described in rodents [6].

Congenital abnormalities

Although there is no evidence of teratogenicity when ARV is given alone during the first trimester, exposure to the combination of ARV and folate antagonists was associated with a significantly higher risk of congenital abnormalities in a study of 195 mother-infant pairs [5].

Conclusion

ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, when considering treatment of pregnant women with HIV infection; antiretroviral monotherapy is now considered suboptimal for treatment, and combination drug therapy is the current standard of care. Public health agencies have recommended that the criteria for the use of highly active antiretroviral therapy should not be modified because of pregnancy.

In conclusion, follow-up of children with antiretroviral exposure should continue into adulthood because of concerns regarding potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. The emergence of drug-resistant strains of HIV may limit the long-term effectiveness of treatment with protease inhibitors. Important questions about protease inhibitors remain. The benefits of antiretroviral therapy in a pregnant woman must be weighed against the risk for adverse events to the woman, fetus and newborn.

References


