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Treating HIV During Pregnancy
An Update on Safety Issues

D. Heather Watts

Pediatric, Adolescent, and Maternal AIDS Branch, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, Rockville, Maryland, USA

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Abstract

The expanded use of multiple antiretroviral drugs during pregnancy has led to a reduction in the occurrence of perinatal transmission of HIV to <2%, but has led to concerns regarding both short-term toxicity and the long-term impact on the woman and her child. Enhanced toxicity of nevirapine has been noted among women with CD4+ lymphocyte counts >250 cells/μL at treatment initiation and among pregnant women on long-term didanosine and stavudine. These drugs should be avoided in such situations if alternatives are available. Efavirenz has been associated with birth defects in monkeys, and several cases of neural tube defects have been reported in humans after first trimester exposure, so treatment with this drug should be avoided during the first trimester. Protease inhibitors have been associated with an increased risk of maternal glucose intolerance, pre-eclampsia and preterm birth in some, but not all, studies. Pregnancies exposed to antiretroviral therapy should be registered with the Antiretroviral Pregnancy Registry as early in pregnancy as possible in order to provide data on the risk of birth defects after exposure.

The pharmacokinetics of nucleoside and non-nucleoside reverse transcriptase inhibitors are not significantly changed in pregnancy, so standard dosing may be used. However, concentrations of several protease inhibitors are lower in pregnancy, so ritonavir-boosting or increased doses are required. Of great theoretical concern is the impact of resistance mutations that develop following single-dose nevirapine therapy on the response to later therapy among women and their infected infants. The use of dual nucleoside therapy for 3–7 days after single-dose nevirapine in the mother reduces but does not eliminate the risk of nevirapine

resistance; alternative regimens for prevention of resistance are under study, as are the subsequent responses of the mother and her infant to therapy. Short courses of prophylactic zidovudine and nevirapine have been well tolerated in neonates. Concern has been raised, however, that these exposures may lead to persistent mitochondrial dysfunction or later cancers, underscoring the need for long-term surveillance of antiretroviral-exposed, HIV-uninfected infants.

The use of antiretroviral drugs during pregnancy has increased dramatically over the past 12 years,[1,2] since the initial findings of the PACTG 076 (Pediatric AIDS Clinical Trials Group protocol 076) trial indicated that zidovudine given to a pregnant woman and her infant dramatically reduced the risk of perinatal transmission of HIV-1.[3] Pregnant women in industrialised countries now most commonly receive combination antiretroviral therapy including three or more drugs.[2,4] The increased use of highly active antiretroviral therapy (HAART) has led to a further reduction in the risk of perinatal HIV transmission, with transmission rates of 1–2% reported in populations receiving HAART.[4,5]

Expanded use of multiple antiretroviral drugs during pregnancy has led to concerns regarding both short-term toxicity and the long-term impact on the woman and her child. Toxicity may be more common during pregnancy, and the effects of combination therapy on pregnancy outcome must be monitored. Effects on the infant that must be monitored include abnormalities in laboratory parameters and birth defects. Theoretical longer term effects include mitochondrial abnormalities and carcinogenesis, which require surveillance of both HIV-infected and HIV-uninfected children who have been exposed to antiretrovirals. The impact of antiretroviral regimens during pregnancy on the development of resistance to therapy in the woman and her infant, if the child is infected with HIV despite therapy, must be monitored and the response to subsequent treatment assessed. Current preferred treatments and potential toxicities are reviewed.

1. Recommended Antiretroviral Use in Pregnancy

Antiretroviral therapy may be used in pregnancy for treatment of maternal HIV-1 infection or solely for prophylaxis to prevent transmission of HIV-1 to the fetus and infant. HIV-1-infected pregnant women should receive antiretroviral therapy for their own health according to guidelines for treatment in adults, which currently recommend therapy for those with a CD4+ lymphocyte count <350 cells/μL or an HIV RNA level >100 000 copies/mL.[6] Generally, a highly active regimen as recommended for nonpregnant adults should be used, but modifications during pregnancy are required because of specific toxicity concerns, pharmacokinetic differences, and a lack of data on use in pregnancy (a summary of the FDA categories for drug use in pregnancy is provided in table I). A regimen including two nucleoside agents, with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or more protease inhibitors (PIs) is recommended for first-line therapy. Zidovudine has been used most extensively in pregnancy and has the most data supporting a reduction in perinatal HIV-1 transmission.[7] Where available, the PACTG 076 regimen of oral zidovudine during pregnancy, intravenous zidovudine during labour, and oral zidovudine therapy in the infant[3] should be included for all pregnant women unless they have experienced intolerance to zidovudine. A second nucleoside agent should be included in the regimen. Stavudine should not be included together with zidovudine because of potential antagonism.[6] The combination of stavudine and didanosine should not be used in pregnancy unless no other nucleoside options can be used, because of an apparent increase in susceptibility to mitochondrial toxicity during pregnancy, dis-

Table I. FDA classes for drug use in pregnancy

FDA pregnancy category	Criteria
A	Adequate and well controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during the later trimesters)
B	Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well controlled studies of pregnant women have not been conducted
C	Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit

cussed in section 2.1.[7] Thus far, no significant changes in the pharmacokinetics of nucleoside agents during pregnancy have been seen, therefore standard dosages may be used[8-12] (table II).

The choice of the additional agent for HAART is more complicated in pregnant women than the broader HIV-infected population. Nevirapine, an agent previously commonly used in pregnancy, has been shown to have a 10-fold increased risk of severe and potentially fatal hepatotoxicity among women with CD4+ lymphocyte counts >250 cells/μL at initiation of therapy compared with those starting therapy with lower CD4+ cell counts.[13] While several deaths from early-onset nevirapine-associated hepatotoxicity have been reported among pregnant women,[14,15] it is unclear whether the risk of toxicity is higher among pregnant women compared with nonpregnant women or whether the use of nevirapine among women with higher CD4+ cell counts is more common during pregnancy because of the use of nevirapine for prophylaxis of perinatal transmission. Nevirapine may be used as initial therapy among women with CD4+ cell counts <250 cells/μL, but should only be used among women with higher CD4+ cell counts if no alternative therapy is available (table III).[7] Regardless of the CD4+ cell count at treatment initiation, pregnant women starting nevirapine therapy should be monitored frequently for evidence of hepatic toxicity and rash during the first 16 weeks of treatment. The pharmacokinetics of nevirapine are similar in pregnant and nonpregnant women, so the dosage is unchanged in pregnancy.[7] Efavirenz is not recommended for use in the first trimester of pregnancy: animal data and consistent case reports in humans suggest an increased risk of CNS defects. In a study in cynomulgus monkeys, defects including anencephaly, anophthalmia, micro-ophthalmia, and cleft palate were seen in 3 (20%) of 15 animals after first trimester efavirenz exposure.[16] Three cases of neural tube defects and a case of Dandy-Walker malformation after first trimester exposure to efavirenz have been reported in humans, suggesting an increased risk, although the denominator for these cases is unknown.[17] Efavirenz may be considered for use later in pregnancy if no other alternatives are available.

Given the concerns with nevirapine toxicity and efavirenz teratogenicity, PIs, where available, are generally the agents chosen to accompany nucleoside agents as the third agent in HAART regimens during pregnancy.[2,4] The concentrations of several PIs have been shown to be lower in pregnancy than among the same women *post partum* or compared with nonpregnant women (table IV).[18-21] Thus, except for nelfinavir, most PIs must be boosted with ritonavir during pregnancy to achieve target concentrations. Nelfinavir and saquinavir/ritonavir are the PIs with the most pharmacokinetic data and clinical experience with use in pregnancy, so are recommended as first-line agents.[7]

Thus far, one fusion inhibitor, enfuvirtide, has been licensed for antiretroviral use (table V). While no specific reproductive concerns with this agent have been identified in animal studies, experience

Table II. Preclinical and clinical data relevant to the use of nucleoside/nucleotide antiretrovirals in pregnancy[6,7]

Nucleoside	FDA pregnancy category[a]	Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities[b]	Concerns specific to pregnancy	Recommended use in pregnancy
Abacavir	C	Crosses placenta in rats; ratio not quantified	Not completed	Anasarca, skeletal abnormalities at 35× human dose in rodents, not seen in rabbits	Potentially fatal hypersensitivity reactions with symptoms of fever, skin rash, fatigue, nausea, vomiting, diarrhoea, abdominal pain	PK study shows no change in dosing required. A study evaluating use among pregnant women with HIV RNA levels <55 000 copies/mL as a class-sparing regimen is in progress	Triple NRTI regimens including abacavir have been less potent virologically compared with PI-based HAART regimens. Should be used only when an NNRTI or PI-based HAART regimen cannot be used, e.g. significant drug interactions. May be used as part of nucleoside backbone in HAART regimen
Didanosine	B	0.5 human	Negative in rodents	No impaired fertility or teratogenicity in rats, rabbits	Pancreatitis, neuropathy	PK study shows no need for dose modification. Possible increased risk of lactic acidosis in pregnancy with long-term didanosine + stavudine	Alternative nucleoside for HAART regimens. Use with stavudine only if no other alternatives are available
Emtricitabine	B	Unknown	Studies in progress	No effect on fertility in rodents; no evidence of teratogenicity in mice, rabbits	Headache, nausea, vomiting, diarrhoea	No studies in human pregnancy	Alternate NRTI for HAART regimens
Lamivudine	C	≈1.0 human	Negative in rodents	Increased resorptions in rabbits but not rats. No increase in malformations	Pancreatitis increased in children	PK study shows no need for dose modification, well tolerated	Because of extensive experience with use of this drug in pregnancy, recommended nucleoside with zidovudine in HAART regimen

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Table II. Contd

Nucleoside	FDA pregnancy category[a]	Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities[b]	Concerns specific to pregnancy	Recommended use in pregnancy
Stavudine	C	0.76 rhesus monkey	Not completed	Increased resorptions at >200× human doses, decreased sternal ossification at >400× human doses	Peripheral neuropathy	PK study shows no need for dose modification. Possible increased risk of lactic acidosis in pregnancy with long-term didanosine + stavudine	Alternative nucleoside for HAART regimens. Use with didanosine only if no other alternatives are available. Do not use with zidovudine as it is antagonistic
Tenofovir	B	0.17 monkeys	Not completed. Some mutagenesis/ clastogenesis tests positive	No teratogenicity in rodents. At high doses (25× human AUC) in monkeys, no structural abnormalities but decreased bodyweight, reduction in bone porosity. Reversible bone changes in immature animals of several species with long-term use	Renal impairment (rare), decreased bone density, diarrhoea, asthenia. Hepatitis B exacerbation when stopped	Phase I study in late pregnancy in progress	Phase I study in late pregnancy in progress. Given limited experience and potential bone effects, use only after careful consideration of alternatives
Zalcitibine	C	0.3–0.5 rhesus monkey	Thymic lymphomas in rats at 1000× human doses	Hydrocephalus in rats at 2000× human dose, skeletal defects and decreased weight at moderate doses	Neuropathy	No studies	Given toxicity in nonpregnant adults and teratogenicity concerns, not recommended for use in pregnant women
Zidovudine	C	0.85 human	Increase in rodent non-invasive vaginal tumours, possible trans-placental carcinogenesis	Increased resorption in rats and rabbits. No teratogenicity in rats, rabbits at usual dose. Increased malformations at near-lethal dose in rats	Bone marrow suppression, myopathy	Most well studied antiretroviral agent, safe in short-term	Preferred nucleoside for use in combination regimen in pregnancy based on efficacy studies, large amount of experience. Should be included in regimen unless intolerance has been observed or stavudine is being used

a Refer to table I.

b Class effects: all nucleosides have the potential to cause mitochondrial dysfunction, usually after long-term use. Manifestations may include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis.

AUC = area under the concentration-time curve; **HAART** = highly active antiretroviral therapy; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; **PK** = pharmacokinetic.

with use in human pregnancy is very limited. Fusion inhibitors should be used in pregnant women only if no other alternatives are appropriate.[7]

In resource-limited settings, the safety and effectiveness of HAART regimens for women who do not meet criteria for treatment for their own health have not been evaluated. While, ideally, all pregnant women should be treated with regimens of three drugs to minimise transmission, the risks of these regimens may outweigh the potential benefits if monitoring of toxicity is not available. Current guidelines for treatment of HIV-infected patients in resource-constrained settings are outlined here and are available online.[22] Briefly, treatment should be offered to women with WHO stage IV disease regardless of their CD4+ cell or total lymphocyte counts; to women with WHO stage III disease who have CD4+ cell counts <350 cells/μL or to all women with stage III disease if CD4+ cell counts are not available; and to women with stage I or II disease who have CD4+ cell counts <200 cells/μL, with consideration of treatment for women with CD4+ counts between 200 and 350 cells/μL, or stage II disease with a total lymphocyte count <1200 cells/μL, if CD4+ cell counts are not available.[22,23] Of the regimens for first-line treatment available using the WHO-recommended five drug formulary, the regimens of zidovudine plus lamivudine plus nevirapine or stavudine plus lamivudine plus nevirapine should be used in pregnant women or women of child-bearing potential.[22] Given the greater experience and amount of data on the efficacy of zidovudine for the prevention of perinatal transmission, zidovudine should be used unless contraindicated or unavailable.

For pregnant women in resource-limited settings who do not require antiretroviral therapy for their own health, several prophylactic regimens may be used, depending on the level of antenatal care and other infrastructure available.[23] Completed randomised trials providing data on which to base such choices are summarised in table VI.[3,4,24-35] If women are receiving care, are known to be HIV-infected, and drugs are available, zidovudine started at 28 weeks into the pregnancy and continued orally during labour, along with single-dose nevirapine *intra partum* for the mother and single-dose nevirapine and 1 week of zidovudine for the infant, is highly effective. If the mother receives at least 4 weeks of zidovudine, maternal nevirapine may be omitted.[23] If the mother receives less than 4 weeks of zidovudine, zidovudine treatment for the infant should be extended to a duration of 4 weeks.[23] Alternative regimens include shorter courses of zidovudine with or without nevirapine administration *intra partum* or to the infant, short-course zidovudine plus lamivudine for the mother and infant, or nevirapine administered *intra partum* and to the infant (table VI). For infants born to women not receiving antiretroviral therapy during pregnancy, a combination of zidovudine and nevirapine reduces transmission more effectively than nevirapine alone.[35] The benefits of short-course regimens are reduced over time in breast feeding populations. Several trials of either maternal or infant antiretroviral therapy during breast feeding to reduce the risk of transmission are underway.

Women who become pregnant while receiving antiretrovirals should generally continue their regimen during early pregnancy unless efavirenz is included in the regimen.[7] If pregnancy is detected early, efavirenz should be stopped and either nevirapine or a PI substituted. If pregnancy is diagnosed after the first trimester, efavirenz may be continued along with the other drugs. If a woman chooses to discontinue therapy because of teratogenicity concerns or intolerance during early pregnancy, all drugs with similar half-lives should be discontinued and reinstituted at the same time to minimise the chance of development of resistance. If drugs with prolonged half-lives, such as nevirapine or efavirenz, are stopped, continuation of the nucleoside agents for 3–7 days after stopping the non-nucleoside drug may decrease the chance of developing resistance.[7] Discontinuing therapy in the first trimester could theoretically lead to viral rebound and an increased risk of transmission, although this has not been well studied.[36] Women who enter pregnancy while receiving antiretroviral therapy should be counselled regarding the limited

Table III. Preclinical and clinical data relevant to the use of non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretrovirals in pregnancy[6,7]

NNRTI	FDA pregnancy category[a]	Newborn/maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities	Concerns specific to pregnancy	Recommended use in pregnancy
Delavirdine	C	Unknown	Not completed	Increased resorptions, fetal deaths in rats, rabbits at high doses. Increased atrial and ventricular septal defects in rats at high doses	Rash, drug interactions	No studies	Not recommended because of animal teratogenicity data, lack of human experience in pregnancy
Efavirenz	D	≈1.0 cynomulgus monkey	Not completed	Increased fetal resorptions in rats. Anencephaly, anophthalmia, micro-ophthalmia, cleft palate in cynomulgus monkeys at doses similar to those administered in humans	Rash, drug interactions, CNS effects	PK study in later-stage pregnancy in progress. Use in pregnancy should be avoided because of primate teratogenicity, three case reports of neural tube defects in humans after first trimester exposure	Use of efavirenz should be avoided in the first trimester, and women of child-bearing potential must be counselled regarding the risks of treatment and avoidance of pregnancy. Use after the first trimester of pregnancy can be considered if other alternatives are not available
Nevirapine	C	≈1.0 human	Not completed	Impaired fertility in female rats, decreased fetal weight. No increase in malformations in rats, rabbits	Rash, drug interactions. Increased risk of symptomatic, often rash-associated and potentially fatal liver toxicity among women with CD4+ lymphocyte counts >250/μL at the time of initiation of therapy	Not clear if pregnancy increases the risk of hepatic toxicity. Not recommended for women starting therapy who have a CD4+ lymphocyte count >250/μL. Women entering pregnancy whilst receiving nevirapine and who tolerate it well may continue treatment, regardless of their CD4+ cell count	*Intra partum*/infant single-dose regimen when other options are not available. As a component of HAART for women with CD4+ cell counts <250/μL or those continuing pre-existing therapy

a Refer to table I.

HAART = highly active antiretroviral therapy; **PK** = pharmacokinetic.

Table IV. Preclinical and clinical data relevant to the use of protease inhibitor (PI) antiretrovirals in pregnancy[6,7]

Protease inhibitor	FDA pregnancy category[a]	Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities[b]	Concerns specific to pregnancy	Recommended use in pregnancy
Amprenavir	C	Unknown	Increased occurrence of liver tumours in male rats and mice	No effect on fertility in rodents. Negative teratogenicity but deficient ossification and thymic elongation in rats, rabbits	Nausea, vomiting, diarrhoea, rash, oral paraesthesias, increased liver function test values	No studies. Oral solution contraindicated in pregnancy because of propylene glycol in formulation; may be decreased metabolism of propylene glycol in pregnancy	Data regarding safety and PK in pregnancy are insufficient to recommend use of capsules during pregnancy. Oral solution contraindicated
Atazanavir	B	Unknown	Not completed	No effect on fertility in rodents. No evidence of teratogenicity in rats, rabbits	Abdominal pain, diarrhoea, nausea, hyperbilirubinaemia, rash, prolonged P-R interval	No studies. Theoretical concern regarding increased indirect bilirubin levels which may exacerbate physiological hyperbilirubinaemia in the neonate, although transplacental passage of other PIs has been low	Data regarding safety and PK in pregnancy are insufficient to recommend use during pregnancy
Fosamprenavir	C	Unknown	Increase in the occurrence of liver tumours in male mice, rats	No effect on fertility in rodents. Increased pregnancy loss, lower birthweight and decreased pup survival in rats. Increased pregnancy loss, skeletal variants in rabbits	Nausea, vomiting, diarrhoea, rash, oral paraesthesias, increased liver function test values	No studies	Data regarding safety and PK in pregnancy are insufficient to recommend use during pregnancy

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Table IV. Contd

Protease inhibitor	FDA pregnancy category[a]	Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities[b]	Concerns specific to pregnancy	Recommended use in pregnancy
Indinavir	C	Crosses the placenta in rats; ratio has not been quantified. Low ratio in rabbits	Not completed	No effect on fertility in rodents. No teratogenicity in rats, rabbits, or dogs. Developmental abnormalities (extra ribs) in rats	Kidney stones, hyperbilirubinaemia, drug interactions	AUC low with 800mg tid; ritonavir boosting indicated in pregnancy, though specific dosing not studied. Theoretical concerns regarding kidney stones, hyperbilirubinaemia in neonates from maternal exposure	Alternative PI to consider if unable to use nelfinavir or saquinavir/ritonavir
Lopinavir	C	Unknown	Not completed	Increased resorptions, developmental abnormalities at toxic maternal doses in rats. No effects in rabbits. No teratogenicity	Nausea, vomiting, diarrhoea, pancreatitis, drug interactions	Preliminary studies suggest increased dose may be required in third trimester; PK studies in progress	Alternative PI regimen, pending more data on use and dosing in pregnancy. If used during pregnancy, monitor response to therapy closely and consider increasing the dose if the expected response is not obtained
Nelfinavir	B	Unknown	Not completed	No effect on fertility, no teratogenicity in rats, rabbits	Diarrhoea, drug interactions	Low AUC with 750mg tid in pregnancy; adequate concentrations with 1250mg bid	Given the PK data available and extensive experience with use in pregnancy compared with other PIs, preferred PI for HAART regimens in pregnancy

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Table IV. Contd

Protease inhibitor	FDA pregnancy category[a]	Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities[b]	Concerns specific to pregnancy	Recommended use in pregnancy
Ritonavir	B	Crosses the placenta in rats; ratio not available	Positive in male but not female rats at 4× human dose	Increased resorptions, decreased fetal weight in rats, rabbits at maternal toxic doses. No teratogenicity in rats, rabbits	Nausea, vomiting, diarrhoea; increased levels of triglycerides, transaminases; occurrence of drug interactions	Limited data as single agent; well tolerated at boosting doses	Not recommended as single agent, used for boosting other PIs
Saquinavir	B	Minimal in rats, rabbits	Not completed	No effect on fertility, no teratogenicity in rats, rabbits	Nausea, diarrhoea	Inadequate concentrations with saquinavir alone at 1200mg bid. Saquinavir 800mg with ritonavir 100mg, both bid, produced adequate concentrations and was well tolerated in a study of 13 women. No specific toxicity concerns identified	Given the PK data available and moderate experience with use in pregnancy, can be considered a preferred PI for HAART regimens in pregnancy
Tipranavir	C	Unknown	Studies in progress	No effect on fertility in rats. No teratogenicity in rats, rabbits	Multiple drug interactions; hepatitis including hepatic decompensation; rash; contains sulphonamide moiety so use with caution in sulpha-allergic patients	No studies	Not currently recommended for use in pregnancy because of lack of data on safety, PK in pregnancy

a Refer to table I.

b Class effects: hyperglycaemia, possible fat redistribution and lipid abnormalities, increased bleeding episodes in haemophiliacs.

AUC = area under the concentration-time curve; **bid** = twice daily; **HAART** = highly active antiretroviral therapy; **PK** = pharmacokinetic; **tid** = three times daily.

Table V. Preclinical and clinical data relevant to use of enfuvirtide[a] in pregnancy[6,7]

Newborn/ maternal drug ratio	Long-term animal carcinogenicity studies	Animal reproduction studies	Major toxicities	Concerns specific to pregnancy	Recommended use in pregnancy
Unknown	Not completed	No effect on fertility in rats, rabbits; no teratogenicity detected	Injection site reactions, fatigue, insomnia, anorexia, nausea, diarrhoea, neuropathy, pancreatitis	No specific concerns based on animal studies; no experience in human pregnancy	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy

a FDA pregnancy category B (refer to table I).

data on the impact of most antiretroviral agents in early pregnancy, the risk of viral rebound with temporary discontinuation, and options including continuing, stopping, or altering therapy as appropriate.

2. Maternal Toxicity

2.1 Short-Term Toxicity

Clinicians caring for HIV-infected pregnant women should be familiar with the toxicities expected with the various antiretroviral drugs. For the most part, these toxicities are similar between pregnant and nonpregnant women, however some adverse effects, such as anaemia, may be more common during pregnancy.[37] Common toxicities of antiretroviral drugs approved in the US are summarised in table II, table III, table IV and table V. The most common toxicity of zidovudine is bone marrow suppression, resulting in anaemia or neutropenia.[6] Pregnancy may increase the risk of anaemia because of the 50% increase in plasma volume with only a 30% increase in red cell mass, leading to a dilutional drop in haematocrit.[37] Pregnant women receiving zidovudine should be monitored regularly for anaemia and neutropenia. Women with significant anaemia whilst receiving zidovudine may have the dose reduced or have stavudine substituted for zidovudine.

A less frequent but more serious concern with the use of nucleoside agents is the development of toxicity related to mitochondrial dysfunction. Nucleoside agents bind to mitochondrial γ DNA polymerase and interfere with mitochondrial replication, leading to depletion and dysfunction.[38] *In vitro*, the relative potencies of the antiretrovirals for inhibition of mitochondrial DNA polymerase are zalcitabine (highest), didanosine, stavudine, lamivudine, zidovudine and abacavir (lowest).[39] Mitochondrial toxicity, when reported, has been associated with long-term use of nucleoside agents and generally resolves when the drugs are stopped. Conditions associated with mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis.[38] Pregnancy may increase the susceptibility to mitochondrial dysfunction, based on evidence from studies in mice showing significant reductions in fatty acid oxidation in late gestation and after exogenously administered estradiol and progesterone, mimicking levels in pregnancy.[40,41] Several cases of severe lactic acidosis, including three deaths, have been reported in pregnant women receiving stavudine with another nucleoside, usually didanosine, from before pregnancy.[42-44] Symptoms developed late in pregnancy. It is unclear whether pregnancy contributed to development of lactic acidosis, but animal data are suggestive. Given the increased affinity of stavudine and didanosine for mitochondrial γ DNA polymerase and the reported cases in women receiving these drugs, the combination of stavudine and didanosine should be avoided in pregnancy unless no other alternative nucleoside agents are available. Pregnant women on antiretrovirals should be educated regarding the symptoms of mitochondrial dysfunction and should have levels of hepatic transaminases and electrolytes assessed frequently during the third trimester.

The most common toxicities of the NNRTIs, in addition to the hepatotoxicity associated with nevirapine that was discussed in section 1, are rash and the potential for drug interactions with agents

Table VI. Completed, randomised, phase III trials of antiretroviral drugs to reduce transmission of HIV

Study (site)	Comparators	Infant feeding	Maternal therapy			Infant therapy	Time of assessment	Transmission rate (%)	Reduction in transmission (%)
			AP start time	IP	PP				
Connor et al. (USA, France)[3]	Placebo vs ZDV	Non-breast-fed	14–34 weeks	IV ZDV or placebo	None	6 weeks	18 months	Placebo 25.5 ZDV 8.3	68
Shaffer et al. (Thailand)[24]	Placebo vs ZDV	Non-breast-fed	36 weeks	Orally every 3 hours	None	None	6 months	Placebo 18.9 ZDV 9.4	50
Lallemont et al. (Thailand)[25]	ZDV – long-long vs long-short vs short-short vs short-long[a]	Non-breast-fed	28 or 36 weeks	Orally every 3 hours	None	6 weeks or 3 days	6 months	Short-short 10[b] Short-long 8.6 Long-short 4.7 Long-long 6.5	No significant difference between completed arms; decreased *in utero* transmission with long AP
Wiktor et al. (Ivory Coast)[26]	Placebo vs ZDV	Breast-fed	36 weeks	Orally every 3 hours	None	None	3 months	Placebo 24.9 ZDV 15.7	37
							24 months[c]	Placebo 30.2 ZDV 22.5	26
DITRAME (Ivory Coast, Burkina Faso)[27-29]	Placebo vs ZDV	Breast-fed	36–38 weeks	Orally at onset of labour	1 week	None	6 months	Placebo 27.5 ZDV 18.0	38
							15 months	Placebo 30.6 ZDV 21.5	30
PETRA (South Africa, Uganda, Tanzania)[30]	Placebo vs ZDV/3TC – AP/IP/PP vs IP/PP vs IP	Both breast- and formula-fed	Start at 36 weeks	Continued orally in labour	1 week	1 week	6 weeks	Placebo 17.2 AP/IP/PP 5.7 IP/PP 8.9 IP 14.2	63 for AP/IP/PP compared with placebo; 42 for IP/PP vs placebo No significant difference for IP vs placebo
							18 months	Placebo 22.2 AP/IP/PP 14.9 IP/PP 18.1 IP 20.2	
HIVNET 012 (Uganda)[31,32]	NVP vs ZDV	Breast-fed	None	Single-dose NVP orally or ZDV every 3 hours	None	Single-dose NVP at 48 hours or ZDV for 1 week	14–16 weeks	ZDV 25.1 NVP 13.1	47

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Table VI. Contd

Study (site)	Comparators	Infant feeding	Maternal therapy			Infant therapy	Time of assessment	Transmission rate (%)	Reduction in transmission (%)
			AP start time	IP	PP				
							18 months	ZDV 25.8 NVP 15.7	41
PACTG 316 (US, Europe, Brazil, Bahamas)[4]	NVP vs placebo in addition to standard antiretrovirals (minimum of ZDV)	Non-breast-fed	No study therapy, current antiretroviral regimen	Single-dose NVP	None	Single-dose NVP or placebo, plus standard ZDV	3 months	Placebo 1.4 NVP 1.5	No difference
SAINT (South Africa)[33]	ZDV/3TC vs NVP	Breast- and non-breast-fed	None	Single-dose NVP or ZDV/3TC orally	None	Single-dose NVP or ZDV/3TC for 1 week	8 weeks	ZDV/3TC 9.3 NVP 12.3	No difference
PHPT2 (Thailand)[34]	ZDV only vs ZDV + NVP (mother) vs ZDV + NVP (mother and infant)	Non-breast-fed	ZDV from 28 weeks in all arms	ZDV only vs ZDV plus NVP	None	ZDV for 1 week or ZDV for 1 week plus single-dose NVP	6 months	ZDV only 6.3 ZDV + NVP (mother) 2.8 ZDV + NVP (mother and infant) 1.9	NVP arms not different
NVAZ (Malawi)[35]	Infant NVP ± IP NVP vs Infant NVP + ZDV ± IP NVP	Breast-fed	None	Single-dose NVP if time allowed, both arms	None	Single-dose NVP or single-dose NVP plus ZDV for 1 week	6–8 weeks	IP NVP/infant NVP 14.1 IP NVP/infant NVP + ZDV 16.3 No IP NVP/ infant NVP 20.9 No IP NVP/ infant NVP + ZDV 15.3	No difference between the two arms involving IP NVP 27% reduction with the addition of ZDV to the regimen without IPNVP

a long-long = maternal therapy initiated at 28 weeks, infant therapy for 6 weeks; long-short = maternal therapy initiated at 28 weeks, infant therapy for 3 days; short-long = maternal therapy initiated at 36 weeks, infant therapy for 6 weeks; short-short = maternal therapy initiated at 36 weeks, infant therapy for 3 days.

b Treatment arm discontinued.

c Combined analysis with next study.

3TC = lamivudine, **AP** = *ante partum*; **HIVNET** = HIV Network; **IP** = *intra partum*; **IV** = intravenous; **NVAZ** = NeVirapine And Zidovudine; **NVP** = nevirapine; **PACTG** = Pediatric AIDS Clinical Trial Group; **PETRA** = PErinatal TRAnsmission; **PHPT** = Perinatal HIV Prevention Trial; **PP** = *post partum*; **SAINT** = South African Intrapartum Nevirapine Trial; **ZDV** = zidovudine,

such as PIs, antituberculous drugs, and other commonly used agents.[6] These interactions may lead to subtherapeutic levels of the antiretrovirals or other agents, or to higher levels with enhanced toxicity. Rash is common among patients initiating nevirapine or efavirenz, and mild rashes may resolve with continued treatment.[6] Stevens-Johnson syndrome has been reported with both nevirapine and efavirenz.[6] If rash is associated with blistering, desquamation, mucosal involvement or fever, NNRTI drugs should be stopped immediately and not reinstituted. The rate of occurrence of rash may be decreased with nevirapine by starting with a dosage of 200mg daily for 2 weeks and then increasing the dosage to 200mg twice daily. Significant psychiatric symptoms such as severe depression and suicidal ideation may occur rarely with the use of efavirenz, but other CNS effects such as somnolence and unusual dreams occur more frequently and usually resolve over time.[6] Delavirdine is rarely used and not recommended for use in pregnancy because of malformations seen in animal studies.[7] Of note, the single-dose nevirapine regimen for the neonate and *intra partum* for the mother has not been associated with significant toxicity.[31-33]

Common toxicities seen with PI drugs include nausea, vomiting, diarrhoea, glucose intolerance, fat redistribution and lipid abnormalities, and increased bleeding among haemophiliacs.[6] Indinavir and atazanavir are also associated with hyperbilirubinaemia due to impaired bilirubin metabolism.[6] This effect has led to concern that these drugs may inhibit bilirubin metabolism in the newborn after maternal use during pregnancy, leading to an increased risk of kernicterus. Thus far, this problem has not been observed, probably because of the limited transplacental passage of most of the PIs.[45,46] Other specific toxicities are listed in table IV. While impaired glucose metabolism with PIs has been seen in nonpregnant adults,[6] the impact on glucose metabolism in pregnancy is unclear. A retrospective review found the rate of abnormal screening 50g glucose tests among women on PI regimens to be 12 (31%) of 39 compared with 3 (13%) of 23 among those on zidovudine monotherapy.[47] However, the rate of gestational diabetes mellitus as diagnosed by an abnormal 3-hour glucose tolerance test was similar in the two groups, with two cases (5.1%) in the PI group and one case (4.3%) in the zidovudine group. In a secondary analysis of the PACTG 316 study, long-term therapy with a PI regimen was associated with an increased risk of gestational diabetes, although the rate in this group (4.6%) was within the range reported in the general obstetric population.[48] In an analysis from the WITS (Women and Infants Transmission Study),[49] the rate of gestational diabetes was 2.8% overall. While the rate of gestational diabetes was significantly increased among women starting antiretrovirals after 32 weeks, the diagnosis of gestational diabetes would have been made prior to initiation of therapy, suggesting population differences rather than a drug effect.[49] The results of studies are suggestive but not definitive about whether PI therapy may increase the risk of gestational diabetes. Given the observed effects of PI therapy on glucose metabolism in nonpregnant individuals and the effects of pregnancy on glucose metabolism, pregnant women on PI therapy should be monitored closely for evidence of glucose intolerance, in addition to standard glucose screening at 24–28 weeks of gestation. Because of the diabetogenic effects of corticosteroids, pregnant women on PI therapy who require corticosteroids, (e.g. for fetal lung maturation), should be monitored closely.[50]

2.2 Long-Term Toxicity

Most of the toxicities, such as laboratory parameter abnormalities, seen with use of antiretrovirals in pregnancy are reversible upon discontinuation of therapy. However, use of short-course therapy specifically to prevent perinatal transmission can result in the development of a treatment-resistant virus which may have implications for future treatment responses. The most striking example of this situation is the detection of resistant HIV in up to 67% of women receiving short-course nevirapine for prophylaxis of perinatal transmission, depending on the timing of testing, number of doses received, concomitant therapy and viral clade.[51-60] Concentra-

tions of nevirapine remain detectable (above 50 ng/mL) in 50% of women at 2 weeks after a single *intra partum* dose of 200mg.[61] These persistent low levels allow selection of resistant mutants that occur because of the error-prone process of HIV replication. Only a single mutation is required for development of nevirapine resistance such that, among women with detectable HIV RNA, resistance is detected in 20% of women at 2 weeks after a delivery dose, in 15–67% at 4–6 weeks, and 25–40% at 7–8 weeks.[51-60] In addition, if the infant is infected despite prophylaxis, resistance may be detected in up to 52% of such children.[60] Factors associated with an increased rate of detection of nevirapine resistance include receiving more than one dose of *peri partum* nevirapine, higher HIV RNA level or lower CD4+ lymphocyte count, viral clade C, time of sampling, and the assay used for detection.[51-60] In the absence of continued nevirapine therapy, the frequency of detection of nevirapine resistance mutations using standard consensus techniques declines over time, but, using more sensitive techniques such as real time polymerase chain reaction assays, mutations can be detected among 40–88% of treated women.[62,63]

The most important issue regarding the detection of resistance mutations after single-dose or short-course monotherapy regimens is how it will affect the woman's response to subsequent antiretroviral therapy, especially since that therapy is likely to include an NNRTI – either nevirapine or efavirenz. Data are available from two studies, and other studies are ongoing. The first study was a follow-up evaluation of subsequent response to therapy among women initially enrolled in a randomised trial of adding nevirapine to zidovudine therapy that was performed in Thailand.[54] Women who developed CD4+ lymphocyte counts of <250 cells/μL were treated with NNRTI-based regimens (usually stavudine/lamivudine/nevirapine), and their responses to therapy were monitored. Comparing women with or without previous single-dose nevirapine exposure during labour, the clinical responses, measured by weight gain and CD4+ lymphocyte count increases, were similar between groups. The proportions of patients with HIV RNA levels of <50 copies/mL were similar between groups at 3 months, however women with previous nevirapine exposure were less likely than those without previous nevirapine exposure to have achieved HIV RNA levels <50 copies/mL following 6 months on therapy, i.e. 49% versus 68% ($p = 0.03$). Women in the nevirapine-exposed groups with nevirapine resistance mutations detected by the ViroSeq™[1] HIV-1 Genotyping System version 2 (Applied Biosystems) were less likely to achieve viral suppression than those without such mutations. In a follow-up report from this study, no further difference in response was seen at 18 months.[64] Among those patients who had HIV RNA levels of <50 copies/mL at 6 months, virological response was maintained at 18 months in both groups. Data have recently been presented from the MASHI[65] trial in Botswana, which evaluated the response to therapy among women who were previously treated with zidovudine from 34 weeks of pregnancy until delivery and who were randomised to receive either single-dose nevirapine or placebo during labour. Among the entire group of 218 women, the virological failure rate was significantly higher at 6, 12 and 24 months among women who had received nevirapine compared with placebo. However, on further analysis, the higher rate of failure occurred among women who started therapy for their own health within 6 months of receiving single-dose nevirapine, a group likely to be eligible for HAART during pregnancy as availability increases. More than 6 months after receipt of treatment during labour, responses were similar among women who had received nevirapine and those who had received placebo, with the proportion of patients with an HIV RNA level of <50 copies/mL being 77% in both groups. These preliminary data are of concern, but further evaluation is needed, especially among women receiving nevirapine alone, without zidovudine, during pregnancy.

In addition, the response to single-dose nevirapine in subsequent pregnancies has been as-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

sessed to a limited extent. Preliminary data from a case control study performed in South Africa suggest that the transmission rate may be higher among women receiving single-dose nevirapine prophylaxis in a second pregnancy (13.7% of 66 mother-infant pairs) compared with similar controls receiving nevirapine for the first time (4.2% of 119).[66] However, the transmission rate of 13.7% is similar to transmission rates in other studies of first use of single-dose nevirapine, making these data difficult to interpret. Further study is needed.

In areas where HAART regimens are available, the use of suppressive combination therapy should minimise the development of resistance. In areas where single-dose nevirapine remains the primary option for reduction of perinatal transmission of HIV-1, studies are underway to evaluate the addition of one or more drugs for a short time after delivery to minimise the risk of resistance. In a small, randomised trial from South Africa, nevirapine resistance was significantly reduced among women receiving zidovudine and lamivudine for 3 or 7 days after delivery compared with women receiving only nevirapine.[67] Resistance was detected among 13% of the women receiving *post partum* therapy compared with 56% in those receiving only nevirapine. These data are consistent with rates of nevirapine resistance of 12-17% noted in observational studies of women receiving lamivudine/lamivudine for 5–6 days *post partum* after discontinuation of nevirapine from the three-drug regimen at delivery.[53,68] Additional studies are evaluating longer *post partum* antiretroviral regimens for possible further reductions in nevirapine resistance.

3. Effects on Pregnancy Outcome

Early studies among women in developed countries that included appropriate control groups did not suggest an adverse effect of HIV infection itself on pregnancy outcome, although rates of complications were high due to maternal drug use and other risk factors.[69,70] Studies from resource-limited settings have been more suggestive of a negative impact of HIV on pregnancy outcome, with rates of low birthweight increasing with more advanced disease.[70] Studies evaluating the effects of zidovudine monotherapy on pregnancy outcome have found either similar or improved pregnancy outcomes among women receiving zidovudine compared with those not receiving antiretroviral agents.[71,72] Risk factors for preterm delivery among HIV-infected women are similar to those in women without HIV.[73,74]

The effects of HAART on pregnancy have been less clear. Several studies from Europe have demonstrated an increased risk of preterm delivery as the number of antiretroviral agents increased, with the highest risk occurring among pregnant women receiving combination therapy that included a PI. Rates of preterm birth of 29% among women receiving PI regimens have been reported from the ECS (European Collaborative Study) and Swiss investigators.[75] Most recently, a 4.4-fold increased risk of preterm birth before 34 weeks was seen for women who began pregnancy on HAART and continued treatment throughout pregnancy.[76] However, a combined analysis from several studies in the US did not find a difference in the rate of preterm birth between HIV-infected women who were not receiving antiretrovirals, those receiving zidovudine, those receiving combination therapy that did not include a PI, and those receiving combination regimens that did include a PI.[77] There was a slightly increased risk of giving birth to an infant of very low birthweight among women receiving PI regimens. A more recent analysis of the WITS cohort did not find combination regimens, with or without PIs, to be a risk factor for preterm delivery.[49] The difference in findings may to some extent reflect differences in obstetric populations and management between Europe and the US. Currently, the benefits of HAART regimens, including those with a PI component, on reduction of perinatal transmission appear to outweigh the potential risk of preterm birth, but continuing surveillance of the effects of antiretrovirals on pregnancy outcome is needed, and women receiving therapy should be educated about the symptoms of preterm labour.

Another concern that has been raised regarding the use of HAART in pregnancy is that multiagent therapy may increase the risk of other pregnancy complications, including pre-eclampsia and stillbirth. A case-control study of 214 HIV-infected women and 214 uninfected women matched for age, ethnicity and parity, suggested that pre-eclampsia was less common among HIV-infected women who were not receiving antiretroviral therapy or who were receiving single or dual nucleoside therapy, but were increased among HIV-infected women who were receiving HAART, although only the rate in the untreated group differed significantly from the HIV-uninfected group.[78] In a study from South Africa, the rate of pre-eclampsia and other hypertensive disorders of pregnancy was not different among HIV-infected women compared with uninfected women, but none of the HIV-infected women were receiving antiretrovirals.[79] A case-control study from Brazil, that included 78 women on HAART, found a lower rate of pre-eclampsia among HIV-infected women compared with controls.[80] Data from Spain that have been presented in abstract form showed a relative risk of 11.5 for pre-eclampsia and 17.3 for stillbirth among HIV-infected women on antiretroviral therapy compared with women without HIV.[81] Any change in the risk of pre-eclampsia associated with HIV infection or HAART has not been confirmed, but continued evaluation is indicated.

Another concern related to antiretroviral drug exposure in pregnancy is the potential for teratogenesis, especially as an increasing proportion of women enter pregnancy already on antiretroviral therapy. Data from studies in animals are summarised in table II, table III, table IV and table V, but the predictive value of animal studies for human pregnancy is unclear. Commonly used nucleoside agents have not been associated with an increased risk of birth defects in animals when administered at doses similar to those used in humans. Among the NNRTIs, both efavirenz and delavirdine have been associated with birth defects in animals. As mentioned in section 1, efavirenz exposure in the first trimester in cynomulgus monkeys resulted in anencephaly, or midline facial defects including anophthalmia and cleft palate in 3 (20%) of 15 monkeys.[16] No specific birth defects have been seen with PIs in animal studies, although maternal toxicity often limited the doses that could be studied and resulted in resorption of the pregnancy or decreased pup weight.

Data in humans are available from pregnancy registries, cohort studies, and case reports. The Antiretroviral Pregnancy Registry is a prospective multinational exposure-registration cohort study designed to evaluate the potential increased risk of birth defects with antiretroviral drugs.[17] All clinicians caring for women who are using antiretrovirals during pregnancy should register their patients with the registry as early in pregnancy as possible, before the outcome is known. More information is available at www.APRegistry.com. Currently >5000 prospective exposures have been reported to the registry. The rate of birth defects detected among infants born to women with first trimester exposure to any antiretroviral agent is 54 (2.9%) of 1835, and among those with later exposures during pregnancy it is 63 (2.1%) of 2956; these rates are not significantly different. These rates compare favourably to rates from the US Centers for Disease Control (CDC) population-based birth defects surveillance system that detected a rate of birth defects in the *ante partum* and newborn period of 2.2 per 100 live births and 3.1 per 100 live births with follow-up through to 6 years of age. A threshold of 200 exposed births is required to detect a doubling in the overall rate of birth defects, whereas a sample of >1000 is required to rule out even a tripling of the rate of defects that occur at a rate of 1 per 1000 or less, such as neural tube defects. Thus far, eight drugs have reached the threshold of 200 individuals exposed during the first trimester, including lamivudine (39 defects/1432 exposures; 2.7%), zidovudine (38/1278; 3.0%), nelfinavir (19/496; 3.8%), stavudine (11/431, 2.6%), nevirapine (9/419, 2.1%), abacavir (9/286, 3.1%), efavirenz (5/206, 2.4%) and didanosine (13/205, 6.3%). The increased rate of birth defects with didanosine is concerning, but a thorough review of the defects observed revealed no pattern of defects. This rate will be moni-

tored closely but may reflect the relatively small number of exposures. The primary analysis of the registry is of the prospectively reported cases, but retrospective cases are also reviewed to detect patterns or clusters. While no signal of concern for efavirenz has been detected among the relatively small number of prospective cases in which there was first trimester exposure, three cases of neural tube defects and a case of Dandy-Walker malformation have been reported after first trimester efavirenz exposure, prompting a change in product labelling and a switch from FDA category C to D status. The denominator for these cases is unknown, but given the consistent animal data, concern is warranted. Improved reporting of prospective cases will allow more timely assessment of the risk associated with new antiretroviral agents and combinations of antiretrovirals.

Additional data have been reported from other cohorts. A retrospective review of outcomes among 195 infants found an increased rate of birth defects among infants exposed to the combination of first trimester antiretroviral drugs and folate antagonists (3/13, 23%), but not among those with exposure to antiretrovirals (0/15) or folate antagonists (0/19) alone, compared with those without first trimester exposure (6/148, 4%).[82] In a recent report from the ECS, no increased risk of birth defects was seen among infants born to HIV-infected women who were exposed to antiretrovirals during pregnancy (13/906, 1.4%) compared with those with no antiretroviral exposure (24/1508, 1.6%).[83] No specific pattern of defects was seen among those with first trimester exposure. Continued surveillance for birth defects after exposure to antiretroviral drugs in pregnancy is warranted as new drugs are approved on a regular basis and new combinations of drugs are used, which may change the risk. Ideally, the need for folate antagonist drugs such as cotrimoxazole (trimethoprim/sulfamethoxazole) in the first trimester could be avoided by optimising maternal health before pregnancy with antiretroviral therapy, obviating the need for opportunistic infection prophylaxis.

4. Infant Toxicity

4.1 Short-Term Toxicity

The most well studied prophylactic regimens have been zidovudine monotherapy and single-dose nevirapine. Comparing toxicity in infants between zidovudine and placebo groups in several trials, with regards to laboratory parameters, the only difference noted after maternal zidovudine regimens of 4–26 weeks during pregnancy and 1–6 weeks in the infant was mild, transient anaemia.[24,26,27,71] No difference was seen in the occurrence of liver enzyme abnormalities or toxicity requiring treatment discontinuation. In an evaluation of infants enrolled in the ECS, anaemia was associated with exposure to antiretroviral therapy but resolved once therapy was discontinued.[83] In an open-label study of zidovudine with lamivudine from 32 weeks of gestation in the mother and for 6 weeks in the newborn performed in France, higher rates of anaemia and neutropenia were seen compared with historical controls receiving zidovudine alone.[84] In a follow-up study of 2745 antiretroviral-exposed and 1504 unexposed, all uninfected, infants born to HIV-infected women in the French Perinatal Cohort, haemoglobin levels were noted to be transiently decreased among antiretroviral exposed infants.[85] Of note, neutrophil, lymphocyte and platelet counts were slightly but significantly lower until the age of 18 months after antiretroviral exposure, and combination therapy was associated with larger decreases than monotherapy. In the HIVNET (HIV Network) 012 trial, rates of adverse events were similar among 320 infants who received nevirapine and 309 who received zidovudine.[32] Among >4000 infants evaluated after receiving single-dose nevirapine prophylaxis in studies other than HIVNET 012, no significant differences in clinical or laboratory toxicities were seen compared with those receiving placebo, zidovudine or zidovudine/lamivudine.[4,33-35,86] Thus, in the short term, haematological and hepatic toxicity in infants exposed to maternal antiretroviral therapy and short-course neonatal therapy is minimal and transient. Infants should be monitored for anaemia if they receive neonatal therapy for more than 1 week.

Because of the known effect of nucleoside agents on mitochondrial function and the frequent use of these agents for treatment and prophylaxis during pregnancy and the neonatal period, several studies have evaluated lactic acid levels in infants exposed to nucleosides.[87-89] In normal infants, mild elevations in lactate levels may be seen after delivery, rarely exceeding 5 mmol/L and decreasing to adult levels of <2 mmol/L by 1 week of age.[87] In a study of 20 infants with perinatal antiretroviral exposure in whom samples were taken monthly for 3 months and then every 3 months, 85% had at least one lactate level measurement above 2.5 mmol/L, but all levels returned to normal during follow-up and none of the children had any clinical signs or symptoms.[87] In a study of 38 infants who had been exposed to antiretrovirals, 35 (92%) had at least one elevated lactate level, and 26% had levels >5 mmol/L.[88] Two infants exposed to HAART *in utero* and zidovudine neonatally experienced vomiting and irritability associated with lactate levels >5 mmol/L. When their zidovudine regimen was stopped, symptoms resolved and lactate levels decreased. Among infants tested after 28 weeks of age, 95% had normal values, but lactate levels remained elevated in two infants. In another study of 127 antiretroviral exposed infants, 63 (50%) had at least one elevated lactate level.[89] Three of the infants with elevated levels had neurological symptoms, which resolved over time as lactate levels decreased. Thus, elevated lactate levels are seen commonly among infants with *ante partum* and neonatal antiretroviral exposure. Most elevations are transient and not associated with symptoms. Routine evaluation of lactate levels in the neonate is not recommended, but may be helpful to rule out lactic acidosis in symptomatic infants.

4.2 Long-Term Toxicity

In general, long-term follow-up data from cohort studies of uninfected children born to HIV-infected women have been reassuring. In the ECS evaluation of 2414 children, including 1008 with antiretroviral exposure, there was no difference in the rate of severe or moderate symptomatic events related to antiretroviral exposure.[83] In an ECS report focusing on growth in HIV-exposed children, the height, weight and body mass index were normal for children who were not infected with HIV but lagged over time among those who were infected with HIV.[90] In a follow-up study of children born to women enrolled into the PACTG 076 study, which had placebo and zidovudine treatment arms, no differences were seen between placebo and zidovudine-exposed children in growth, cognitive and motor development, and lymphocyte subset results.[91] One zidovudine-exposed child had asymptomatic borderline cardiac dilatation at 48 months of age and two children had minor ophthalmological abnormalities with normal vision. Follow-up of these cohorts continues.

A specific concern raised for infants exposed to antiretroviral therapy, especially combination regimens, is that of mitochondrial toxicity, which may persist after discontinuation of therapy. Symptoms and laboratory abnormalities suggestive of mitochondrial dysfunction were first detected in eight of 1754 uninfected infants in the French Perinatal Cohort.[92] Two infants had progressive neurological symptoms and died at 11 and 13 months of age, respectively. Three additional infants had neurological symptoms and one of these also had a transient cardiomyopathy. Two infants had mild transient metabolic abnormalities but were asymptomatic. Subsequently, four additional cases of suspected mitochondrial dysfunction were identified among a combined cohort of 2644 children, for an 18-month incidence of 0.26% and an 18-month mortality rate of 0.07%.[93] In a separate report from the same cohort, investigators evaluated the rate of seizure among antiretroviral-exposed and unexposed children.[94] The rate of neonatal or afebrile seizure did not differ between the two groups, but the rate of febrile seizures among those exposed to antiretrovirals was 11.0 per 1000 compared with 4.1 per 1000 among the unexposed individuals. These data are of concern in light of data from several small studies evaluating mitochondrial DNA levels after nucleoside exposure. In a study of HIV-exposed children who were and were not exposed to

zidovudine compared with children who were not exposed to HIV, mitochondrial DNA levels were lower among infants born to HIV-infected women even without antiretroviral exposure and lowest among infants born to women who received zidovudine.[95] Differences in mitochondrial DNA levels persisted through to 2 years of age, but correlations between mitochondrial DNA levels and clinical outcomes were not provided. Two other studies evaluating mitochondrial DNA levels in cord blood and placentae found lower mitochondrial DNA levels or more evidence of DNA damage among samples from antiretroviral-exposed infants compared with samples from controls that were not HIV infected, but no HIV-exposed groups that were not exposed to antiretrovirals were included.[96,97]

So far, these findings have not been replicated in other cohorts. In the ECS, which included follow-up of 1008 antiretroviral-exposed children, no symptoms consistent with moderate or severe mitochondrial dysfunction were detected among antiretroviral-exposed infants, and all seizures (febrile and afebrile) occurred among infants with no antiretroviral exposure.[83] In a review of data from five US cohorts totalling >16 000 children born to HIV-infected women during 1985–99, no deaths attributable to or associated with symptoms, signs or laboratory abnormalities that indicated mitochondrial dysfunction were detected.[98] Follow-up of living children is ongoing. In a follow-up of 1798 children born to women enrolled into an African trial that compared placebo with three different durations of zidovudine and lamivudine therapy during pregnancy and in the neonate, no difference in the rate of neurological events was observed among children exposed to zidovudine and lamivudine compared with those exposed to placebo.[30] In a follow-up study of infants born to HIV-infected women – 10% who were exposed to zidovudine – echocardiograms were performed every 4–6 months through to the age of 5 years.[99] Exposure to zidovudine was not associated with acute or chronic abnormalities in left ventricular structure or function. Thus, the development of severe or fatal disease related to mitochondrial dysfunction after *in utero* and neonatal antiretroviral exposure appears to be extremely rare, and does not outweigh the benefits of antiretroviral therapy in the prevention of perinatal transmission of HIV. However, given the increasing complexity and duration of antiretroviral therapy in pregnancy, continued surveillance is required.

Animal studies have also raised concern about the potential for carcinogenicity of antiretrovirals after *in utero* or neonatal exposure. An increased risk of benign vaginal tumours in rodents was likely related to reflux of urine containing high concentrations of unmetabolised zidovudine onto the vaginal mucosa of rats, conditions that are not present in humans.[100] However, a subsequent study in pregnant mice that used 25–50 times the human dose given in the third trimester demonstrated an increased rate of tumours of the lung, liver and reproductive organs in the offspring of the highest dose group compared with untreated controls.[101] A subsequent study by the manufacturer of zidovudine that administered three times the human dose to female rats during pregnancy and in some of the offspring did not detect an increase in tumours in the offspring except for the expected benign vaginal tumours.[102] Studies in humans have thus far not detected an increase in the risk of cancers in children born to women receiving antiretroviral therapy during pregnancy. In a study of 727 children born to HIV-infected women receiving zidovudine, no tumours were detected after 1111 person-years of follow-up.[103] Similarly, no cancers have been detected among antiretroviral-exposed children in the ECS.[83] In a case-control study of HIV-infected children – 43 with cancer and 74 controls – exposure to zidovudine was not associated with the risk of cancer.[104] Since the lag time from exposure to tumour development may be many years, continued surveillance of antiretroviral-exposed children into adulthood is indicated.

5. Conclusions

As antiretroviral therapy during pregnancy becomes more complex, the potential for both short-term toxicity and long-term negative effects increases. Clinicians must be aware of the dosage

adjustments required during pregnancy and of toxicities that may be specific to pregnancy or to women, such as hepatic toxicity with nevirapine. Pregnancies exposed to antiretroviral therapy should be registered with the Antiretroviral Pregnancy Registry as early in pregnancy as possible to provide data on the risks of birth defects after exposure. Pregnant women receiving antiretroviral therapy should be educated about symptoms of preterm labour and pre-eclampsia, given the potential for an increased risk of preterm birth. Infants should be evaluated while on neonatal antiretroviral therapy for laboratory abnormalities such as anaemia. All antiretroviral-exposed children should have long-term follow-up to detect any potential delayed effects of antiretroviral therapy. Current data indicate that the benefits of antiretroviral therapy during pregnancy and in the neonate with regards to the reduction of perinatal transmission and maintenance of maternal health outweigh the risks of short- and long-term toxicity from the therapy. However, long-term surveillance of exposed children is required to more clearly delineate these risks.

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Correspondence and offprints: Dr *D. Heather Watts*, Pediatric, Adolescent, and Maternal AIDS Branch, CRMC/NICHD/NIH, 6100 Executive Boulevard, Room 4B11, MSC 7510, Bethesda, MD 20892, USA.
E-mail: wattsh@mail.nih.gov