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Safety of Agents Used to Prevent Mother-to-Child Transmission of HIV

Is There Any Cause for Concern?

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Abstract

Antiretroviral drugs have been used routinely to reduce the risk of mother-to-child transmission of HIV infection since 1994, following the AIDS Clinical Trials Group 076 trial, which demonstrated the efficacy of zidovudine in reducing the risk of *in utero* and intrapartum transmission. The use of antiretroviral drugs in pregnancy varies geographically, with widespread use of highly active antiretroviral therapy (HAART) in resource-rich settings for delaying maternal HIV disease progression as well as the prevention of mother-to-child transmission; however, in low- and middle-income settings, abbreviated prophylactic regimens focus on the perinatal period, with very limited access to HAART to date.

The potential risks associated with antiretroviral exposure for pregnant women, fetuses and infants depend on the duration of this exposure as well as the number and type of drugs. As the benefits of HAART regimens in reducing the risk of mother-to-child transmission and in delaying disease progression are so great, their widespread use has been accepted, despite the relative lack of safety data from human pregnancies.

Animal studies have suggested an increased risk of malformations associated with exposure to specific antiretroviral drugs, although evidence to support this from human studies is limited. Trials, cohorts and surveillance studies have shown no evidence of an increased risk of congenital malformations associated with *in utero* exposure to zidovudine, or other commonly used antiretroviral drugs, with an estimated 2–3% prevalence of birth defects (i.e. similar to that seen in the general population). Exposure to prophylactic zidovudine for prevention of mother-to-child transmission is associated with a usually mild and reversible, but rarely severe, anaemia in infants. However, a medium-term impact on haematological parameters of antiretroviral-exposed infants has been reported, with small but persistent reductions in levels of neutrophils, platelets and lymphocytes in children up to 8 years of age; the clinical significance of this remains uncertain. To date, there is no evidence to suggest that exposure to antiretroviral drugs *in utero* or neonatally is associated with an increased risk of childhood cancer, but the potential for mutagenic and carcinogenic effects at older ages cannot be excluded. Nucleoside analogue-related mitochondrial toxicity is well recognised from studies in non-pregnant individuals, whilst animal studies have provided evidence of mitochondrial toxicity resulting from *in utero* antiretroviral exposure. Clinically evident mitochondrial disease in children with antiretroviral exposure has only been described in Europe, with an estimated 18-month incidence of 'established' mitochondrial dysfunction of 0.26% among exposed children.

Regarding pregnancy-related adverse effects, increased risks of prematurity, pre-eclampsia and gestational diabetes mellitus have been reported by a variety of observational studies with varying strengths of evidence and with conflicting results. Based on current knowledge, the immense benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission far outweigh the potential for adverse effects. However, these potential adverse effects require further and longer term monitoring because they are likely to be rare and to occur later in childhood.

By early 2006, 17 million women were living with HIV infection worldwide; the vast majority in sub-Saharan Africa. Each day, approximately 1800 infants acquire HIV infection vertically from their mothers, with an estimated 700 000 children newly infected in 2005.[1] Mother-to-child transmission of HIV infection can take place *in utero*, during labour and delivery, or postnatally through breastfeeding.[2] The pre-eminent risk factor for mother-to-child transmission is maternal plasma HIV RNA load.[3-7] Antiretroviral drugs reduce transmission risk by decreasing viral replication in the pregnant woman, thus reducing plasma HIV RNA load, and through a prophylactic effect on the neonate.

There are four major classes of antiretroviral drugs in general use, the nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs/NtRTIs), the protease inhibitors (PIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the fusion inhibitors. Although most NRTIs and NNRTIs have been shown to cross the placenta in humans and/or animals,[8,9] there is low-placental transfer or no transplacental passage of the PIs.[10-15] With insufficient safety data from studies involving pregnant women, no antiretroviral drug has a US FDA pregnancy classification of A, with most having a B or C classification, although efavirenz, an NNRTI, was changed to a D classification in 2005 (see section 1.1)[16] [table I].

The use of an antiretroviral drug as an intervention for the prevention of mother-to-child transmission was first evaluated in the ACTG (AIDS Clinical Trials Group) 076 trial in 1994.[17] The finding that zidovudine monotherapy, used antenatally (started at between 14 and 34 weeks' gestation), intrapartum and as neonatal prophylaxis for 6 weeks reduced the risk of mother-to-child transmission by 68%, resulted in a rapid change in clinical practice in developed country settings[18-21] and triggered research in less-developed country settings to evaluate the efficacy of less intensive and thus more affordable antiretroviral prophylaxis regimens.[22]

Table I. US FDA safety classifications (2006) of antiretroviral drugs for use in pregnancy

Category class	Drugs
B: reproduction studies in animals failed to demonstrate a risk to the fetus; adequate, well controlled studies involving pregnant women have not been conducted.	NRTIs: didanosine; emtricitabine; tenofovir PIs: ritonavir; saquinavir; nelfinavir; atazanavir FIs: enfuvirtide
C: safety in human pregnancy has not been assessed; animal studies are either positive for fetal risk or have not been carried out; the drug should not be used unless the potential benefits outweigh the potential risks to the fetus.	NRTIs: zidovudine; lamivudine; zalcitabine; stavudine; abacavir NNRTIs: nevirapine; delavirdine PIs: indinavir; amprenavir; lopinavir/ritonavir; fosamprenavir; tipranavir
D: evidence of risk to human fetuses, although the benefits of the drug may justify the risk in some pregnant women when other options are not available.	NNRTIs: efavirenz FIs: hydroxycarbamide (hydroxyurea)

FI = fusion inhibitors; **NNRTI** = non-nucleoside analogue reverse transcriptase inhibitors; **NRTI** = nucleotide analogue reverse transcriptase inhibitors; **PI** = protease inhibitors.

Highly active antiretroviral therapy (HAART), involving a potent combination of at least three antiretroviral drugs, was first identified 10 years ago as being substantially more effective than mono- or dual therapy. In resource-rich settings, HAART is now the standard of care for HIV-infected patients with clinical and immunological indications for treatment. In such settings, a substantial proportion of HIV-infected women are already on HAART when they become pregnant.[7,10] Although guide-

lines for the therapeutic management of pregnant HIV-infected women vary between and within countries, most antiretroviral therapy (ART)-naive pregnant women will initiate HAART during pregnancy to delay their own disease progression and/or for prevention of mother-to-child transmission. However, some immunocompetent women may be offered zidovudine prophylaxis according to the 076 protocol in combination with an elective caesarean section.[23] In resource-rich countries with access to universal HAART, mother-to-child transmission rates have declined from around 20–25% in the pre-ACTG 076 era to <2%.[5,10,24]

In resource-poor settings, regimens for the prevention of mother-to-child transmission have focused on the perinatal period, with abbreviated regimens of antiretroviral drugs. The most commonly used regimen to date is single-dose nevirapine given orally to mothers intrapartum and to newborns, reflecting its relative ease of use, low cost and efficacy.[25,26] However, there are concerns regarding the rapid emergence of nevirapine resistance associated with use of single-dose nevirapine and the potential impact on future response to treatment among exposed mothers and their infected infants.[26-28] One week maternal postnatal zidovudine and lamivudine administered in addition to peri-partum single-dose nevirapine significantly reduces prevalence of nevirapine resistance.[22,29,30] However, such regimens have yet to be introduced on a population-level scale in sub-Saharan Africa.

The potential risk for pregnant women, fetuses and infants exposed to antiretroviral drugs depends on the duration of the exposure and the intensity, i.e. the number and type of drugs. As the benefits of HAART regimens in reducing the risk of mother-to-child transmission are so great, in addition to their effectiveness in delaying maternal disease progression, widespread use of combinations of antiretroviral drugs has been accepted, despite the relative lack of safety data from human pregnancies.

This review synthesises the evidence for short- to medium-term adverse effects and toxicities associated with the use of antiretroviral drugs in pregnancy for prevention of mother-to-child transmission of HIV. An English language literature search was undertaken using PubMed and other databases of publications available up to the end of June 2006. Hand searches of reference lists of relevant studies and abstracts from scientific conferences were also conducted. Key words used in the search were 'HIV', 'human immunodeficiency virus', 'mother-to-child transmission', 'vertical transmission', 'safety', 'toxicity', 'infants', 'children', 'pregnancy' and 'in utero'.

1. Safety Issues for the Fetus/Infant

1.1 Teratogenicity

Animal studies have suggested an increased risk of malformations associated with the use of certain antiretroviral drugs, reflected in the FDA pregnancy classifications (table I). CNS malformations were observed in cynomolgus monkeys with *in utero* exposure to efavirenz and subsequently there have been several case reports of CNS malformations (mainly neural tube defects) in infants exposed to efavirenz,[31-33] resulting in the reclassification of efavirenz as a FDA class D drug. *In utero* exposure to high doses of delavirdine in rats was associated with ventricular septal defects.[34] Use of both these drugs should be avoided in pregnancy or in women planning to become pregnant.

Data from trials, cohort and surveillance studies have shown no evidence of an increased risk of congenital malformations associated with exposure to zidovudine prophylaxis.[17,35-37] As HAART has now been used in pregnancy for over a decade, albeit relatively infrequently in the earlier years of the HAART era, there are accumulating data available to indicate whether risk of congenital abnormalities is increased by HAART use, particularly in the first trimester.

In the European Collaborative Study, the total prevalence of congenital abnormalities was 1.5% in around 2000 infants with *in utero* antiretroviral exposure (602 with HAART exposure); there was no increase in any particular defect with *in utero* exposure to zidovudine monotherapy, dual combination therapy or HAART, and the birth defect prevalence in infants exposed to any antiretroviral drugs in the first trimester was 1.8%, not statistically different from the 1.4% seen in infants with later exposure.[38]

In the UK National Study on HIV in Pregnancy and Childhood, there was similarly no statistically

significant difference in prevalence of congenital abnormalities between 2657 pregnancies with exposure to any ART and 463 unexposed pregnancies, at 3.4% and 2.2%, respectively; prevalence was similar for pregnancies with first trimester (3.7%) and later exposures (3.1%) to ART.[39]

The Antiretroviral Pregnancy Registry was established by the pharmaceutical industry in 1988 and depends on and encourages voluntary reports from clinicians of exposures to antiretroviral drugs in pregnancy and pregnancy outcomes. The Registry estimates a birth defect prevalence of 3.0% (95% CI 2.3, 3.8) among infants with first trimester exposure to antiretrovirals.[40]

1.2 Haematological Toxicity

Exposure to prophylactic zidovudine for prevention of mother-to-child transmission is associated with a usually mild and reversible anaemia in infants; rarely, this anaemia may be severe.[17,35,37,41-43] However, two large European cohort studies have reported a medium-term impact on haematological parameters of infants with antiretroviral exposure *in utero* and neonatally. In the French Perinatal Cohort among 4249 uninfected infants (2745 with antiretroviral exposure) aged up to 18 months, with a median duration of exposure of 171 days, levels of platelets, lymphocytes and neutrophils were slightly lower, but highly statistically significant, in exposed than in unexposed infants, after adjusting for age, maternal illicit drug use, prematurity, maternal geographical origin and maternal CD4+ count.[44]

In the European Collaborative Study, analysis of neutrophil counts and patterns in around 1500 uninfected children with a longer period of follow-up provided further evidence of a significantly lower neutrophil count in children exposed to antiretroviral prophylaxis (mainly zidovudine monotherapy) *in utero* and/or neonatally compared with those unexposed persisting up to at least the age of 8 years.[45] In a subsequent extended analysis of 1663 uninfected children, *in utero* and/or neonatal antiretroviral exposure was associated with decreased lymphocyte levels and CD8+ counts for up to 8 years, with decreased CD4+ counts in the first year of life; duration and intensity of exposure to antiretroviral drugs (monotherapy and combination therapy, including HAART) were associated with neutrophil and lymphocyte levels.[46]

The consistency of results from these studies adds weight to the hypothesis that the observed findings are caused by antiretroviral exposure, and a potential mechanism might be toxicity to nuclear DNA of haematopoietic stem cells.[44] The clinical consequences of slightly reduced lymphocytes, neutrophils and platelets in childhood in this population are uncertain and require further investigation. However, in a small study in The Netherlands, where 16 of 92 (17%) ART-exposed children had neutrophil counts suggesting moderate-to-severe toxicity, no clinical implications of such toxicity were detected on the basis of parental reports and hospital-based recording of infections or antibacterial use up to the age of 2 years.[47]

1.3 Cancer

There is potential for carcinogenic effects associated with fetal exposure to antiretroviral drugs, as shown by animal studies.[48,49] To date, there is no evidence to suggest that exposure to antiretroviral drugs *in utero* or neonatally for prevention of mother-to-child transmission is associated with an increased risk of childhood cancer. Initial results from cohorts of antiretroviral-exposed children in Europe and the US were reassuring regarding lack of malignancies;[35,50,51] however, the duration of follow-up in these analyses was short (between 2 and 4 years median follow-up). In an updated analysis from the PACTG (Pediatric AIDS Clinical Trials Group) 219 and 219C cohorts, in which the median age at last follow-up was 3 years (with information on 2077 uninfected children of whom 90% were exposed to antiretroviral drugs *in utero*), one child, without antiretroviral exposure, was diagnosed with cancer.[52]

Although all these findings are reassuring, indicating that *in utero* antiretroviral exposure (mainly to zidovudine in these studies) is not associated with an increased risk of early childhood cancer, the possibility that exposed children may be at risk of mutagenic and carcinogenic effects at older ages cannot be excluded. Continued follow-up of uninfected children exposed to these drugs is important, but whether this is achievable in the very long-term is uncertain.[53,54] Experience in the UK has

shown that clinic-based follow-up of uninfected children on a national level is challenging, mainly due to logistical issues; however, follow-up strategies based on linking surveillance data with other national sources of routinely collected morbidity and mortality data are feasible.[55]

1.4 Mitochondrial Abnormalities

Some NRTI drugs are well known to induce mitochondrial depletion and dysfunction, as a result of their affinity for mitochondrial gamma DNA polymerase, whilst primate (non-human) studies provided evidence of the potential for mitochondrial toxicity resulting from *in utero* antiretroviral exposure.[56,57] Chan et al.[58] recently showed that in mice, exposure to two NRTI drugs (zidovudine and lamivudine) was associated with greater mitochondrial DNA damage than exposure to single drugs, but that mitochondrial DNA damage resolved once exposure ceased. Mitochondrial DNA depletion and abnormal morphology of mitochondria have been reported in infants born to HIV-infected women and monkey newborns exposed to NRTIs *in utero* in cord blood leukocytes and umbilical cord endothelial cells.[59-61]

Clinically evident mitochondrial disease in children with ART exposure has so far only been described in Europe – the first cases were reported from France, with subsequent cases from Italy and Spain. In 1999, eight uninfected, antiretroviral-exposed children with mitochondrial dysfunction were identified from a French clinical study and paediatric cohort.[62] Subsequent larger-scale screening in the French Perinatal Cohort resulted in identification of further cases, and an estimated 18-month incidence of 'established' mitochondrial dysfunction (involving investigations of mitochondrial pathology, mitochondrial respiratory chain studies and magnetic resonance imaging) of at least 0.26% (95% CI 0.10, 0.54) among children with perinatal exposure to antiretroviral drugs.[63] All of the children with established dysfunction had hyperlactataemia and most had significant cognitive developmental delay, with one case each of cardiomyopathy/myopathy, motor abnormalities/brainstem symptoms and haemiplegia. No evidence of mitochondrial depletion was apparent.

Three cases of mitochondrial dysfunction in uninfected, ART-exposed children have been reported from Spain by Noguera and colleagues:[64] all had hyperlactataemia and concurrent neurological symptoms, with a median age at presentation of 5 months. The hyperlactataemia was transient in all three children: two had complete resolution of clinical symptoms and the third showed clinical improvement at 1 year of age.

The final case report of an uninfected, zidovudine-exposed infant with mitochondrial dysfunction has come from Italy.[65] The infant presented with neonatal encephalomyopathy and hyperlactataemia, and by 30 months had severe psychomotor delay and visual problems, which improved by 5 years of age. Although there was severe mitochondrial depletion in the neonatal period, by 6 months of age this was less marked.

Although most observational cohort studies of children born to HIV-infected women and exposed to antiretroviral drugs probably lack the sensitivity to identify mild cases of mitochondrial dysfunction, they would enable identification of any excess mortality in these children. Large observational studies in the US have not been able to confirm an excess of deaths in uninfected, ART-exposed children,[66,67] and there was no evidence of an association between antiretroviral exposure and serious clinical manifestations among approximately 2500 uninfected children in a European cohort, although no specific investigations were carried out with regard to mitochondrial functioning.[35]

Although these studies could not exclude a risk of mitochondrial disorders associated with ART exposure they, together with all the data published to date, suggest that the risk is very small and the long-term consequences of mitochondrial dysfunction may be even smaller.

Hyperlactataemia may indicate a degree of mitochondrial damage and several studies have described raised lactate levels (generally short-term and transient) in HIV-uninfected infants exposed to nucleoside analogues, which the authors have hypothesised may be due to mitochondrial toxicity from transplacental and/or neonatal exposure to antiretrovirals.[64,68-71] However, in the only study investigating lactate levels in infants exposed to short-course antiretroviral prophylaxis in a developing

country setting, no association was found between hyperlactataemia and exposure to nucleoside analogues.[72] Quantification of plasma lactate levels is an imperfect screening tool for mitochondrial dysfunction, as it lacks specificity and is difficult to measure accurately, with spurious increases due to sample collection and handling.

2. Pregnancy-Related Safety Issues

2.1 Prematurity

There are inconsistent results in the literature with regard to the impact of use of antiretroviral drugs on premature delivery (before 37 weeks). The initial reports of an increased risk of prematurity associated with PI-containing HAART came from Europe.[35,73-75] In an analysis combining data from the Swiss Mother+Child HIV Cohort Study and the European Collaborative Study, involving 3920 mother-child pairs (573 of whom received ART) enrolled between 1986 and 2000, the premature delivery rate was 16%; women receiving PI-containing regimens in pregnancy (n=108) had a 2.6-fold (95% CI 1.43, 1.74) increased risk of premature delivery compared with women receiving no antenatal treatment, independent of maternal CD4+ count and use of illicit drugs.[74] In an updated analysis from the European Collaborative Study, including enrolments up to 2004, the adjusted odds ratio (OR) for premature delivery for HAART use started before pregnancy was 1.88 (95% CI 1.34, 2.65) compared with any mono- or dual therapy, after adjusting for maternal age, injecting drug use in pregnancy, maternal CD4+ count and mode of delivery.[75]

In a US-based study combining data from seven clinical cohorts, a large number of mother-child pairs were assessed with regard to prematurity risk and PI-containing ART (n = 3266), spanning the pre-HAART and early HAART periods 1990–8. In this study, the preterm rate was 16% and the adjusted OR of preterm delivery for women receiving PI-containing ART was 1.5 (95% CI 0.72, 3.01), not statistically different from the baseline (no ART) [= 2229] Covariates adjusted for in this analysis included CD4+ count, previous preterm delivery and use of alcohol/tobacco/illicit drugs but not duration of antenatal therapy. However, among women receiving combination therapy, those receiving PI-containing regimens were at a significantly increased risk of very low birth weight (<1500g) [adjusted OR 3.56 with non-PI combination therapy as baseline], possibly a more sensitive marker of prematurity.[76]

In the Women and Infants Transmission Study, a US-based study that contributed data to the aforementioned combined analysis, a decrease in preterm delivery associated with the use of any ART was found in an analysis of 2543 women enrolled up to 2002.[5]

Recent results from a single site observational study by Cotter et al.[77] represent the first data from the US consistent with the European studies in identifying PI-containing combination therapy as an independent risk factor for premature delivery. In an analysis of 1133 HIV-infected women delivering between 1990 and 2002, of whom 999 received antenatal ART (492 on monotherapy, 373 combination therapy without a PI, 134 on combination therapy with a PI), combination therapy with a PI was associated with an increased risk of prematurity (adjusted OR 1.8; 95% CI 1.1, 3.0) versus other combination therapy, and adjusted OR 2.3 (95% CI 1.2, 4.3) versus none/monotherapy. Adjustment was made for multiple factors, including previous preterm delivery, HIV disease status, lowest CD4+ count, viral load, use of illicit drugs, alcohol consumption and coinfection with sexually transmitted diseases.

Differences in the populations studied, methodology and management have all been suggested as possible reasons for the inconsistencies in the literature.[78] Recent data from a small immunological study in Italy indicate that the increased risk of prematurity in women on HAART may be mediated through changes in the cytokine environment in pregnancy.[79]

2.2 Pre-Eclampsia

Pre-eclampsia is estimated to affect between 3% and 10% of pregnancies in the general obstetric population. Pre-eclampsia appeared to be less common in untreated HIV-infected women than in uninfected women in two studies.[80,81] However, a study from a large referral hospital in Spain reported

Table II. Summary of potential adverse effects of *in utero*/neonatal exposure to antiretroviral drugs

Adverse effect	Evidence source and strength of evidence	References
Teratogenicity		
CNS malformations associated with *in utero* exposure to efavirenz	Animal work; case reports +	31,32
Rate of birth defects with other commonly used antiretrovirals is unlikely to be increased above the background rate of 2–3%		9,38-40
Haematological toxicity		
Severe neonatal anaemia appears to be a rare adverse effect of NRTI drug exposure	Clinical trials, cohort studies	2,9,17,35,37,41
Small but persistent reductions in levels of neutrophils, platelets and lymphocytes reported in children with exposure to zidovudine and/or other antiretroviral drugs	Multi-centre cohort studies ++	44-47
Mitochondrial abnormalities		
Clinically-evident mitochondrial disease in children with antiretroviral exposure appears very rare and may be partially reversible in some cases	Multi-centre cohort studies; national surveillance +	62,64-67
Prematurity		
Exposure to PI-containing HAART has been associated with a 2- to 3.5-fold increased risk of delivery before 37 weeks' gestation and a 4-fold increased risk of very premature delivery in some studies	Multi- and single centre cohort studies ++	35,73-75,77
Pre-eclampsia		
Use of HAART throughout pregnancy may be associated with a 9-fold increased risk of pre-eclampsia	Single centre cohort +	82
Gestational diabetes mellitus		
Prolonged use of PI-containing HAART may be associated with increased risk of gestational diabetes. However, the limited data available to date are conflicting	Secondary analysis of clinical trial, small retrospective and prospective studies +	83,87
Lactic acidosis		
Severe, sometimes fatal, lactic acidosis has been reported with use of HAART containing didanosine and stavudine for prolonged periods in pregnancy	Case reports +	89-91

HAART = highly active antiretroviral therapy; **NRTI** = nucleoside analogue reverse transcriptase inhibitors; **PI** = protease inhibitors; **+** indicates moderate strength; **++** indicates high strength.

a significantly higher risk for pre-eclampsia in HIV-infected women taking HAART in pregnancy.[82] They documented no cases of pre-eclampsia in infected women delivering in 1985–2000, but a rate of 110 per 1000 deliveries in 2001–3. The use of HAART from before pregnancy was the most important risk factor for pre-eclampsia identified in this population, associated with an almost 9-fold increase in risk. Further research is needed to confirm this finding in other settings and populations.

2.3 Insulin Resistance, Hyperglycaemia and Gestational Diabetes Mellitus

PI use has been associated with abnormalities of glucose and lipid metabolism in non-pregnant populations, leading to concerns that its antenatal use may exacerbate pregnancy-associated increases in insulin resistance. Among women in the PACTG 316 trial, three-quarters received antenatal HAART in addition to the study drug (single-dose nevirapine) and around half of these were on PI-containing HAART. An increased risk of gestational diabetes mellitus in women on PI-containing HAART (starting before pregnancy or at early gestation) was reported, with a 4.6% versus 1.7% prevalence for women on PI and non-PI regimens, respectively.[83]

Smaller retrospective studies have had discordant results regarding an association between PI use in pregnancy and glucose intolerance.[84,85] The two

prospective studies addressing this issue have also had conflicting results: El Beitune and colleagues[86] reported an association between PI use and glucose intolerance among a limited number of pregnant women (n = 57); in the larger ACTG 5084 study, which involved 76 women on PI-containing regimens and 73 controls (69 on non-PI regimens and 4 untreated), no differences in the risk of glucose intolerance or gestational diabetes were found.[87]

2.4 Mitochondrial Toxicity

Women are thought to be more susceptible to certain clinical manifestations suggestive of mitochondrial toxicity than men, including lactic acidosis.[88] Lactic acidosis is a severe, often fatal adverse reaction to NRTIs and a small number of cases of lactic acidosis in pregnant women receiving HAART regimens including didanosine and stavudine have been reported. All these women had prolonged exposure and all presented with lactic acidosis in late pregnancy.[89-91] The FDA and Bristol-Myers Squibb subsequently published a warning that this combination of NRTIs should be avoided in pregnancy, unless no other combination was feasible.

2.5 Hepatotoxicity

Severe hepatotoxicity is a well documented but rare adverse effect of continuous nevirapine use in non-pregnant individuals, with symptoms ranging from hepatitis to hepatic failure, and also including severe hypersensitivity skin reactions, including Stevens-Johnson syndrome.[9,92-94] Women are at increased risk of nevirapine-related hepatotoxicity compared with men.[9,95,96] The degree of immune suppression is strongly associated with risk,[95,96] with women with CD4+ counts >250 cells/mm^3 having a nearly 10-fold increased risk of severe hepatotoxicity compared with more immunosuppressed women. Deaths from fulminant hepatitis in pregnant women receiving nevirapine have been reported,[97,98] in addition to other less severe adverse effects.[99,100] There is currently insufficient evidence to show a pregnancy-associated increased risk of hepatotoxicity over and above the increased risk associated with the female sex. Of note, single dose nevirapine is not associated with hepatotoxicity.

3. Conclusions

The potential adverse effects associated with use of antiretroviral drugs in pregnancy, including risks to the fetus, pregnancy outcome, pregnant woman and child, are incompletely quantified (table II). The increasing reports of undesirable pregnancy outcomes associated with early and prolonged HAART use and the finding that haematological effects of antiretroviral exposure persist into mid-childhood are of concern and require further monitoring and research. Nonetheless, increasing numbers of pregnant women and fetuses are and will continue to be exposed to combinations of antiretroviral drugs, reflecting the effectiveness of these agents in preventing mother-to-child transmission. On the basis of the current evidence-base, the benefits of prophylactic antiretrovirals in pregnancy outweigh the risks with regard to potential adverse effects. The potential adverse effects of exposure to antiretrovirals *in utero* and in neonatal life require further and longer term monitoring, as these are likely to be rare and occur later in childhood.

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