PRACTICAL DRUG SAFETY

Drug Safety 2001; 24 (9): 683-702
0114-5916/01/0009-0683/$22.00/0

Antiretroviral Therapy in Pregnancy
A Focus on Safety

Graham P. Taylor and *Naomi Low-Beer*

Imperial College School of Medicine, London, England

Contents

Abstract

Antiretroviral compounds differ from most other new pharmaceutical agents in that they have become widely prescribed in pregnancy in the absence of proof of safety. They are prescribed for the treatment of the mother and to reduce the risk of transmission of HIV to the fetus. In the animal models tested to date, no increased risk of malformations has been demonstrated for some compounds whereas others have been associated with malformations or developmental abnormalities in rats, mice or rabbits and, in the case of efavirenz, monkeys.

Zidovudine monotherapy is still prescribed to reduce the risk of mother-to-child transmission of HIV. Combinations of 3 or more compounds are recommended when treatment of the mother is deemed necessary because of advanced

HIV infection. Until recently, *in vitro* toxicity studies relevant to pregnancy were restricted to single agents; no animal teratogenicity or carcinogenesis studies of combination therapy have been published.

Despite many thousands of women having taken antiretroviral therapy to reduce the risk of transmission, documented experience in human pregnancy remains sadly lacking, with the possible exception of zidovudine which has been prescribed in clinical trials to several hundred mother–infant pairs. For other compounds and for the numerous permutations of combination therapy, data are available only from small phase I/II studies, from retrospective investigations and from the prospective arm of the Antiretroviral Pregnancy Register (i.e. pregnancies in women taking antiretrovirals who were registered before delivery and then followed up).

Antiretroviral monotherapy and combination therapy is widely prescribed in pregnancy because: (i) with appropriate management, which includes antiretroviral therapy, the risk of mother-to-child transmission can be reduced from 15 to 25% to less than 1%; (ii) pregnant women with advanced HIV infection require therapy; (iii) combination therapy with at least 3 compounds significantly reduces morbidity and mortality compared with dual or monotherapy; and (iv) the benefits of therapy for both the mother and the infant outweigh the risk.

The choice of antiretroviral therapy in pregnancy may be influenced by the indication (prevention of transmission or maternal treatment), past antiretroviral therapy exposure/drug resistance, effects of pregnancy on the pharmacokinetics of the drug and factors influencing tolerability and adherence. In pregnancy, tolerability may be even more important than usual, especially if therapy exacerbates common complications of pregnancy, such as vomiting and glucose intolerance.

The first specific therapy for human immunodeficiency virus type 1 (HIV-1) infection was the nucleoside analogue zidovudine (3′-azido-2′,3′-dideoxythymidine; AZT), which was initially administered to patients with advanced immunodeficiency.[1,2] During the 15 ensuing years a further 14 compounds have been licensed for use in adults, the majority of which are only licensed to be used as part of combination therapy. Since 1996, dual nucleoside analogue therapy, and then triple therapy with dual therapy plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI) became the recommended treatment for HIV infection.[3] Latterly, triple therapy with 3 nucleoside analogues has become an acceptable alternative for some patients.[3]

Pregnancy or the unwillingness or inability to use effective contraception are routinely among the exclusion criteria for clinical trials of novel therapies. However, the possibility of preventing mother-to-child transmission of HIV with antiretroviral therapy was examined in the sentinel Pediatric Aids Clinical Trial Group (PACTG) 076 study which demonstrated a 67% reduction in transmission with zidovudine.[4] Since 1994, zidovudine has become widely used in pregnancy. Meanwhile, the need to treat pregnant women with advanced HIV infection with effective therapy has been increasingly recognised. Although zidovudine remains the only therapy licensed for use in pregnancy, combination therapy with 3, 4 or more drugs is now commonly initiated during pregnancy. Furthermore, an increasing number of women of childbearing potential are starting combination therapies and as their prognosis improves some of these women wish to conceive. At preconception consultation or some weeks into the first trimester of pregnancy, they

will wish to know whether they should interrupt, continue or change therapy.

None of the antiretroviral therapies are currently classified as safe to use in pregnancy, i.e. in category A of the US Food and Drug Administration (FDA) pregnancy classification (table I) and therefore advice has to be based on a variety of data from cellular, animal and human studies. The difficulty for the physician is that few studies have addressed current practice, the diversity of which is reflected in the most recent interim report of the Antiretroviral Pregnancy Register (APR),[5] which records exposure to 98 different combinations of antiretroviral therapy. Not surprisingly, the median number of reports per combination was 1.

The aims of this paper are to provide a comprehensive summary of maternal and fetal safety data for antiretrovirals, both as monotherapy and when used in combination therapy, in order to allow prescribers to balance the needs of the mother and infant with the attendant risks of therapy. We summarise the current knowledge base, highlight the relatively limited evidence for prescribing antiretroviral therapy in pregnancy and provide some guidance for practical prescribing beyond that addressed by the clinical trials. In preparing the paper, relevant literature was sought by interrogating PubMed for each individual named compound using terms such as 'safety', 'pregnancy', 'teratogenicity' or 'animal studies' to refine the search. In addition, abstracts presented at major international meetings (Conference on Retroviruses and Opportunistic Infections, World AIDS Conference, Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, and European Conferences on Clinical Aspects and Treatments of HIV Infection) were reviewed.

Table I. US Food and Drug Administration pregnancy categories

Category	Description
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 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. The drug should not be used unless the potential benefit outweighs the potential risk to the fetus
D	Positive evidence of human 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 in pregnant women clearly outweighs any possible benefit

1. Monotherapy

1.1 Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)

Reverse transcription was the first stage of the HIV-1 lifecycle to be targeted for pharmacological intervention. The manufacture of viral DNA from the viral nuclear RNA is the unusual and essential characteristic of retroviruses. Nucleoside analogue reverse transcription inhibitors (NRTIs) compete with the cellular pool of natural nucleosides for incorporation into the viral chain. Lack of the normal 3′-hydroxy group on the analogue prevents the addition of the next nucleoside in the code and elongation of the DNA chain is terminated. Safety data are summarised in table II.

1.1.1 Zidovudine

Zidovudine has been the most widely used antiretroviral in pregnancy both alone and more recently in combination therapy. This thymidine analogue, originally tested as an anticancer therapy, was found to inhibit HIV reverse transcriptase in 1985, underwent clinical trials in 1986 and was licensed in 1987. Zidovudine has been shown to block 90% of detectable HIV replication *in vitro* at concentrations of less than 0.13 mg/L (<0.3 μmol/L), while plasma concentrations are consistently above 1 μmol/L with oral dosages of 10 mg/kg/day.[6]

Table II. Safety data relating to potential *in utero* exposure to nucleoside analogues

Drug	FDA pregnancy category	Placental passage (newborn : maternal drug ratio)	Long term animal carcinogenicity studies	Teratogenicity (rodent)
Zidovudine	C	Yes (0.85) [human]	Positive (vaginal tumours in mice, lung and liver tumours at high dose)	Positive (at approx. 300 × human therapeutic exposure i.e. near-lethal dose in rabbits)
Zalcitabine	C	Yes (0.3 to 0.5) [rhesus]	Positive (rodent thymic lymphomas)	Positive (hydrocephalus at 1071 x MRHD in rats)
Didanosine	B	Yes (0.5) [human]	Negative (no tumours, lifetime rodent study)	Negative
Stavudine	C	Yes (0.76)	Positive (bladder and liver tumours at ≥250 to 732 human therapeutic exposure)	Negative (decreased sternum calcium at high dose)
Lamivudine	C	Yes (approx.1.0)	Negative (no tumours, lifetime rodent study)	Negative
Abacavir	C	Yes (rat)	Studies in progress, no data	Positive (anasarca and skeletal malformations in rats as exposures equivalent to 35 times human dose)

FDA = US Food and Drug Administration; **MRHD** = maximum recommended human dose.

Safety

Preimplantation mouse embryos exposed to micromolar concentrations of zidovudine have been shown to arrest at the 4-cell stage,[7] but there have been no epidemiological reports to indicate decreased fertility among women taking zidovudine. Trophoblasts in culture have been shown to tolerate exposure to high concentrations of zidovudine.[8]

Zidovudine passively diffuses across the placenta,[9] resulting in concentrations in the fetal circulation which approximate to 85% of the maternal plasma concentrations.[10] Oral doses of zidovudine 300mg initiated in, and administered 3 hourly during, labour resulted in lower median maternal plasma concentrations compared with intravenous administration during labour (2 mg/kg over 1 hour, followed by 1 mg/kg hourly) and with oral administration earlier in pregnancy.[11] In women receiving intravenous zidovudine during labour, zidovudine triphosphate concentrations in cord blood cells were similar to those found in maternal lymphocytes although the concentrations were highly variable.[12] Zidovudine becomes incorporated into the DNA of the placenta and most fetal organs during short term intravenous infusion in pregnant rhesus monkeys,[13] and incorporation into human lymphocyte DNA with *in utero* exposure has also been demonstrated.[14]

There has been concern that exposure to zidovudine *in utero* (and *ex utero*) may affect mitochondrial function. Studies in *Erythrocebus patas* monkeys exposed *in utero* to doses equivalent to the normal human dose have shown mitochondrial damage in fetal cerebrum and cardiac and skeletal muscle but not in the cerebellum.[15,16] In muscle, depletion of mitochondrial DNA levels was zidovudine dose-dependent. Blanche et al.[17] diagnosed 8 cases of mitochondrial disease among the French Cohort of children born to HIV-positive mothers. All had been exposed to antiretrovirals *in utero*, 4 to zidovudine alone and 4 to zidovudine plus lamivudine. Two died of central nervous system manifestations, whereas at the other extreme 3 were asymptomatic. A study of babies exposed to zidovudine *in utero* revealed no evidence of cardiac dysfunction although numbers were small.[18,19] In a review of deaths of children exposed to zidovudine *in utero* in the US, using data from a variety of studies, no cases were attributable to mitochondrial disease.[20] In PACTG 219, a long term prospective study of children born to mothers who participated in Aids Clinical Trial Group (ACTG) 076, 2 children with ophthalmic abnormalities and 1 with a

mild cardiomyopathy have been identified – all were zidovudine exposed but the aetiology of each condition was uncertain.[21]

In mice exposed to high concentrations of zidovudine *in utero* and for a prolonged postnatal period, vaginal tumours were observed in adult life. However, this may be attributable to long term chemical irritation, as in mice zidovudine is predominantly excreted unchanged in urine, which commonly refluxes into the vagina. These tumours were not found in mice only exposed *in utero*.[22] An increased incidence of lung, liver and female reproductive tract tumours has also been reported in 1-year-old CD-1 Swiss mice exposed to high dose zidovudine (maternal dose 25mg or 12.5mg) *in utero*.[23] In a subsequent study of 2-year-old mice, the zidovudine effect was predominantly seen in females with a 3-fold increase in lung tumours and a dose-dependent increase in histiocytic sarcomas which occurred in 8% of mice exposed to the higher dose compared with no occurrences in control mice ($p = 0.022$). Dose-dependent increases were also seen for mammary, ovarian and seminal vesicle tumours, but lymphoblastic and follicle centre cell lymphomas were less common than among controls. More than 50% of female mice compared with 12% of controls developed tumours thought to be zidovudine-related.[24] However, no tumours have been found among 727 children exposed to zidovudine *in utero*, either as part of the PACTG 076/219 study and followed up to a mean age of 38.3 months, or in the Women Infants Transmission Study (WITS) and followed up for a mean of 14.5 months.[25]

Neurobehavioural studies in rodents exposed to zidovudine *in utero* have produced conflicting results with impairment,[26] no effect[27] and a gender-dependent effect[28,29] variously reported. As with the carcinogenesis studies, the significance for humans of these neurobehavioural studies in rodents is uncertain and no cognitive or developmental abnormalities were found among the 122 zidovudine-exposed children followed to a median age of 4.2 years in PACTG 219.[21]

Teratogenic effects with zidovudine have been reported in rodents only when exposed to near-lethal maternal doses. No teratogenic effect was found in a whole rat embryo culture system.[30] The APR, established by the pharmaceutical industry in 1988, collates voluntary reports from clinicians prescribing antiretroviral therapy in pregnancy.[5] Of the 129 prospective reports on babies exposed to zidovudine alone during the first trimester, only 1 had a documented defect (0.8%), which is lower than the expected background rate of congenital malformations and lower than the rate observed with second or third trimester exposure to nucleoside analogues (2.6%). In the Metropolitan Atlanta Congenital Defects Program, which is a population-based birth defects surveillance system, 3.2% of 195 642 births had defects.[31] It has been noted that registries, including the APR, generate lower rates of congenital defects (2.7%) than population-based surveillance and that the number of reported defects per affected infant is also lower.[32] The 2.7% rate is however similar to population rates based only on examinations in the first few days of life.[1]

As with monotherapy in nonpregnant women, zidovudine transiently reduces HIV-1 plasma viraemia and increases CD4+ lymphocyte counts. In ACTG 076, in which mothers commenced zidovudine 100mg 5 times daily between weeks 14 and 28 of gestation, therapy was associated with a 0.24 $\log_{10}$ reduction in plasma viraemia at the time of delivery.[33] In the Bangkok study,[34] zidovudine 300mg twice daily was commenced at week 36, resulting in a 0.57 $\log_{10}$ reduction in plasma viraemia

1 The advisory committee of the Antiretroviral Pregnancy Registry have requested that the following consensus statement concerning the registry is included with any presentation of data from the registry: 'The Registry's analytic approach is to evaluate specific classes of antiretroviral drugs (NRTIs, nnRTIs and PIs) [nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors]. To date, however, accumulated cases of exposures to the antiretroviral agents followed in the Registry used alone or in combination are insufficient for reaching any reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses.'

at delivery. This was considered to account for 80% of the efficacy of zidovudine to reduce transmission.

Sequence changes in the HIV-1 reverse transcriptase associated with decreased viral sensitivity to zidovudine were found, at the time of delivery, in 1 of 36 mothers in the zidovudine arm of ACTG 076[35] and in 2 of 10 mothers receiving zidovudine monotherapy in a cohort in the UK.[36] This has caused concern that zidovudine monotherapy, although effective in reducing mother-to-child transmission, may in the long term reduce maternal options for therapy. Higher plasma viral load and longer duration of therapy have been associated with the risk of resistance mutations at delivery,[37] while in the Retrovirus-Côte d'Ivoire (RETRO-CI) study none of the 10 women tested had evidence of zidovudine-related mutations following a median of 27 days therapy.[38] In comparison with some other antiretroviral compounds, zidovudine-related mutations develop slowly, therefore shorter courses and restricting the use of zidovudine monotherapy to mothers with low viral load and high CD4+ counts may limit the emergence of viral strains with reduced sensitivity to zidovudine. With increasing use of antiretroviral therapy, primary (at the time of infection) or secondary (following therapy) acquisition of viral strains with reduced sensitivity to zidovudine may become increasingly important. In the Swiss Collaborative 'HIV and Pregnancy' Study, mutations associated with 'high level' zidovudine resistance were found in 6 of 62 (9.6%) of mothers,[39] whereas in the WITS, which included many women with advanced HIV disease and prior (prepregnancy) zidovudine exposure, 34 of 142 (25%) of maternal isolates had at least 1 zidovudine-associated resistance mutation.[40] In this study the presence of zidovudine-associated resistance mutations was identified as a risk factor for transmission independent of maternal viral load.

Zidovudine appears to be relatively risk-free for the mother, in the long as well as the short term. In ACTG 288, a prospective study following delivery of women who participated in ACTG 076, the use of zidovudine was not associated with increased risk of clinical or immunological progression.[41] Indeed, evidence of improved maternal mortality following short course zidovudine has been observed in 2 studies. Among breastfeeding African women treated with short course zidovudine (commenced at week 36 and discontinued at delivery), the relative risk of mortality after 2 years follow-up was 0.44 compared with placebo.[38] Although this was not statistically significant, with the 95% confidence intervals (CIs) including 1, the same effect has been observed in Thailand, with mortality reduced from 8% to 1% at 18 months ($p = 0.004$).[42]

Efficacy

The efficacy of zidovudine in reducing mother-to-child transmission of HIV-1 has been demonstrated in several large randomised controlled studies and is supported by epidemiological surveys. In these studies, zidovudine was administered from the start of the second trimester (here described as long prepartum), or from week 36 (short prepartum), peripartum to the mother by mouth or by intravenous infusion and postpartum to the neonate (or to the mother if breastfeeding) for 1 (short) to 6 (long) weeks. In PACTG 076, among nonbreastfeeding generally healthy mothers with a CD4+ lymphocyte count >200 cells/μl, (median 550 cells/μl) in France and the US, long prepartum, intravenous peripartum and long neonatal zidovudine reduced mother-to-child transmission by 67% from 22.6% in the placebo arm to 7.6%.

Epidemiological studies have confirmed similar reductions in transmission outside of the clinical trial setting: in New York and Puerto Rico transmission was reduced from 19 to 8%,[43] in France transmission fell from 14 to 5%[44] and across multiple centres in Europe transmission among 669 mother–infant pairs between 1994 to 1997 was 9% when at least part of the zidovudine regime had been used compared to 15% without any zidovudine prophylaxis.[45]

The contributions of the various components of the ACTG 076 regimen were partially dissected out in an observational study in New York State in which HIV-1 transmission occurred in 28.8% of

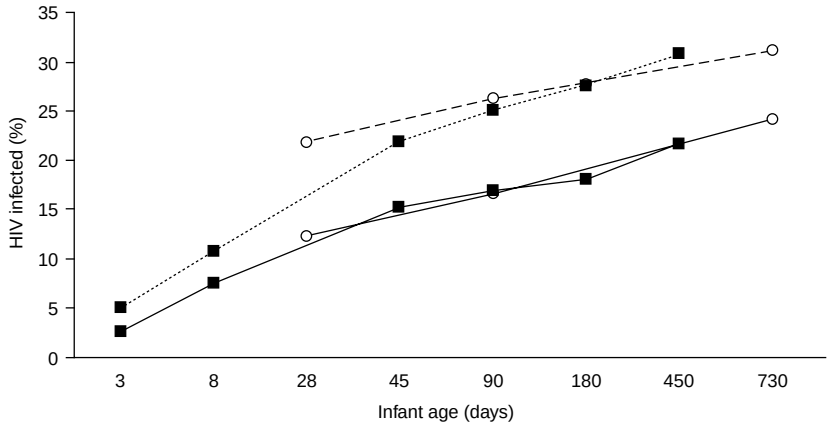

Fig. 1. Cumulative HIV mother-to-child transmission rates in breastfed infants in 2 double-blind placebo-controlled studies of zidovudine versus placebo in Africa. Filled squares refer to the DITRAME (Diminunation de la Transmission Mère-Enfant) study; open circles refer to the RETRO-CI (Retrovirus-Côte d'Ivoire) study; solid lines indicate zidovudine; broken lines indicate placebo.[49]

mother–infant pairs untreated, in 9.7% if zidovudine was initiated during delivery or postpartum and in 5.2% if zidovudine was commenced prepartum. No benefit was gained by initiating zidovudine more than 48 hours after delivery.[46] In a placebo-controlled study among nonbreastfeeding Thai women, transmission was reduced by 51%, from 18.6% (35 of 198) to 9.2% (17 of 193) with short prepartum (300mg twice daily) plus oral peripartum (300mg 3 hourly) zidovudine alone.[47] The relative importance of each component has been further defined in a subsequent study in Thailand, the Prevention of HIV Perinatal Transmission (PHPT) study. In this study of 1437 women, all mothers received oral zidovudine 300mg 3-hourly during labour, but were otherwise randomised to 4 arms comparing different duration of pre- and postpartum therapy. The transmission rates were 6.7% in the long prepartum (commence at 28 weeks), long postpartum arm, 5.7% in the long/short, 8.4% in the short/long and 10.6% in the short/short. The short/short arm data cannot be directly compared with the other arms, as this arm was prematurely halted following an interim analysis at which point the transmission rate in the long/long arm was 4.1%.[48] Among breastfeeding mothers in Africa, short/short and short/none regimens have been shown to reduce transmission by 35 to 37% at 3 to 6 months, but transmission subsequently rose from 16.9 to 22.1% at 2 years. However despite prolonged breastfeeding (56% still breastfeeding at 1 year), zidovudine administered perinatally was still associated with a 27% reduction in transmission at 2 years compared with placebo (30.1%) [fig. 1].[49]

1.1.2 Lamivudine

Lamivudine [(–)-2′-deoxy-3′-thiacytidine; 3TC] is a cytosine analogue that crosses the placenta by simple diffusion,[50] resulting in cord plasma concentrations similar to maternal plasma concentrations.[51] The pharmacokinetics of lamivudine are not affected by pregnancy nor by co-administration of zidovudine.[51] No evidence of mutagenesis was found in bacterial assays but a weak effect was seen in human and mouse cells. No tumours were observed in lifetime rodent studies nor any teratogenicity in rodents. In most parameters, no short or long term neurobehavioural effects were found in mice exposed *in utero* to lamivudine except at high doses (125 to 500 mg/kg).[52,53] With the exception of the aforementioned pharmacokinetic study, there are no data on lamivudine monotherapy in pregnancy. Lamivudine is category C in the FDA preg-

nancy classification and will be further considered in section 2 on combination therapies.

1.1.3 Didanosine

Didanosine (2′,3′-dideoxyinosine; ddI) is an adenosine analogue that rapidly crosses the placenta by simple diffusion[9,54] and this transfer is not affected by concurrent administration of zidovudine.[55] However transfer is less efficient than for zidovudine or lamivudine and human cord blood concentrations indicate only 30% transfer. Although no effect of pregnancy on didanosine pharmacokinetics was found following intravenous administration in *Macaca nemestrina* monkeys near term,[56] didanosine is more rapidly cleared in pregnant (compared with postpartum) women because of their increased glomerular filtration rate.[57] However no significant effect was seen with the oral dose and no change in the 2 × 100mg twice daily regimen was recommended. No pharmacokinetic studies of once daily didanosine in pregnancy with either the reduced volume or enteric coated formulations have been reported.

No mutagenesis was detected in bacterial assays and effects on mammalian cells was only seen at high concentrations. There is no evidence of carcinogenesis in life-long rodent studies. Human trophoblasts tolerate high dose exposure to didanosine[8] and no adverse effect of didanosine was found in pre- or postimplantation mice embryos[7,58] nor in a whole rat embryo culture system.[30] At 30 μmol/L didanosine reduced rat thymocyte numbers in whole organ culture.[59] Didanosine did not affect fertility in rabbits nor harm the fetus at doses more than 10 times those expected to be used in therapy.

Didanosine is the only nucleoside analogue in FDA category B. Birth outcomes of children exposed to didanosine in the first trimester have been reported to the International Registry for 52 children, however only 4 were exposed to monotherapy.

1.1.4 Zalcitabine

Zalcitabine (2′,3′-dideoxycytidine; ddC) is a cytidine analogue that crosses the placenta passively, but less efficiently than lamivudine, with fetal concentrations approximately 60% of maternal plasma concentrations in near term *Macaca nemestrina*.[60] Zalcitabine clearance was however significantly less in neonatal macaques aged 1 to 2 weeks compared with age 4 weeks following an intravenous bolus.[61] Human data are not available, but dose reduction would seem to be indicated from these data. Zalcitabine seems not to be toxic to the blastocyst[58] nor associated with developmental toxicity in the whole rat embryo culture system.[30] However when administered to pregnant C57B1/6N mice at doses of 1000 to 2000 mg/kg/day, zalcitabine was associated with fetal malformations, reduced fetal bodyweight and increased fetal resorptions in the absence of obvious maternal toxicity.[62] In addition, zalcitabine was toxic to thymocytes at concentrations considerably lower than seen with zidovudine or didanosine.[59] Teratogenicity in rats and mice has only been demonstrated at doses equivalent to 1000 times the maximum recommended human dose.

Only 12 first trimester exposures to zalcitabine have been reported to the APR, of which 5 were exposed to combinations. Zalcitabine is in category C of the FDA pregnancy classification.

1.1.5 Stavudine

Stavudine (2′,3′-didehydro-3′-deoxythymidine; d4T) is a thymidine analogue that crosses the placenta passively producing concentrations in the fetal macaque which are 77 to 85% of the maternal plasma concentration.[63,64] Stavudine was not mutagenic in bacterial assays, but an increased frequency of chromosomal abnormalities have been found in cultured human lymphocytes. Stavudine was less likely than zidovudine, but more likely than zalcitabine or didanosine, to inhibit blastocyst formation.[58] Rodent studies for teratogenicity were negative although a decrease in sternal calcium was noted with high doses. Carcinogenesis studies are incomplete and thus stavudine has a C classification for use in pregnancy.

Stavudine has been one of the most widely prescribed therapies in the first trimester of pregnancy, with exposures reported in 159 babies. In 157 of

Table III. Safety data relating to potential *in utero* exposure to protease inhibitors

Drug	FDA pregnancy category	Placental passage (newborn : maternal drug ratio)	Long term animal carcinogenicity studies	Teratogenicity (rodent)
Saquinavir	B	Low (rats)	In progress	Negative
Indinavir	C	Yes (rats and dogs but low in rabbits)	In progress	Positive[a] (extra rib in rats, unilateral anophthalmia in 3% of rats)
Ritonavir	B	Yes (rats)	In progress	Negative but developmental toxicity in rabbits at maternally toxic doses (equivalent to 30% human dose)
Nelfinavir	B	Low (humans)	In progress	Negative
Amprenavir	C	?	In progress	Positive (abortions in rabbits; ossification defects in rats and rabbits at exposures less than human therapeutic dose)
Lopinavir	C	?	In progress	Negative (skeletal variations and delayed ossification at maternal toxic doses)

a Data not included in the most recent revision of guidelines from the US Public Health Service[66] in which indinavir was graded negative in this category.

FDA = US Food and Drug Administration.

these stavudine was prescribed as part of combination therapy.[5]

1.1.6 Abacavir

Abacavir, a guanosine analogue and the most recently licensed of the NRTIs, has a high placental clearance index.[65] Abacavir was not mutagenic in bacterial assays but was mutagenic in a study of human lymphocytes. At doses 35 times higher than the human therapeutic dose, fetal rat developmental toxicity was seen with anasarca and skeletal malformations. Increased fetal resorptions and stillbirths were also noted in rats. However no abnormalities were observed in rabbits exposed to abacavir at concentrations 8.5 times higher than the expected human exposure.

Only 2 cases of first trimester abacavir exposure have been reported to the APR.[5] Abacavir is classified C for use in pregnancy.

1.2 Protease Inhibitors (PIs)

Whereas reverse transcriptase inhibitors prevent incorporation of HIV DNA into a host cell chromosome, thereby aborting infection, protease inhibitors (PIs) inhibit the splicing of the viral polyproteins in the cytoplasm. This results in the production of noninfectious virus which on electron microscopy frequently lacks a visible nucleus. The absence of a cellular homologue permitted the design of inhibitors specific for HIV protease. The adverse events seen with PIs are unrelated to their antiprotease activity. The first PIs entered phase 1 clinical trials in the early 1990s. The safety data for PIs are summarised in table III.

1.2.1 Ritonavir

Ritonavir was not mutagenic in bacteria or mammalian cells including human lymphocytes. In rats, maternal hepatotoxicity and fetal developmental toxicity were seen at or at less than the human equivalent doses. Since malformations were not seen in rats or rabbits except for a slight increase in cryptorchidism, ritonavir is included in category B by the FDA. *Ex vivo* studies indicate that very little ritonavir crosses the placenta.[67] In a safety, tolerability and efficacy study of 86 pregnant women, ritonavir monotherapy was initiated at gestation week 36 at a dose of 300mg twice daily increased incrementally to 600mg twice daily by day 15 and taken for a mean of 20 days. The median viral load reduction was 2.8 $\log_{10}$ and the transmission rate was 9.5%, but 12 women discontinued treatment, 10 because of elevated liver enzyme levels.[68]

In more than half the 15 cases of first trimester exposure reported to the APR by 31 January 2000,

ritonavir had been prescribed not only as part of a combination but as a double PI combination.[5]

1.2.2 Indinavir

Indinavir crosses rat and dog placentas but little transfer is seen in rabbits. Indinavir was not mutagenic, nor carcinogenic in mice. However rats administered a dose equivalent to 1.3 times the normal human dose had an increase in thyroid adenomas. Administration of indinavir to rats during days 6 to 15 of gestation was associated with an increased incidence of supernumerary ribs, delayed fur development, eye opening and testis descent, microscopic liver changes and, in 3% of pups, with unilateral anophthalmia.[69] Indinavir is therefore a category C compound, but has been the most widely prescribed PI in the first trimester with 115 exposed babies reported, of which 6 were exposed to a double PI.[5]

1.2.3 Saquinavir

Saquinavir was not mutagenic in standard bacterial assays nor teratogenic in rabbits and is thus category B. Less than 5% of the maternal concentrations are found in fetal blood in rats. Carcinogenicity studies have not been completed.

Three cases of first trimester saquinavir exposure alone and 39 cases of saquinavir in combination with other antiretroviral therapy, including 11 cases of double PI therapy, have been reported to the APR.[5]

1.2.4 Nelfinavir

Nelfinavir was not mutagenic in bacteria or mammalian cells including human lymphocytes. Carcinogenicity studies have not been completed. No evidence of teratogenicity was found in rabbits. Pharmacokinetic studies of nelfinavir in human pregnancy conducted as part of a combination therapy revealed normal maternal concentrations but very low or undetectable concentrations in the cord blood.[70] Nelfinavir is in category B of the FDA pregnancy classification. Nelfinavir was the second most commonly prescribed PI during the first trimester, with 85 cases reported to the APR.[5]

1.2.5 Amprenavir

Amprenavir exposure was associated with abortions and with deficient ossification in pregnant rabbits, but the doses used were lower than the equivalent therapeutic dose in humans. Amprenavir was also associated with abnormalities of ossification in rats, exposed to doses equivalent to less than the human therapeutic dose, and with thymic elongation. The transplacental pharmacokinetics of amprenavir have not been reported. Rodent carcinogenesis studies are ongoing.

There are only 2 reports of first trimester exposure to amprenavir in humans.[5] Amprenavir is in category C of the FDA pregnancy classification.

1.2.6 Lopinavir

Lopinavir is a derivative of ritonavir, and has recently been licensed as a combination of lopinavir and ritonavir. The small dose of ritonavir serves to increase lopinavir concentrations by inhibition of the cytochrome P450 isoform CYP3A. There have been no studies of lopinavir/ritonavir in human pregnancy, no case reports to the APR or published animal studies. According to the manufacturer's information sheet, developmental toxicity was observed at maternally toxic doses of lopinavir/ritonavir but no drug-induced malformations were seen in animal studies. However the number of animals and the species tested were not stated. The transplacental pharmacokinetics of lopinavir have not been reported and carcinogenesis studies are continuing.

1.3 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

These compounds inhibit HIV reverse transcriptase by binding to and disturbing the reverse transcriptase catalytic site. The safety data are summarised in table IV.

1.3.1 Nevirapine

Nevirapine was not mutagenic in bacteria or in mammalian cells. Carcinogenesis studies are incomplete but exposure was not associated with teratogenicity in rabbits or rats and nevirapine has been classified a category C compound. Two major

Table IV. Safety data relating to potential *in utero* exposure to non-nucleoside reverse transcriptase inhibitors

Drug	FDA pregnancy category	Placental passage (newborn : maternal drug ratio)	Long term animal carcinogenicity studies	Teratogenicity	
				rodent	primate
Nevirapine	C	Yes (approx. 1.0) [human]	Not completed	Negative	
Efavirenz	C	Yes (approx. 1.0) [cynomolgus monkeys, rats, rabbits]	Not completed	Negative (increased fetal resorptions)	Malformations in 3 of 20 cynomolgus monkeys: anencephaly, anophthalmia, microphthalmia
Delavirdine	C	Yes (rats)	Not completed	Ventricular septal defect	

FDA = US Food and Drug Administration.

congenital malformations have been reported among 55 infants exposed to a nevirapine-containing regimen in the first trimester.[71] The long half life of nevirapine (45 hours following a single dose in adults) is even longer in term pregnant women (66 hours). In addition, nevirapine rapidly crosses the placenta and, provided that a minimum of 2 hours have elapsed between maternal administration and delivery, cord blood concentrations are equal to maternal plasma concentrations. A regimen of 200mg given to the mother early in labour followed 48 to 72 hours later by a single dose of 2 mg/kg to the neonate results in neonatal plasma nevirapine concentrations that remain above the 90% inhibitory concentration (IC_{90}) of wild-type HIV-1 for at least 7 days.[72] Nevirapine is also excreted in breast milk and this may have resulted in the higher neonatal plasma concentrations seen with the same regimen in African women who were breastfeeding.[73] Earlier maternal administration results in higher cord blood concentrations but when administered for more than a few days prior to delivery nevirapine is more rapidly cleared in the neonate. Thus, more frequent administration may be necessary to maintain neonatal concentrations during the first week of life, but no change in the maternal dose or dose schedule is required for therapy administered during the second or third trimesters.[74]

The rapid placental transfer and long half-life of nevirapine have led to a number of studies which indicate that mother-to-child transmission may be reduced by 50% (compared with peripartum and short postpartum zidovudine) with the 2-dose regimen of nevirapine.[75] As with short-course zidovudine, the transmission rates are less than expected (15.7% with nevirapine and 24.1% with zidovudine) and the increased protection of nevirapine persists at 1 year even though the infants were breastfed.[76]

Mutations associated with decreased susceptibility to nevirapine occurred rapidly and frequently in studies of nevirapine monotherapy in nonpregnant adults.[77] In the HIV Network for Prevention Trials (HIVNET) 012 study comparing 2 doses of nevirapine with zidovudine initiated in labour and prescribed to the neonate for 1 week, nevirapine resistance mutations were found in 7 of 30 mothers and in 3 of 7 infected infants tested.[78,79] In the SAINT study, transmission rates at 8 weeks with the HIVNET 012 study regimen (14%) were not significantly different from the rate of transmission in mother–infant pairs receiving zidovudine 300mg plus lamivudine 150mg in labour and twice daily to mother and infant for 1 week postpartum (10.8%).[80] 32 pregnancies with first trimester exposure to nevirapine have been reported and in 2 cases the mothers were taking a double NNRTI combination.

1.3.2 Efavirenz

Efavirenz is not mutagenic and carcinogenesis studies are ongoing. Although rodent studies have been normal, teratogenicity was noted in cynomolgus monkeys, with severe defects (anencephaly, microphthalmia and cleft palate) found in 3 of 13 fetuses, subsequently updated to 3 of 20

fetuses.[81] Similar primate studies have not been conducted for other antiretroviral therapies either singly or in combination.

Efavirenz is included in category C. Efavirenz is now widely licensed but should not be prescribed to women unless they are willing and able to use effective methods of contraception. Despite these restrictions, up until 6 June 2001, 158 exposures to efavirenz-containing regimens in pregnancy had been reported to the Dupont Worldwide Pharmacovigilance Database, including 127 exposures which included the first trimester. Of the 61 live births (all trimesters of exposure) 53 neonates were apparently well and 8 had a medical condition. The congenital defects were a lumbosacral meningomyelocele, an angioma on the back of the neck, an unspecified heart murmur, laryngeal malacia and cystic fibrosis. Other conditions reported were neutropenia and anaemia. As with reporting to the APR the data are too few to draw conclusions about association. Furthermore, these are retrospective reports which are unreliable for prevalence estimates (A. Sutherland, Dupont Pharma, personal communication).

1.3.3 Delavirdine

Delavirdine has not been licensed in the UK but is available to named patients. Delavirdine was mutagenic in some bacteria after metabolic activation. Carcinogenesis studies are incomplete. In Sprague-Dawley rats, at doses equivalent to human therapeutic exposure, ventricular septal defects were identified at a significantly high rate. This may represent teratogenesis or developmental toxicity. In addition, hydrocephalus was observed in some offspring. In rabbits, doses about 6-fold higher than expected in humans were associated with maternal toxicity and abortions.

Delavirdine is classified as FDA pregnancy category C. In 7 unplanned pregnancies reported, 3 were ectopic and 1 baby was born with a ventricular septal defect.[5]

1.3.4 Emivirine

Emivirine is not available in Europe. In a pharmacokinetic and safety study, clearance of emivirine was reduced by 50% compared with nonpregnant women. Neonatal plasma concentrations were 77% of the maternal plasma concentration after 21 days of maternal therapy. The combination of emivirine with zidovudine plus lamivudine was well tolerated and associated with a reduction of HIV viraemia to <400 copies/ml in 9 of 12 mothers.[82]

2. Combination Therapy

Determining the safety of *in utero* exposure to combination therapy is even more difficult than for monotherapy. 98 different combinations of therapies have already been reported to the APR, ranging from monotherapy to 6 compounds. The median number of pregnancies reported per combination is 1, with only zidovudine monotherapy generating more the 100 pregnancies for evaluation. Zidovudine plus lamivudine was reported from 85 pregnancies and zidovudine, lamivudine and any PI from 97 pregnancies.

2.1 Dual Nucleoside Analogue Therapy

Few studies have examined the pharmacokinetics, tolerability and safety of combination therapy, and efficacy has only been reported from observational data. The most extensive data on combination therapy is for zidovudine plus lamivudine. First trimester exposure to this combination has been reported from 85 pregnancies. In a further 197 pregnancies lamivudine was prescribed with other or additional therapies. The pharmacokinetics of lamivudine in combination with zidovudine are the same as in nonpregnant adults, and no dosage adjustments are required to maintain adequate drug concentrations in near term pregnant women.[51]

In a nonblind prospective study of 19 women starting therapy in the second and third trimesters, zidovudine plus lamivudine was associated with a mean reduction in HIV-1 plasma viraemia of 1.5 $\log_{10}$ at delivery, compared with a 0.3 $\log_{10}$ reduction with zidovudine monotherapy. However the genotypic mutation M184V that confers resistance to lamivudine was found in 4 of 5 women at delivery.[36] In a multicentre study of 40 newborns, zidovudine plus lamivudine was well tolerated and

associated with an HIV transmission rate of 2.5% (95% CI 0.1 to 13.2%). Although neonatal anaemia was documented in 62% of neonates, none required transfusion. Similarly, 58% of neonates had mildly raised transaminase levels but none were jaundiced.[83]

In a large French prospective nonrandomised study of 440 women treated with zidovudine plus lamivudine from gestational week 32, maternal plasma HIV viraemia was reduced by 0.95 $\log_{10}$ and the mother-to-child transmission rate was 2.6% (compared with 6.5% with zidovudine monotherapy). Treatment was well tolerated by mothers and infants, but at 6 weeks postpartum M184V was detected in 52 of 132 women but not in any women treated for less than 4 weeks.[84] In the APR, 4 of 152 (2.6%) babies exposed in the first trimester to any combination of NRTIs (but excluding other classes of antiretroviral therapy) had documented congenital malformations. For zidovudine monotherapy the rate was 0.75% (1 of 132). Although no increase in congenital malformations has been noted with dual therapy, numbers remain very small.[5]

In the rat whole embryo culture system the combination of zidovudine with zalcitabine resulted in severe growth retardation and morphological abnormalities not seen with either agent alone, although the concentration of zalcitabine (>100 μmol/L) was higher than might be expected *in vivo*.[30] *In vitro* studies suggest that any risk of tumours (thus far not seen) with zidovudine may be increased by co-exposure with didanosine. Using concentrations 3 to 30 times higher than normally seen in patients on therapy, the frequency of incorporation of zidovudine into human DNA and the frequency of mutations detected in an hypoxanthine-guanine phosphoribosyltransferase assay were increased with combined exposure.[85]

2.2 Triple Therapy (NRTIs with a PI)

The pharmacokinetics of nelfinavir (coadministered with zidovudine and lamivudine) in pregnancy have been studied in 10 women who commenced therapy between weeks 14 and 34 of gestation. Pregnancy appeared not to affect nelfinavir concentrations compared with 6 weeks postpartum. Although the median maternal nelfinavir plasma concentration at delivery was 2 mg/ml, cord concentrations were either low or undetectable. Additionally, the initial infant dose of 10 mg/kg resulted in low nelfinavir concentrations at age 1 week (trough 0.74 mg/L), and a dosage of 40mg twice daily is now under investigation.[70] Similarly, in a study of infants treated with nelfinavir 15 mg/kg twice daily (combined with stavudine plus didanosine) the median nelfinavir trough concentrations were 0.19 mg/L on day 1, 1.21 mg/L on day 7, 0.51 mg/L on day 14 and 0.33 mg/L on day 28. Even though these concentrations are mostly well below the target trough concentration of 1 mg/L, high triglyceride levels were documented transiently in 2 of 6 infants.[86]

In a study of the safety and tolerability of ritonavir in combination with lamivudine and zidovudine, 3 of 6 infants were born prematurely, 2 with severe hypoglycaemia, and the third infant, delivered severely preterm, died. One infant had grade 3/4 hyperbilirubinaemia, 1 had neutropenia and 2 were significantly anaemic.[87] Congenital malformations were reported in only 2 of 241 (0.83%) babies first exposed to any PI in combination with any other antiretroviral therapy in the APR.[5]

The WITS is a cohort study of HIV-positive North American pregnant women. The most recent analysis of these women demonstrated a reduction in transmission from 7.8% in mother–infant pairs receiving zidovudine monotherapy since the publication of the ACTG 076 results to 1.1% in mother–infant pairs exposed to triple therapy including a protease inhibitor.[88] In a study of 76 women taking a PI as part of combination therapy there were 15 preterm deliveries (<37 weeks) but 60% of the mothers had identifiable risk factors for preterm delivery such as a history of preterm delivery, smoking and substance abuse. HIV transmission had been excluded in the 34 babies with adequate follow-up.[89]

The possibility that protease inhibitor usage was associated with an increased risk of preterm delivery had been suggested by Swiss investigators in 1998,[90] following which recruitment of women to studies of PIs in pregnancy was temporarily suspended. Among 462 women participating in ACTG studies in 1998 to 1999 the preterm delivery rate was 20%, but with no significant difference between women exposed to PIs and those not exposed to PIs [relative risk (RR) 0.7, 95% CI 0.5 to 1.1] and the rate of very premature delivery (<32 weeks) was less among women taking PIs (RR 0.2, 95% CI 0.05 to 0.8). 19 of 462 (4.1%) babies were born with a structural abnormality.[91] Compared with HIV-negative women, HIV-positive women taking NRTIs or no therapy, women taking antiretroviral therapy which includes a PI have a higher (3.5 *vs* 1.35%) risk of developing diabetes mellitus during pregnancy ($p = 0.025$).[92] In a small study, infants exposed to PIs *in utero* had significantly higher γ-glutamyl transferase levels than therapy-naive or zidovudine monotherapy–exposed infants.[93]

2.3 Triple Therapy (NRTIs with an NNRTI)

In a multicentre retrospective study of 46 women receiving nevirapine and 2 NRTIs, this combination was well tolerated. Rash and hepatitis attributed to nevirapine occurred on 2 occasions each but resolved without a change of therapy in 2 mothers, and gastrointestinal symptoms were attributed to didanosine.[94] Of 44 first trimester exposures to an NNRTI either alone (2 cases) or in combination with NRTIs and or PI, only 1 congenital abnormality was reported to the APR.[5]

Unfortunately, in the recent analysis of the WITS cohort, transmission rates for triple therapy which included a NNRTI were not separated from dual therapy exposure and thus cannot be compared either with dual therapy or with other triple therapies.[88]

Abnormal liver function tests without symptoms are common in patients taking nevirapine, and severe disturbance of liver function has been reported in patients infected with HIV-1 established on therapy. Although not part of national prescribing guidelines, nevirapine has been used as a component of triple therapy for postexposure prophylaxis. Attention was first drawn to the development of liver failure in 2 healthcare workers exposed, in this setting, to nevirapine, zidovudine and lamivudine in December 2000.[95,96] A subsequent analysis by the US Centers for Disease Control (CDC) revealed 22 serious adverse events associated with nevirapine in persons not infected with HIV, but the denominator was unknown.[97] In a cohort review of 57 people exposed to HIV through occupation or sexual intercourse and taking nevirapine usually with stavudine plus lamivudine, 13 had grade 1 adverse events (nausea, rash, neutropenia, paraesthesia or elevation of transaminases) but 5 had grade 2/3 adverse events including elevations of transaminases and rash requiring hospitalisation.[98] No serious adverse events have been reported in the studies in Africa of a single dose of nevirapine to prevent mother-to-child transmission of HIV.

3. Conclusions

The most extensive data from *in vitro* models and from clinical experience are for zidovudine monotherapy. The ability of zidovudine to reduce mother-to-child transmission has been demonstrated in 5 randomised controlled studies. The efficacy of zidovudine ranges from 67% when started before the third trimester and given to the neonate as well as to the mother by intravenous infusion during labour, to 50% with shorter courses (started at week 36) without a neonatal component, in non-breastfed babies, to 30% with a similar regimen in breastfed babies. Shorter courses are associated with greater reductions in maternal viral load at delivery and less risk of the development of detectable zidovudine resistance. The risk of resistance may be further reduced by only prescribing monotherapy to mothers with lower viral load and higher CD4+ lymphocyte counts. In resource-poor countries, finance prohibits widespread use of longer (>4 week) courses of therapy to reduce mother-to-child transmission. Viral load is an important pre-

dictor of transmission, and although zidovudine reduces transmission at all levels of maternal viraemia, in mothers with very high viral load (>100 000 RNA copies/ml) the transmission rate is >60% (fig. 2).[99] Since even with a 67% reduction in transmission the risk to the infant would be 20%, additional measures are certainly required for these babies and probably for any mother with a viral load >10 000 to 20 000 copies/ml. Prelabour caesarian section has been demonstrated, in a randomised study, to reduce transmission by as much as zidovudine, and most importantly the rate of transmission was further reduced to <2% when zidovudine and caesarian section were combined.[100] Similarly low transmission rates with triple antiretroviral therapy are being reported from small observational studies.

In utero exposure to zidovudine appears to be relatively safe for the fetus. The only substantiated regular adverse event is anaemia, attributable to bone marrow suppression, which rarely requires intervention and resolves when zidovudine is discontinued. Long term follow-up is required to exclude later events, particularly carcinogenesis, but no problems have been demonstrated in preschool age children exposed *in utero* and peripartum. Although zidovudine is not licensed for use in the first trimester, and this is unnecessary to prevent mother-to-child transmission, there has been no evidence of teratogenicity. The numbers of exposed babies prospectively reported remain too small to exclude a small increase, or a significant increase in rare malformations. Zidovudine is well tolerated by pregnant women and 2 studies have reported survival benefits postpartum with short course therapy.

US[101] and UK[102] guidelines currently recommend that mothers with advanced HIV infection (symptoms, low CD4+ count or high viral load) who would normally be treated with combination antiretroviral therapy should be managed as if they were not pregnant. For these women, for asymptomatic women with high viral load and for women with prior zidovudine exposure and zidovudine-resistant virus, combination therapies are prescribed. Until recently it was thought that with the exception of the third group zidovudine should always be included, as it was the only compound shown to reduce transmission.

In addition to data on combination therapies there are now data for both ritonavir and nevirapine which suggest equivalence with zidovudine. Since PIs have limited placental transfer, reduction in maternal viraemia may be more important than has been thought for zidovudine. Although transmission in mothers with HIV RNA viraemia less than 1000 copies/ml has been reported, at least 1 study has reported no transmissions below this level (fig. 2).[99] Since triple combinations reduce plasma viraemia to less than 50 copies/ml, transmission, unless occurring prior to the initiation of therapy or in mothers in whom the viral load is underestimated, is likely to be a rare event. Although biologically plausible, this assumption needs to be confirmed by larger studies than currently available.

Determining the safety of antiretroviral therapy is likely to take many years. Monotherapy other than with zidovudine is unlikely to be widely used, at least in resource-rich countries. The only exception at present is nevirapine, but this is only prescribed in labour and the first week of neonatal life. Dual combinations have been superseded by triple and more therapies and, as demonstrated by the latest APR interim report,[103] the number of permutations is vast. Voluntary reporting to specific

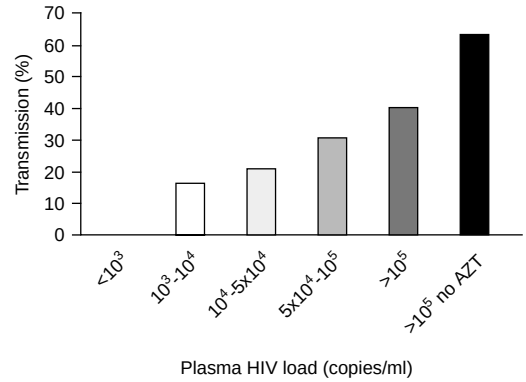

Fig. 2. HIV mother-to-child transmission rates in relation to maternal plasma HIV RNA load.[99] **AZT** = zidovudine.

drug registries results in lower rates of congenital malformations than detected in population-based studies. This is partly explained by the proportion of defects that are not detected at birth and by underreporting when multiple abnormalities are present. Efavirenz has been shown to cause serious congenital malformations in nonhuman primates, but other antiretroviral therapies have not been examined in this model. It is not known whether this is a class-specific or drug-specific effect. The poor transplacental transfer of some PIs may limit their teratogenic potential, but the limited data available suggest that they may be less well tolerated in later pregnancy than nucleoside analogues or nevirapine. Hyperbilirubinaemia, renal calcification and glucose intolerance are particularly undesirable in pregnancy.

Because it is impossible to comment on the teratogenic potential of all but a few combinations, because of the low number of babies exposed to each, the APR data have been analysed by class and combinations of class. This examination has not identified any particular risk with any particular class, nor any increase in risk with first trimester exposure compared with later exposure (table V).

Women who conceive while receiving antiretroviral therapy may wish to discontinue therapy during the first trimester. There are no data to support or refute this action. Consideration should be given to maternal health and immune status at the time of initiating therapy as well as at the current time – viral rebound will occur within 2 to 3 weeks and 'strategic treatment interruptions' have been associated with significant CD4+ lymphocyte decline. This could not only jeopardise maternal health but in theory result in reactivation of infections associated with congenital abnormalities such as toxoplasmosis. Many women will not realise or report their pregnant state until well into the period of organogenesis.

With the exception of efavirenz there are no data to support changing therapy in pregnancy. However, if the mother's treatment is failing then this should be changed in time to ensure the lowest possible viraemia at the time of delivery.

Table V. Incidence of congenital malformations (any drug, any combination) reported prospectively to the Antiretroviral Pregnancy Register[5]

Trimester of exposure	Incidence		
	number[a]	%	95% CI of %
Any	22/1027	2.1	1.4 to 3.3
First	6/444	1.4	0.6 to 3.1
Second/third	16/583	2.7	1.6 to 4.5

a Number of live births with at least 1 defect/total live births.
CI = confidence interval.

Only exceptionally should antiretroviral therapy be initiated in the first trimester. Reasonable exceptions include serious illness for which antiretrovirals are the only recognised therapy.

For treatment-naive mothers requiring combination therapy, consideration should be given to safety and efficacy data, tolerability and whether treatment is likely to be continued after delivery. The most extensive data available on safety and prevention of transmission are for zidovudine and lamivudine; however, the rapid development of lamivudine resistance precludes dual therapy. In a small retrospective study, triple therapies (mostly zidovudine and lamivudine) including nevirapine were well tolerated and effectively reduced maternal viraemia.[94] However, the proposed duration of therapy should be considered when initiating a therapy, such as nevirapine, with a long half-life as this may effectively result in monotherapy for several days after discontinuing therapy. If treatment discontinuation is planned, e.g. for a mother who has elected to take triple therapy in pregnancy to prevent mother-to-child transmission, a PI such as nelfinavir might be preferred. However there are no trial or observational data that address this issue.

Finally, and perhaps most importantly, women receiving antiretroviral therapy are commonly receiving other therapies. In a multicentre retrospective study of 148 infants exposed to antiretroviral therapy *in utero*, the risk of congenital malformation was significantly raised in those exposed to folate antagonists for *Pneumocystis carinii* pneumonia (PCP) prophylaxis.[104] In addition to neural tube defects, first trimester exposure to folate antagonists has been associated with an increased fre-

quency of cardiac and renal tract malformations. The therapeutic needs of all women of childbearing potential should be regularly reviewed, particularly now that PCP and other prophylactic therapies can be safely discontinued as immune function recovers. Regular administration of even small doses of folic acid (such as found in some multivitamin preparations) appears to negate this additional risk.[105]

References

1. Yarchoan R, Klecker RW, Weinhold KJ, et al. Administration of 3′-azido-3′-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. Lancet 1986; I: 575-80
2. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987; 317: 185-91
3. BHIVA Guidelines Co-ordinating Committee. British HIV Association Guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 1997; 349: 1086-92
4. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994; 331: 1173-80
5. The Antiviral Pregnancy Registry (interim report). 1 Jan 89–31 Jan 00. Willmington (NC): Registry Project Office, 2000: 1-39
6. Klecker RW, Collins JM, Yarchoan R, et al. Plasma and cerebrospinal fluid pharmacokinetics of 3′-azido-3′-deoxythymidine: a novel pyrimidine analog with potential application for the treatment of patients with AIDS and related diseases. Clin Pharmacol Ther 1987; 41: 407-12
7. Sieh E, Coluzzi ML, Cusella De Angelis MG, et al. The effects of AZT and DDI on pre- and postimplantation mammalian embryos: and in vivo and in vitro study. AIDS Res Hum Retroviruses 1992; 8: 639-49
8. Esterman AL, Rosenberg C, Brown T, et al. The effect of zidovudine and 2′,3′-dideoxyinosine on human trophoblast in culture. Pharmacol Toxicol 1995; 76: 89-92
9. Bawdon RE, Sobhi S, Dax J. The transfer of anti-human immunodeficiency virus nucleoside compounds by the term human placenta. Am J Obstet Gynaecol 1992; 167: 1570-4
10. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group (protocol 082). Zidovudine Collaborative Working Group. Am J Obstet Gynecol 1993; 168: 1510-6
11. Dorenbaum A, Rodman JH, Mirochnick M, et al. Systemic pharmacokinetics (PK) of oral zidovudine (ZDV) given during labour and delivery to HIV-1 infected pregnant women. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco
12. Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type-1 infected women and newborn infants. J Infect Dis 1999; 1844-50
13. Poirier MC, Patterson TA, Slikker Jr W, et al. Incorporation of 3′-azido-3′-deoxythymidine (AZT) into fetal DNA and fetal tissue distribution after infusion of pregnant late-term rhesus macaques with a human-equivalent AZT dose. J Acquir Immune Defic Syndr 1999; 22: 477-83
14. Oliviero OA, Shearer GM, Chougnet CAS, et al. Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women and cord blood from infants exposed in utero. AIDS 1999; 13: 919-25
15. Ewings EL, Gerschenson M, St Claire MC, et al. Genotoxic and functional consequences of transplacental zidovudine exposure in fetal monkey brain mitochondria. J Acquir Immune Defic Sydnr 2000; 24: 100-5
16. Gerschenson M, Erhart SW, Paik CY, et al. Fetal mitochondrial heart and skeletal muscle damage in *Erythrocebus patas* monkeys exposed in utero to 3′-azido-3′-deoxythymidine. AIDS Res Hum Retroviruses 2000; 16: 635-44
17. Blanche S, Mandelbrot L, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999; 354: 1084-9
18. Lipshultz SL, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. N Engl J Med 2000; 343 (11): 759-66
19. Lipshultz SL, Orav EJ, Sanders SP, et al. Cardiac structure and function in children with human immunodeficiency virus infection treated with zidovudine. N Engl J Med 1992; 327: 1260-5
20. Smith ME. Ongoing nucleoside safety review of HIV-exposed children in US studies. 2nd Conference on Global Strategies for prevention of HIV transmission from Mother to Infants; 1999 Sep 1-6; Montreal
21. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. JAMA 1999; 281: 151-7
22. Ayers KM, Clive D, Tucker W, et al. Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. Fundam Appl Toxicol 1996; 32: 148-58
23. Olivero OA, Anderson LM, Diwan BA, et al. Transplacental effects of 3′-azido-2′,3′-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. J Natl Cancer Inst 1997; 89: 1602-8
24. Diwan BA, Riggs CW, Logsdon D, et al. Multiorgan transplacental and neonatal carcinogenicity of 3′-azido-3′-deoxythymidine in mice. Toxicol Appl Pharmacol 1999; 161: 82-9
25. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. J Acquir Immune Defic Syndr Hum Retrovir 1999; 15: 463-7
26. Calamandrei G, Venerosi A, Branchi I, et al. Effects of prenatal zidovudine treatment on learning and memory capacities of preweanling and young adult mice. Neurotoxicology 1999; 20: 17-25
27. Busidan Y, Dow-Edwards DL. Neurobehavioral effects of perinatal AZT exposure in Sprague-Dawley adult rats. Neurotoxicol Teratol 1999; 21: 359-63
28. Rondinini C, Venerosi A, Branchi I, et al. Long-term effects of prenatal 3′-azido-3′-deoxythymidine (AZT) exposure on intermale aggressive behaviour of mice. Psychopharmacology (Berl) 1999; 145: 317-23
29. Busidan Y, Dow-Edwards DL. Neurobehavioral effects of perinatal AZT exposure in Sprague-Dawley weaning rats. Pharmacol Biochem Behav 1999; 64: 479-85
30. Fujinaga M, Schulte M, Holodniy M. Assessment of developmental toxicity of antiretroviral drugs using a rat whole embryo culture system. Teratology 2000; 62: 108-14

31. Metropolitan Atlanta Congenital Defects Program surveillance data, 1988-1991. Teratology 1993; 48: 695-709
32. Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. Teratology 1999; 60: 356-64
33. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med 1996; 335: 1621-9
34. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. Bangkok Collaborative Perinatal HIV Transmission Study Group. J Infect Dis 2000; 181: 99-106
35. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol 076. J Infect Dis 1998; 177: 557-64
36. Clarke JR, Braganza R, Mirza A, et al. Rapid development of genotypic resistance to lamivudine when combined with zidovudine in pregnancy. J Med Virol 1999; 59: 364-8
37. Palumbo P, Dobbs T, Holland B, et al. Antiretroviral resistance mutations among pregnant HIV-infected women and their newborns in the US: Vertical transmission and clades [abstract]. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuPpB1230
38. Sibailly TS, Ekpini E, Boni-Ouattara E, et al. Clinical course of HIV infection and surveillance for zidovudine resistance among HIV-infected women receiving short-course zidovudine therapy in Abidjan, Cote d'Ivoire [abstract]. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuPeC3354
39. Kully C, Yerly S, Erb P, et al. Codon 215 mutations in human immunodeficiency virus-infected pregnant women. Swiss Collaborative 'HIV and Pregnancy' Study. J Infect Dis 1999; 179: 705-8
40. Welles SL, Pitt J, Colgrove RC, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant transmission in the Women and Infants Transmission Study. AIDS 2000; 14: 263-71
41. Bardeguez A, Mofenson LM, Shapiro D, et al. Reproductive choices and pregnancy outcomes after participation in ACTG 076. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco
42. Roongpisuthipong A, Siriwasin W, Asavapiriyanont S, et al. Predictors of mortality in 18-month postpartum period among HIV infected women enrolled in a trial of short-course antenatal zidovudine, Bangkok, Thailand [abstract]. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuPeB3253
43. Cooper ER, Nugent R, Diaz C, et al. After AIDS Clinical Trial 076: the changing pattern of zidovudine use during pregnancy, and subsequent reduction in the vertical transmission of human immunodeficiency virus in a cohort of infected women and their infants. J Infect Dis 1996; 174: 1207-11
44. Mayaux MJ, Teglas J-P, Mandelbrot L, et al. Acceptability and impact of zidovudine for prevention of mother-to-child human immunodeficiency virus type-1 transmission in France. J Pediatr 1997; 131: 857-62
45. Therapeutic and other interventions to reduce the risk of mother-to-child transmission of HIV-1 in Europe. The European Collaborative Study. Br J Obstet Gynaecol 2000; 105: 704-9
46. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus [abstract]. N Engl J Med 1998; 339: 1409-14
47. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet 1999; 353: 773-80
48. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type I. N Engl J Med 2000; 343: 982-91
49. Wiktor S, Leroy V, Ekpini E, et al. 24 month efficacy of short-course maternal zidovudine for the prevention of mother-to-child HIV-1 transmission in a breast feeding population: a pooled analysis of two randomised clinical trials in West Africa [abstract]. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuOrB345
50. Bloom SL, Dias KM, Bawdon R, et al. The maternal-fetal transfer of lamivudine in the ex-vivo human placenta. Am J Obstet Gynecol 2000; 176: 291-3
51. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when co-administered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. J Infect Dis 1998; 178: 1327-33
52. Calamandrei G, Venerosi A, Branchi I, et al. Neurobehavioural effects of prenatal lamivudine (3TC) exposure in preweaning mice. Neurotoxicol Teratol 1999; 21: 365-73
53. Calamandrei G, Venerosi A, Branchi I, et al. Prenatal exposure to anti-HIV drugs, long-term neurobehavioral effects of lamivudine (3TC) in CD-1 mice. Neurotoxicol Teratol 2000; 22: 369-79
54. Pereira CM, Nosbich C, Winter HR, et al. Transplacental pharmacokinetics of dideoxyinosine in pigtailed macaques. Antimicrob Agents Chemother 1994; 38: 781-6
55. Pereira CM, Nosbich C, Baughman WL, et al. Effect of zidovudine on transplacental pharmacokinetics of ddI in the pigtailed macaque (*Macaca nemestrina*). Antimicrob Agents Chemother 1995; 39: 343-5
56. Odinecs A, Pereira CM, Nosbich C, et al. Prenatal and postpartum pharmacokinetics of stavudine (2′,3′-didehydro-3′-deoxythymidine) and didanosine (dideoxyinosine) in pigtailed macaques (*Macaca nemestrina*). Antimicrob Agents Chemother 1996; 40: 2423-5
57. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didansoine in antepartum and postpartum human immunodeficiency virus-infected women and their neonates: an AIDS Clinical Trials Group study. J Infect Dis 1999; 180: 1536-41
58. Toltzis P, Mourton T, Magnuson T. Comparative embryonic cytotoxicity of antiretroviral nucleosides. J Infect Dis 1994; 169: 1100-2
59. Foerster M, Kastner U, Neubert R. Effect of six virustatic nucleoside analogues on the development of fetal rat thymus in organ culture. Arch Toxicol 1992; 66: 688-99
60. Tuntland T, Nosbich C, Baughman WL, et al. Mechanism and rate of placental transfer of zalcitabine (2′,3′-dideoxycytidine) in *Macaca nemestrina*. Am J Obstet Gynecol 1996; 174: 856-63
61. Tuntland T, Nosbich C, Unadkat J. Effect of pregnancy, mode of administration and neonatal age on the pharmacokinetics of zalcitabine (2′,3′-dideoxycytidine) in the pigtailed macaque (*Macaca nemestrina*). J Antimicrob Chemother 1997; 40: 687-93

62. Lindstrom P, Harris M, Hoberman AM, et al. Developmental toxicity of orally administered 2′,3′-dideoxycytidine in mice. Teratology 1990; 42: 131-6
63. Odinecs A, Nosbich C, Keller RD, et al. In vivo maternal-fetal pharmacokinetics of stavudine (2′,3′-didehydro-3′-deoxythymidine) in pigtailed macaques (*Macaca nemestrina*). Antimicrob Agents Chemother 1996; 40: 196-202
64. Patterson TA, Binienda ZK, Newport GD, et al. Transplacental pharmacokinetics and fetal distribution of 2′,3′-didehydro-3′-deoxythymidine (d4T) and its metabolites in late-term rhesus macaques. Teratology 2000; 62: 93-9
65. Bawdon R. The ex vivo human placental transfer of the anti-HIV nucleoside inhibitor abacavir and the protease inhibitor amprenavir. Infect Dis Obstet Gynecol 1998; 6: 244-6
66. HIV/Aids Treatment Information Service. Public Health Service Task Force recommendations for the use of Antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States [online]. Available from URL: http://hivatis.org/trtgdlns.html#Perinatal [Accessed 2001 Jul 5]
67. Casey B, Bawdon R. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. Am J Obstet Gynecol 1998; 179: 758-61
68. Limpongsanurak S, van Leeuwen R, Macleod C, et al. Safety, tolerability and efficacy of ritonavir in the prevention of vertical transmission. Proceedings of the 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago
69. Riecke K, Schulz T, Shakibaei M, et al. Developmental toxicity of the HIV-protease inhibitor indinavir in rats. Teratology 2000; 62: 291-300
70. Bryson YJ, Stek A, Mirochnick M, et al. PACTG 353. A Phase I study of safety, pharmacokinetics and antiviral activity of combination nelfinavir (NFV), ZDV and 3TC in HIV-infected pregnant women and their infants. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 4; San Francisco. 715
71. The Antiviral Pregnancy Registry (interim report). 1 Jan 89–1 Jan 00. Willmington (NC): Registry Project Office, 2000: 96
72. Mirochnick M, Fenton T, Gagnier P, et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type-1 infected pregnant women and their neonates. J Infect Dis 1998; 178: 368-74
73. Musoke P, Guay LA, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1 infected pregnant Ugandan women and their neonates (HIVNET 006). AIDS 1999; 13: 479-86
74. Taylor GP, Lyall E, Back D, et al. Pharmacological implications of prolonged in utero exposure to nevirapine. Lancet 2000; 355: 2134-5
75. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999; 354: 795-802
76. Owor M, Deseyve M, Dueifeld C, et al. The one year safety and efficacy data of the HIVNET 012 trial. LbOr1, 16-16. 2000. XIII International AIDS Conference; 2000 Jul 9-14; Durban
77. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose Nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. J Infect Dis 1995; 171: 537-45
78. Jackson JB, Becker-Pergola G, Guay LA, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. AIDS 2000; 14: F111-F5
79. Jackson JB, Mracna M, Guay LA, et al. Selection of Nevirapine (NVP) resistance mutations in Ugandan women and infants receiving NVP prophylaxis to prevent HIV-1 vertical transmission (HIVNET 012). XIII International AIDS Conference; 2000 Jul 9-14; Durban
80. Moodley D. The SAINT Trial: Nevirapine (NVP) versus zidovudine (ZDV) + lamivudine (3TC) in prevention of peripartum HIV transmission. XIII International AIDS Conference; 2000 Jul 9-14; Durban
81. Prescribing Information. Sustiva™ (efavirenz) capsules: Rx only [online]. Available from URL: http://www.sustiva.com/-cross_site/patientpi/aNp.Sustiva.Feb00.pdf [Accessed 2001 Jul 5]
82. Gray G, Volaris A, McIntyre J, et al. Transplacental distribution of emivirine (EMV, Coactinon) in HIV-1 infected pregnant women and their infants: pharmacokinetics (PK) and safety. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuPeB3255
83. Silverman NS, Watts DH, Hitti J, et al. Initial multicenter experience with double nucleoside therapy for human immunodeficiency virus infection during pregnancy. Infect Dis Obstet Gynecol 1998; 6: 237-43
84. Blanche S, Rouzioux C, Mandelbrot L, et al. Zidovudine-lamivudine for prevention of mother to child HIV-1 transmission. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago
85. Meng Q, Walker DM, Oliviero OA, et al. Zidovudine-didanosine coexposure potentiates DNA incorporation of zidovudine and mutagenesis in human cells. Proc Natl Acad Sci U S A 2000; 97: 12667-71
86. Rongkavilit C, Prisuwanna P, Van Heewsijk RPG, et al. Safety and pharmacokinetics of nelfinavir when administered with stavudine and didanosine in HIV-1 exposed newborn infants. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. MoPeB2188
87. Scott G, Shapiro DE, Scott W, et al. Safety and tolerance of ritonavir in combination with lamivudine and zidovudine in HIV-1 infected pregnant women and their infants. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago. 688
88. Blattner W, Cooper E, Charurat M, et al. Effectiveness of potent antiretroviral therapy on reducing perinatal transmission of HIV. XIII International AIDS Conference; 2000 Jul 9-14; Durban
89. Morris A, Zorilla C, Vajaranant M, et al. A review of protease inhibitor use in 89 pregnancies. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago
90. Lorenzi P, Spicher VM, Laubereau B, et al. Antiretroviral therapies in pregnancy: maternal, foetal and neonatal effects. AIDS 1998; 12: F241-F7
91. Shapiro DE, Tuomala R, Samelson R, et al. Antepartum antiretroviral therapy and pregnancy outcomes in 462 HIV-1 infected women in 1998-1999 [PACTG 367]. 7th Conference on Retroviruses and Opportunistic Infections; 2000 Jan 30-Feb 2; San Francisco
92. Justman J, Dancff A, Benning L, et al. Association of diabetes and protease inhibitor use in a large natural history cohort of HIV+ women. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31-Feb 4; Chicago. 661
93. Galli L, Peruzzi M, Ballotti S, et al. Combined antiretroviral treatment, but not zidovudine monotherapy, in gestation may

damage biliary epithelium in infants. The XIII International AIDS Conference; 2000 Jul 9-14; Durban. TuPeB3258
94. Edwards S, Larbalestier N, Hay P, et al. Experience of nevirapine (NVP) use in a London cohort of HIV infected pregnant women. HIV Medicine 2001; 2: 89-91
95. Johnson S, Baraboutis JG. Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. JAMA 2000; 284: 2722
96. Sha B, Proia L, Kessler HA. Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. JAMA 2000; 284: 2723
97. Anonymous. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures – worldwide, 1997-2000. MMWR Morb Mortal Wkly Rep 2001; 49: 1153-6
98. Benn PD, Mercey DE, Brink N, et al. Prophylaxis with a nevirapine-containing triple regimen after exposure to HIV-1. Lancet 2001; 357: 687-8
99. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. N Engl J Med 1999; 341: 394-402
100. The European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. Lancet 1999 Mar 27; 353 (9158): 1035-9
101. HIV/Aids Treatment Information Service. Adult and adolescent guidelines: guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Treatment guidelines library [online]. Available from URL: http://hivatis.org/-trtgdlns.html#adult [Accessed 2001 Jul 5]
102. British HIV Association. Guidelines for the management of HIV infection in pregnant women and the prevention of mother to child transmission, 2001 [online]. Available from URL: http://www.aidsmap.com/about/bhiva/bhivagd.asp [Accessed 2001 Jul 5]
103. The Antiviral Pregnancy Registry (interim report). 1 Jan 89–31 Jul 00. Willmington (NC): Registry Project Office, 2000; 11 (2): 1-55
104. Jungmann E, Edwards S, Booth T, et al. ART and PCP prophylaxis in early pregnancy: a highly teratogenic combination? 2nd Conference on Global Strategies for prevention of HIV transmission from Mother to Infants; 2000 Sep 1-6; Montreal
105. Hernandez-Diaz S, Werler MM, Walker AM, et al. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000; 343: 1608-14

Correspondence and offprints: Dr *Graham P. Taylor*, Department of Genito-Urinary Medicine and Communicable Diseases, Imperial College School of Medicine, Norfolk Place, London W2 1PG, England.
E-mail: g.p.taylor@ic.ac.uk