Appendix

Safety and pharmacokintics data on antitretroviral therapy in pregnancy

Monotherapy

Zidovudine (3'-azido-2',3'dideoxythymidine; AZT), has been the most widely used anti-retroviral in pregnancy both alone and in combination therapy. Consequently the safety and efficacy data for its use in pregnancy are greater than for the other compounds.

Safety: Zidovudine passively crosses the placenta resulting in cord blood levels 85% of the maternal plasma concentration. 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 (2mg/kg over 1 hour, followed by 1mg/kg hourly) and with oral administration earlier in pregnancy [1]. In women receiving intravenous zidovudine during labour zidovudine triphosphate levels in cord blood cells were similar to those found in maternal lymphocytes although the concentrations were highly variable [2].

Zidovudine becomes incorporated into the DNA of the placenta and most fetal organs during short-term intravenous infusion in pregnant rhesus monkeys [3] and incorporation into human lymphocyte DNA with *in utero* exposure has also been demonstrated [4].

In mice, exposed to high concentrations of zidovudine *in utero* and for a prolonged post-natal period, vaginal tumours were observed in adult life. However, this may be due to chronic 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* [5]. However an increased incidence of other tumours following exposure in utero has been reported (Table 2) [6; 7]. To date, 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 [8].

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[9; 9; 10]. In muscle, depletion of mitochondrial DNA levels was zidovudine dose dependent. Blanche et al initially diagnosed 8 cases of mitochondrial disease among the French Cohort of children born to HIV positive mothers. All had been exposed to zidovudine *in utero,* including four also exposed to lamivudine. Two died of central nervous system manifestations whilst at the other extreme three were asymptomatic [11]. Further study of this cohort has led to additional diagnoses with an observed prevalence of 0.7% (CROI8). Another study of babies exposed to zidovudine in utero revealed no evidence of cardiac dysfunction although numbers were small[12; 12; 13]. In retrospective studies reviewing the deaths of children exposed to zidovudine in utero in the USA, [14 15] as well as the Pediatric Spectrum of HIV Disease Project which included review of hospitalisations and clinic notes [16] no cases were attributed to mitochondrial disease. Haas has noted among the more than

20,000 children in these studies, given a estimated prevalence of 1 in 3000 to 1 in 4000m some cases of mitochondrial disease would be anticipated [17]. In PACTG 219, a long term prospective study of children born to mothers who participated in ACTG 076 two children with ophthalmic abnormalities and one with a mild cardiomyopathy have been identified – all were zidovudine exposed but the aetiology of each condition was uncertain [18].

Neuro-behavioural studies in rodents exposed to zidovudine in utero have produced conflicting results with impairment[19], no effect[20] and a gender dependent effect [21] [22]variously reported. As with the carcinogenesis studies the significance for humans of these neuro-behavoural 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[18].

Teratogenic effects with zidovudine have been reported in rodents only when exposed to near lethal maternal doses. The Antiretroviral Pregnancy Registry, established by the pharmaceutical industry in 1988, collates voluntary reports from clinicians prescribing antiretroviral therapy in pregnancy[23]. Of the 129 prospective reports on babies exposed to zidovudine alone during the first trimester only one 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 195642 births had defects [24]. It has been noted that registries, including the Antiretroviral Pregnancy Registry, 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[25]. The 2.7% rate is however similar to population rates based only on examinations in the first few days of life.

Zidovudine appears to be safe 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 [26]. Indeed evidence of improved maternal mortality following short course zidovudine has been observed in two studies. Among breast-feeding African women treated with short course zidovudine (commenced at week 36 and discontinued at delivery) the risk of mortality after 2 years follow-up was 0.44 compared with placebo[27]. Although this was not statistically significant with the 95% confidence intervals including 1.0 the same effect has been observed in Thailand, with mortality reduced from 8% to 1% at 18 months (p=0.004)[28].

Lamivudine ([-]-2'-deoxy-3'-thiacytidine; 3TC) is a cytosine analogue which crosses the placenta by simple diffusion [29], resulting in cord plasma levels similar to maternal plasma levels [30]. The pharmacokinetics of lamivudine are not affected by pregnancy nor by co-administration of zidovudine [30]. Studies of lamivudine have been restricted to controlled

studies of zidovudine plus lamivudine given to mothers during the last four weeks of gestation and cohort studies (see dual therapy below).

Didanosine (2',3'-dideoxyinosine; ddI) is an adenosine analogue which rapidly crosses the placenta by simple diffusion [31] [32] and this transfer is not affected by concurrent administration of zidovudine [33]. However transfer is less efficient than for zidovudine or lamivudine (Table 1).

Zalcitabine (2',3'-dideoxycytidine; ddC) is a cytidine analogue which crosses the placenta passively, but less efficiently than lamivudine, with fetal levels approximately 60% of maternal plasma concentrations in near term Macaca nemestrina [34].

Stavudine (2', 3'-didehydro-3'-deoxythymidine; d4T) is a thymidine analogue which crosses the placenta passively producing levels in the foetal macaque which are 77% - 85% of the maternal plasma concentration [35; 36]. Stavudine has been one of the most widely prescribed therapies in the first trimester of pregnancy with 159 babies exposures reported. In 157 of these stavudine was prescribed as part of a combination therapy[23].

Abacavir, a guanosine analogue and the most recently licensed of the nRTIs has a high placental clearance index[37]. There are very limited data on its use in pregnancy.

Protease Inhibitors

Ritonavir In rats maternal hepatotoxicity and fetal developmental toxicity were seen at or at less than the human equivalent doses. However since congenital malformations were not seen in rats or rabbits except for a slight increase in cryptorchidism ritonavir is included category B by the FDA. 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[23].

Indinavir crosses rat and dog placentas but little transfer is seen in rabbits. Administration of indinavir to rats during days 6 – 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 [38]. Indinavir is therefore a Category C compound but has been the most widely prescribed protease inhibitor in the first trimester with 115 exposed babies reported of which 6 were exposed to a double PI [23].

Saquinavir Less than 5% of the maternal concentrations are found in the fetal blood in rats.

Nelfinavir Pharmacokinetic studies of nelfinavir in human pregnancy conducted as part of a combination therapy revealed normal maternal levels but very low or undetectable levels in the cord blood [39]. Nelfinavir a category B compound was the second most commonly prescribed PI during the first trimester with 85 cases reported to the APR[23].

Amprenavir exposure was associated with abortions and with deficient ossification in pregnant rabbits but the doses achieved 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.

Lopinavir has recently been licensed as a Kaletra, a combination of lopinavir and ritonavir. The small dose of ritonavir serving to pharmacologically boost lopinavir concentrations by inhibition of the cytochrome P450 isoform CYP3A. There have been no studies of lopinavir/ritonavir in human pregnancy nor case reports to the ADR.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine 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 a minimum of two hours have elapsed between maternal dosing and delivery cord blood levels are equal to maternal plasma levels. A regimen of 200mg given to the mother early in labour followed 48 – 72 hours later by a single dose 2mg/kg to the neonate results in neonatal plasma nevirapine concentrations which remain above the IC_{90} of wild-type HIV-1 for at least 7 days [40]. 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 breast-feeding [41]. Earlier maternal administration in labour, 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 dosing may be necessary to maintain neonatal concentrations during the first week of life, however no change in the maternal dose or dose schedule is required for therapy administered during the second or third trimesters [42].

Efavirenz Although rodent studies have been normal, teratogenicity was noted in cynomolgus monkeys, with severe defects (anencephaly, microphthalmia and cleft palate) found in 3/13 foetuses. (Dupont Communication 1998) subsequently updated to 3/20 foetuses. Similar primate studies have not been conducted for other anti-retroviral 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 September 2000, 87 babies have been exposed to efavirenz during pregnancy (of which only 12 are included in the APR to 31st January 2000. 28 live births and 1 stillbirth have

been reported to the Dupont World-Wide Pharmacovigilance Database. Of the live-births all were exposed to at least two other anti-retroviral therapies. Seven were exposed only in the third trimester and no defects were reported. Twenty were exposed in the first trimester only and one throughout pregnancy. Of these 21 babies 14 were healthy at delivery, three were preterm, one had laryngeal malacia and the outcome is not known for three. (Personal Communication, Y Makinde).

Delavirdine has not been licensed in the UK but is available to named patients. 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 in rabbits (Delavirdine is classified FDA Pregnancy Category C). Of 7 unplanned pregnancies 3 were ectopic and one baby was born with a ventricular septal defect.

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 six compounds. The median number of pregnancies reported per combination is one 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.

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 are 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 non-pregnant adults and no dose adjustments are required to maintain adequate drug concentrations in near-term pregnant women[30].

In the APR four of 152 (2.6%) babies exposed in the first trimester to any combination of nRTIs (but excluding other classes of ART) had documented congenital malformations. For zidovudine monotherapy the rate was 0.75% (1/132). Although no increase in congenital malformations has been noted with dual therapy numbers remain very small[23].

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 ddC (>100mM) was higher than might be expected *in vivo* [43]. *In vitro* studies suggest that any risk of tumours (thus far not seen) with AZT may be increased by co-exposure with ddI. Using concentrations 3- 30 times higher than normally seen in patients on therapy the frequency of incorporation of AZT into human DNA and the frequency of mutations detected in an HPRT assay were increased with combined exposure [44].

Triple therapy (nRTI with PI)

The pharmacokinetics of nelfinavir (co-administered with AZT and 3TC) 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 post-partum. Although the median maternal nelfinavir plasma concentration at delivery was 2mg/ml, cord levels were either low or undetectable**.**

Cord blood levels of the various maternally prescribed protease inhibitors from neonates in the PACTG 316 study revealed very low levels for saquinavir, nelfinavir and ritonavir in cord blood samples obtained when delivery occurred less than 8hrs after the last dose. The observation that the median time from last dose to delivery was 12.2 hours highlights the need to ensure ingestion of medication during labour/before prelabour caesarian section [45].
Congenital malformations were reported in only 2/241 (0.83%) babies first exposed to any PI in combination with any other ART in the APR[23].

Triple therapy with an NNRTI

In a multicentre retrospective study of 46 women receiving nevirapine and two nRTIs this combination was well tolerated. Rash and hepatitis attributed to nevirapine occurred on two occasions each but resolved without a change of therapy, whilst in two mothers gastrointestinal symptoms were attributed to didanosine[46]. Of 44 first trimester exposures to an NNRTI either alone (two cases) or in combination with NRTIs and or PI, only one congenital abnormality was reported to the APR [23].

Conclusions

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 the number of permutations is vast. Voluntary reporting to specific drug registries results in lower rates of congenital malformations than detected in population-based studies. This is partly explained by the proportion of defects which are not detected at birth and by

under-reporting when multiple abnormalities are present. Efavirenz has been shown to cause serious congenital malformations in non-human primates but other antiretroviral therapies have not been examined in this model. It is not known whether this is a class or drug specific effect. The poor transplacental transfer of some protease inhibitors may limit their teratogenic potential but the limited data available suggest 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 due to the low number of babies exposed to each, the APR data has been analysed by class and combinations of class. This examination has not identified any particular risk to any particular class nor any increase risk with first trimester exposure compared with later exposure (Table 3).

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