Guidelines for the Management of HIV infection in Pregnant Women and the Prevention of mother-to-child transmission.

British HIV Association

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Aims of the guidelines

These guidelines have been drawn up by a multidisciplinary group of clinicians and lay workers active in the management of pregnant women infected with HIV. The guidelines aim to give up-to-date information in this fast moving field on interventions to reduce the risk of mother to child transmission of the virus. The evidence for the recommendations has been graded according to the strength of the data on the use of interventions to prevent mother-to-child transmission of HIV (Table 1) as per the definitions of the US Agency for Health Care Policy and Research [1]. Weighted evidence on the use of antiretroviral therapy for the treatment of HIV infection per se is presented in the BHIVA guidelines for adults [2 3]. The highest level evidence (i.e. randomised controlled trials or large, well conducted meta-analyses) is only available for mode of delivery and zidovudine monotherapy. In reality the need to treat mothers for HIV infection has led to the widespread use of combination antiretroviral therapy (ART) in pregnancy which in turn results in new questions such as how to deliver when the mother, on therapy, has no detectable plasma viraemia with the most sensitive assays. In addressing many common and/or difficult clinical scenarios in the absence of 'best evidence' the guidelines rely heavily on 'expert opinion'.

The table of contents lists the major topics addressed. Recommendations for management are given in the section 9, on clinical scenarios, and summarised in table 4. The authors are available to discuss individual cases.

1) HIV in pregnancy and risk of transmission - Background

Approximately 260 HIV positive women gave birth in London in 1999, a prevalence of 1 in 400, the highest ever recorded in the UK. Prevalence according to district of residence varied from none to 1 in 120. Elsewhere in the UK the prevalence remains lower; 120 births in 1999 (1 in 4,500) [4; 5].

The risk of transmission is related to maternal health, obstetric factors and infant prematurity. Overall there is a close linear correlation between maternal viral load and risk of transmission, but as yet the evidence for a threshold below which transmission never occurs is limited[6]. This may be due to discrepancies between plasma and genital tract viral loads. However, the major studies of viral load and transmission have used data from assays with a lower limit of detection of 500-1000 HIV RNA copies/ml, and a relative insensitivity to detect some non-B sub-types. CD4 counts and clinical disease stage have been shown in some cohorts to have an association with the risk of transmission even after controlling for viral load [7]. The only obstetric factors that consistently show an association with risk of transmission are mode of delivery and duration of membrane rupture but invasive procedures in labour are generally avoided as they pose a theoretical risk of iatrogenic transmission. Delivery before 34 weeks of gestation has been shown to be associated with an increased risk of transmission [8].

Formula feeding has been advocated for positive women since the association with breast feeding and increased transmission was noted in 1992 [9]. The protective role of caesarean section has been clarified with both a meta-analysis [10] and a RCT reported in 1999 [11].
The findings of the first RCT, published in 1994, showing that monotherapy with zidovudine (AZT) could reduce transmission from 25% to 8% in a non breast feeding population[12], have been supported by numerous observational studies confirming this reduction in clinical practice. Subsequent studies have shown equivalent benefit in mothers with more advanced disease and in those who are more heavily pre-treated. As standard treatment for non-pregnant adults is now with at least three antiretrovirals more women are taking combination therapy in pregnancy [2]. There are still relatively few data, however, on the safety of antiretroviral therapy (ART) in pregnancy and the management of any HIV positive pregnant woman requires a careful consideration of the balance between the mother's own health needs, the need to reduce vertical transmission and possible adverse effects of ART to the fetus (see Appendix).
Assuming an untreated vertical transmission risk of around 25%, it is estimated that between 20 and 45 infants were infected in London in 1999, but that if all mothers had been diagnosed prior to delivery (as opposed to only 76%) this would have been reduced to only 5.
1999 also saw a significant increase in the number and proportion of positive women who became pregnant after their HIV diagnosis, necessitating consideration of the management of women who are already taking ART[4].
Women with HIV are probably at a small increased risk of adverse pregnancy outcomes such as spontaneous abortion, stillbirth and intra-uterine growth retardation. Furthermore, an increased risk of premature delivery has important implications for any treatment to reduce vertical transmission.

2) Preconception and fertility management in men and women infected with HIV

There are three groups to consider: HIV positive men with negative female partners, HIV negative men with positive female partners and HIV infected couples. All three groups may have fertility problems but for the first two groups there is also a risk of primary HIV infection to the uninfected partner.

Positive man, negative woman

Until a few years ago, couples in this position could only conceive by having unprotected intercourse. The risk of transmission to the woman, approximately 1:500 per sexual encounter [13; 14] could be reduced by limiting exposure to the most fertile period. In one study, four of 103 women seroconverted by practicing this method of achieving a pregnancy [15]. In 1992 Semprini invented the technique of 'sperm washing' [16]. This is a process whereby spermatozoa are removed from the surrounding seminal plasma by a sperm swim-up technique. It has been demonstrated that HIV is found in the white cell component of seminal plasma but not bound to spermatozoa themselves. To date there have been no seroconversions in women inseminated with washed sperm [17]. A proportion

of HIV positive men have low sperm counts, it is possible to offer them intracytoplasmic sperm injection following the sperm washing process [18]. Sperm washing programmes are available in London, at the Chelsea & Westminster Hospital and St Thomas's, and in Birmingham. This technique is not currently available on the NHS.

Positive woman, negative man

Fertility problems can arise here by the practice of safer sex. Following counselling, couples are distributed with quills, syringes and Gallipots and are instructed in how to perform artificial insemination by husband at the time of ovulation. This protects the male partner from infection and allows pregnancy to be achieved [19].

Positive couples

This group of patients are still encouraged to practice safer sex to reduce transmission of viral variants, however many couples understandably do not follow this advice. Currently, positive couples wishing to achieve a pregnancy are advised to practice unprotected intercourse during the fertile period and not to go down a sperm washing route. Although in the past in vitro fertilisation (IVF) has been much disputed for HIV infected couples with infertility, IVF is now ethically acceptable since the vertical transmission rate has fallen to < 1% along with an increased life expectancy for parents on HAART [20].

3) Sexual Health of HIV positive pregnant women

The sexual health of pregnant HIV-positive women has not received much attention previously. There are few data regarding the prevalence of genital infections in HIV positive women in the United Kingdom [21]. The majority of pregnant HIV infected women in the United Kingdom come from, and probably became infected with HIV in, Sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV infected population, can be high [22]. The diagnosis and treatment of genital infections in any individual have clear benefits, both in terms of individual morbidity, and possible infectivity to any sexual partner. In pregnancy, the welfare of the baby is an additional issue. Apart from the recommendation that all pregnant women should be screened for HIV, hepatitis B and syphilis, asymptomatic pregnant women are not routinely screened for genital infections.

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [23; 24]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with mother-to-child transmission (MCT) of HIV and may be inter-linked [25-27]. Although both *Chlamydia trachomatis* and *Neisseria gonnorrhoea* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma Urealyticum* [23; 24]. A strong association between bacterial vaginosis and premature delivery has been reported [24; 28]. There is preliminary data from Malawi which suggests that BV may be associated with an increased risk of maternal HIV infection in pregnancy as well as premature delivery and mother to child transmission of HIV [29]. Future studies will throw more light on this. Currently, there are no randomised trials to support the routine screening and treatment of

all pregnant women with BV as a means of preventing preterm birth or vertical transmission of HIV [30; 31].

It has long been recognised that genital infections, in particular ulcerative diseases, are associated with sexual transmission of HIV [32; 33]. This may be due to an increase in local HIV replication resulting in a higher viral load in genital secretions, secondary to the presence of specific organisms, and /or ulceration and inflammation [34; 35]. Organisms associated with bacterial vaginosis have been shown to stimulate HIV expression in vitro [36; 37]. A recent study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis [38]. Viral load in cervico-vaginal specimens has been shown to be correlated with MCT of HIV-1 [39].

Although the majority of HIV infected pregnant women in the United Kingdom will be offered, and will accept, an elective caesarean section, a vaginal delivery may occur either through maternal choice or because of spontaneous vaginal delivery prior to a planned caesarean section. In addition, preterm prelabour rupture of the membranes may expose the fetus to cervico-vaginal secretions prior to a later caesarean section. A number of women will have an undetectable plasma viral load secondary to antiviral therapy. Usually, the genital tract VL will mirror the plasma VL [40], any discordance may be related to genital infection. In these situations, an increased genital tract viral load secondary to infection could conceivably increase the risk of MCT.

In the absence of randomised controlled trials, but for the reasons outlined above, it would appear prudent to screen HIV positive pregnant women for genital infections. This should be done as early as possible in pregnancy and should be repeated at around 28 weeks. In addition, any infection detected should be treated according to the UK national guidelines, followed by a test of cure [41]. Partner notification should take place where indicated, to avoid re-infection.

4) Psycho-social support for pregnant women with HIV

Strategies for reducing mother to child transmission of HIV are described in detail in this paper. However, in order that women feel able to take advantage of the interventions available, professionals should be aware of the psycho - social issues that might impact upon their lives. If a woman feels supported throughout the pregnancy she will be more likely to take up the interventions to benefit both herself and her baby.

The usual message to women who are pregnant is to avoid taking medication of any kind if possible. However, women with HIV are encouraged to take therapy to help prevent the vertical transmission of HIV, and some women may struggle with this decision. It is important for professionals to give women all the information available regarding drug therapy in pregnancy, including some discussion about what is still unknown. If a full discussion has taken place this will increase the likelihood of adherence.

For many women with HIV being advised to avoid breast-feeding can be very painful. Women who come from countries where it is the norm to breast-feed may find this

particularly difficult. Questions from family and friends may also prove difficult to answer when they are not aware of the HIV diagnosis.

When a woman is advised not to breast feed for a medical reason, professionals have a responsibility to ensure that she has the wherewithal to formula-feed safely. For some women this may mean giving advice on the purchasing of bottles and sterilising equipment. Women who are seeking asylum and therefore do not have access to public funds should be referred to a social worker who is familiar with the issues.

Living with an HIV diagnosis can lead to fear about a breach of confidentiality, especially if the woman has been diagnosed during the pregnancy or not yet told anyone her status. This may make taking medication difficult as well as the need to explain why she is bottle-feeding and had a caesarean delivery.

There should be a clear local referral pathway for HIV positive pregnant women. This should include: an HIV physician; midwife/obstetrician; paediatrician and may include a social worker, health advocate and voluntary groups. If there is a specialist nurse or health visitor responsible for post natal and paediatric follow up, then it is good practice for the woman to have met them as well as the paediatrician prior to delivery. Follow up of the baby may be the main concern for the women, so it is important that she is clear what will happen following delivery and when she can expect to have a result for the baby.

An important aspect of postnatal care is the provision of family planning advice. Women should be advised that there is a risk of diminished efficacy of the oral contraceptive pill when taken in conjunction with protease and non-nucleoside reverse transcriptase inhibitors. It is important that when seeking family planning advice the woman is open about her status with the professional she sees, so that best advice can be given.

To ensure that the wider psychosocial issues are addressed with HIV positive pregnant women a multi-disciplinary approach is most effective.

5) Prescribing Antiretroviral therapy in Pregnancy

Fifteen compounds are currently available for the specific treatment of human immunodeficiency virus type 1 (HIV-1) infection in the UK, either through named patient access or licensed by the Medicines Control Agency. Of these only zidovudine is specifically indicated for use in pregnancy (excluding the first trimester) to prevent mother to child transmission of HIV. For most antiretroviral therapy (ART), prescription in pregnancy is cautioned.

The introduction of government targets to recommend HIV testing to all pregnant women has already led to a significant increase in identification of HIV infected women needing advice on the management of HIV in pregnancy. Furthermore an increasing number of women of child-bearing 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. The difficulty for the physician is that few studies

have addressed current practice. Indeed a Cochrane reviewer concluded that zidovudine monotherapy, nevirapine monotherapy and prelabour Caesarian section (PLCS) were the only interventions shown to be very effective in decreasing the risk of mother-to-child transmission of HIV, with no reference to avoidance of breast-feeding [42]. In this section we will summarise the efficacy data from observational and controlled studies (Table 2) and make weighted recommendations on the use of ART in pregnancy which balance the needs of the mother and infant with the limitations of the available data. Pre- clinical and clinical safety data can be found in the appendix.

Monotherapy for reduction of mother to child transmission of HIV

The only published studies are for zidovudine, nevirapine and ritonavir.

Nucleoside Analogue Reverse Transcription Inhibitors (NRTIs)

The efficacy of zidovudine to reduce mother-to-child transmission of HIV-1 has been demonstrated in several large randomised controlled studies [12; 43; 44]and supported by epidemiological surveys [45 46 47; 48]. 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 iv infusion during labour, to 50% with shorter courses, (started at week 36) without a neonatal component, in non breast fed babies, to 30% with a similar regimen in breast-fed babies[49 50]. In a non-breast feeding population the transmission rate with addition of AZT has been reduced to 6-8%[12; 46]. As with monotherapy in non-pregnant women zidovudine transiently reduces HIV-1 plasma viraemia and increases CD4 positive lymphocyte counts. In ACTG 076, in which mothers commenced zidovudine 100mg five 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 [51]. In the Bangkok study zidovudine 300mg twice daily was commenced at week 36 resulting in a 0.57 $\log_{10}$ reduction in plasma viraemia at delivery[44]. This was considered to account for 80% of the efficacy of zidovudine to reduce transmission.

Viral load is an important predictor of transmission and zidovudine reduces transmission at all levels of maternal viraemia. However, in mothers with very high viral load (>100,000 RNA copies/ml) the transmission rate may be >60% and even with a 2/3 reduction in transmission the risk to the infant would still be around 20%. Additional measures are therefore required for these babies and probably for any mother with a viral load >10 – 20,000 copies/ml. Pre-labour caesarian section has been demonstrated to reduce transmission by as much as zidovudine (see section 7). When zidovudine and PLCS section were combined in a cohort of women at all levels of viral load, transmission was further reduced to <2 % [52]. The safety and efficacy of didanosine and stavudine seperately and combined is part of an on-going investigation [53].

Resistance to AZT in pregnancy

Sequence changes in the HIV-1 RT associated with decreased viral sensitivity to zidovudine were found, at the time of delivery, in 1/36 mothers in the zidovudine arm of ACTG 076[54] and in 2/10 mothers receiving zidovudine monotherapy in a cohort in the UK[55]. This has caused concern that zidovudine monotherapy whilst 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 presence of resistance mutations at delivery[56] whilst in the RETRO-CI study none of the ten women tested had evidence of zidovudine related mutations following a median of 27 days therapy[57] . 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 6/62 (9.6%) of mothers[58] whilst in the WITS which included many women with advanced HIV disease and prior (pre-pregnancy) zidovudine exposure 34/142 (25%) of maternal isolates had at least one zidovudine-associated resistance mutation[59]. Whether resistant mutants are more or less transmissible remains controversial.

Protease inhibitors (PIs).

PIs are highly protein bound and the limited data indicate that placental transfer in humans is limited. In a safety, tolerability and efficacy study of 86 pregnant women ritonavir monotherapy was initiated at gestation week 36 at a dose of 300mg bd increased incrementally to 600mg bd 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 twelve women discontinued treatment, ten because of elevated liver enzymes (see section 6) [60].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The rapid placental transfer and long half life of nevirapine have led to studies of the efficacy of nevirapine to reduce the risk of mother-to-child transmission of HIV. In HIVNET 012 two doses of nevirapine, the first given to the mother in labour and the second to the neonate age 48-72 hours, were compared with zidovudine initiated in labour and prescribed to the neonate for one week. Transmission was reduced by 50% with nevirapine[61]. As with short-course zidovudine the transmission rates at one year are less than expected (15.7% with nevirapine and 24.1% with zidovudine) and the increased protection of nevirapine persisted even though the infants were breast-fed [62].

Mutations associated with decreased susceptibility to nevirapine occurred rapidly and frequently in studies of nevirapine monotherapy in non-pregnant adults [63]. In a preliminary analysis of the emergence of resistance in HIVNET 012, nevirapine resistance mutations were found in 7/30 mothers and in 3/7 infected infants tested [64; 65]. In the latest analysis 19% (21/111) of mothers and 11/24 infected infants had genotypic evidence of nevirapine resistant virus including one infected after age 6 months [66].

In the SAINT study transmission rates at eight 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 one week post-partum (10.8%) [67]

Combination Therapy for reduction of mother to child transmission of HIV
Dual nucleoside analogue therapy

In an open 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 AZT monotherapy. However the genotypic mutation (M184V) which confers resistance to lamivudine was found in 4/5 women at delivery [55]. 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 – 13.2%) [68]. In a large French prospective non-randomised 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 historically with 6.5% on zidovudine monotherapy). Treatment was well tolerated by mothers and infants but at 6 weeks post-partum the M184V was detected in 52/132 women but not in any women treated for less than 4 weeks [69]. In an international randomised controlled study in breast-feeding women there was a 22% reduction in transmission at 18 months follow up compared with placebo in children perinatally exposed to zidovudine plus lamivudine from 36 weeks gestation to 1 week post-partum although this did not quite reach statistical significance[70].

Triple therapy (NRTI with PI)

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 to 1.1% in mother-infant pairs exposed to triple therapy including a protease inhibitor [71]. In a study of 76 women taking a PI as part of combination therapy during pregnancy there were 15 pre-term deliveries (PTD) (<37 weeks) but 60% of the mother had identifiable risk factors for PTD such as a history of PTD, smoking and substance abuse. HIV transmission had been excluded in the 34 babies with adequate follow-up [72]. The possibility that protease inhibitor usage was associated with an increased risk of PTD had been suggested by Swiss investigators in

1998[73] following which recruitment of women to studies of protease inhibitors in pregnancy was temporarily suspended. Among 462 women participating in ACTG studies in 1998 – 1999 the PTD rate was 20% but with no significant difference between women exposed to PIs and those not exposed to PIs (RR 0.7 95% CI 0.5 – 1.1) whilst the rate of very premature delivery (<32 weeks) was less among women taking PIs (RR 0.2; 95% CI 0.05 – 0.8). 19/462 (4.1%) babies were born with a structural abnormality [74]. An increased rate of preterm delivery has also been reported in women on combination ART with PI's in Europe[75].

Triple therapy with an NNRTI

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 [71]. In the ACTG 316 study nevirapine was added at labour to maternal and neonatal therapy whether it be mono, dual or triple. The 1.5% transmission rate among the 1174 mother-infant pairs, which was considerably less than anticipated at study design (5%), confirms the potency of current management strategies. Forty-nine percent of mothers had no detectable plasma viraemia at delivery. The study was closed when it became clear that it was not powered to demonstrate any benefit from Nevirapine used in this way [76]. Genotypic studies have demonstrated the emergence of mutations associated with resistance to nevirapine in 11% (5/46) of mothers with detectable (>400 copies/ml) plasma viraemia at delivery [77].

6) Maternal drug toxicities in pregnancy

Information about the safety of drugs in pregnancy is limited. Data are usually from animal studies, anecdotal experience, registries and clinical trials. This section aims to summarise the current data available on the short-term toxicity of ART during pregnancy.

General Consideration for Maternal Toxicity

Physiological changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing. During pregnancy, GI transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in metabolic enzyme pathway in the liver.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside analogue drugs are generally well tolerated in pregnancy; reported incidences of adverse effects are similar to those reported in non-pregnant HIV-infected individuals. A French group investigating the use of zidovudine-lamivudine for prevention of mother to child HIV-1 transmission, reported satisfactory maternal tolerance despite slight differences in serum transaminases, creatinine and neutrophils (ref Abs 267 6th CROI). A

retrospective Swiss report evaluated the pregnancy outcome in 37 HIV-infected pregnant women treated with combination therapy; all received two NRTIs and 16 received one or two protease inhibitors [73]. Almost 80 percent of women developed one or more typical adverse effects of the drugs such as anaemia, nausea/vomiting, raised transaminases, or hyperglycaemia.

Nucleoside analogues may cause mitochondrial dysfunction as they have varying affinity for mitochondrial DNA γpolymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion [78]. The relative potency of the nucleoside analogues in inhibiting mitochondrial DNA γ polymerase in vitro is highest with zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), zidovudine (AZT) and abacavir (ABC) [79]. Toxicity related to mitochondrial dysfunction has been reported in patients receiving long-term treatment with nucleoside analogues and although this generally resolves with discontinuation of the drug or drugs fatalities have been reported.

Early in 2001 the US Food and Drugs Administration and the European Medicines Authority advised doctors that they had received reports of three pregnant women who had died of lactic acidosis following treatment with stavudine and didanosine (as part of triple therapy) and a further 4 cases of lactic acidosis in pregnancy with this combination. It is not clear whether the frequency of this recognised complication is higher in pregnant compared with non-pregnant women. In one London centre lactic acidaemia (one with acidosis) with deranged liver enzymes has been documented in two of five women taking stavudine, didanosine and nevirapine. Both recovered following discontinuation of therapy. No cases were documented in a further 28 women taking other triple therapy combinations [G Taylor personal communication]. Monitoring liver function and blood lactate in pregnant women on this combination is therefore recommended. The use of ddI/d4T in pregnancy should for the time-being be restricted to woman with resistance or intolerance to other nucleoside analogues.

Protease Inhibitors

Hyperglycaemia, new onset diabetes, exacerbation of existing diabetes mellitis and diabetic ketoacidosis have been reported with administration of protease inhibitors [80-82]. Women taking ART which includes a PI have a higher risk of developing diabetes mellitus during pregnancy (3.5%) than HIV negative women or HIV positive women taking either NRTIs or on no therapy (1.35%) (p 0.025)[83].

In a study of 86 HIV-positive, treatment naïve women, ritonavir montherapy commenced in the 36th week of pregnancy was not well tolerated and 12 women stopped treatment (10 due to elevated liver enzymes; 1 severe vomiting, diarrhoea, headache and fever; 1 inability to take capsule). The most frequently reported maternal adverse events included diarrhoea (30), nausea (22), altered taste (15) and vomiting (10). There were 51 maternal grade 3/4 laboratory abnormalities (mostly elevated liver enzymes) [60]

In a small phase I study of ritonavir/AZT/3TC (PACTG 354) this combination was well tolerated by the six mothers with only Grade 1/2 toxicities including GI symptoms, abnormal biochemistry, anaemia and neutropenia. One infant died following caesarian delivery at 31 weeks for oligohydramnios and fetal distress[84].

The use of protease inhibitors in combination therapy has been reviewed in 89 pregnancies, from six sites in the USA. 36 women received nelfinavir, 33-saquinavir, 23-indinavir and 5-ritonavir. Obstretric complications reported were: one full placenta previa; two abruptions; four oligohydramnios; three pre-eclampsia and one spontaneous abortion. Protease inhibitors were generally reported to be well tolerated and appeared safe in pregnancy [72]

An evaluation of 64 HIV-infected pregnant women receiving three or more antiretrovirals including a PI in 27, nevirapine in 22 and combinations of a PI with nevirapine in 15 women also found combination therapy to cause few side effects. Maternal drug related complications included: nevirapine: rash (3), hepatitis (1); PI: vomiting (2), ureteral obstruction (1) [85].

Nevirapine

The use of nevirapine (NVP) as part of combination antiretroviral therapy was retrospectively reviewed in a London cohort of 46 HIV-infected pregnant women. Thirty initiated NVP during pregnancy, 16 in the second trimester and 14 in the third. Nevirapine was usually well tolerated and the only adverse effects probably related to NVP were rash (2) and biochemical hepatitis (2). Six 6 women developed GI symptoms, which were attributed to, and settled on changing, the nucleoside analogues [86].

Experience with triple or more drug combinations in pregnancy is increasing. Although data from controlled studies is still limited, retrospective reviews and cohort analyses suggest that the incidence of antiretroviral related adverse effects in HIV-infected pregnant women is similar to that in the non-pregnant population. All the studies have shown combination therapy to be effective in reducing mother to child transmission and therefore the potential benefits of the intervention must be assessed against the risk of toxicity.

Other Drug Treatments

Women on antiretroviral therapy are commonly on 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 in the first trimester to folate antagonists used for Pneumocystis carinii pneumonia prophylaxis combined with ART [87]. In addition to neural tube defects first trimester exposure to folate antagonists has been associated with an increased frequency of cardiac and renal tract malformations. The therapeutic needs of all women of child-bearing 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 [88].

7) Obstetric management of pregnancy and delivery

Important evidence of the efficacy of pre-labour caesarean section in the prevention of vertical transmission of HIV-1 now exists. Caesarean section should be considered as the optimal mode of delivery for women with HIV-1 infection.

Since the majority of vertical transmission occurs during the intrapartum period, it was proposed that pre-labour caesarean section with avoidance of labour and the birth canal might reduce the risk of transmission [89-91]. However, early cohort studies gave conflicting results as to the effectiveness of this intervention due to methodological differences [92-95]. Definitive support for the protective effect of elective caesarean section came from a trans-Atlantic meta-analysis of 15 prospective cohort studies [96] and a randomised controlled study of mode of delivery in Europe[52] (Table 3).

The meta-analysis included 8533 mother-child pairs and the group was divided into four categories depending on mode of delivery and other confounding obstetric factors such as the interval from rupture of the membranes to delivery. Other factors such as the use of antiretroviral drugs, maternal CD4 count and the gestational age at delivery were also taken into account. This analysis confirmed that the vertical transmission rate was 50% lower in women who underwent pre-labour caesarean section before the onset of labour or rupture of the membranes and this protective effect persisted when the use of antiretroviral therapy was taken into account (Table 3). The study also confirmed the additive protective effect of antiretrovirals in the antenatal, intrapartum, and neonatal period with pre-labour caesarean section over and above that predicted for either intervention alone.

A randomised controlled trial of delivery either by pre-labour caesarean section or vaginal delivery in HIV infected women was carried out in Europe [52]. With an over all reduction in transmission of 70%, this study confirmed the role of elective pre-labour caesarean section in prevention of transmission of HIV in a cohort of women with all levels of CD4 and disease status (Table 3). Sixty three percent of women received ZDV monotherapy and none breastfed. The maternal complication rate of caesarean section, including postoperative infections was very low, but all women received intra-operative antibiotics.

A further meta-analysis of the cohorts detailed above examined the effect of duration of rupture of membranes (ROM) (up to 24 hours) on vertical transmission of HIV[97]. The risk of transmission increased approximately 2% for every hour of rupture of membranes (adjusted odds ratio, 1.02; 95% CI 1.01-1.04 for each hour of increment). In women with an AIDS diagnosis the risk of transmission increased from 8% after 2 hours of ROM to 31% after 24 hours of ROM.

Maternal viral load data was not available for the meta-analyses or the mode of delivery randomised controlled trial. It has subsequently been suggested that mothers with very low / undetectable viral load might consider vaginal delivery. In a recent meta-analysis of seven prospective studies from the US and Europe there were 44 mother to child transmissions in 1020 deliveries where maternal plasma viral load was < 1000 HIV RNA copies / ml at or around delivery [6]. The transmission rate for mothers on ART was 1% (95% CI 0.4%-1.9%) compared to 9.8% (95% CI 7.0%-13.4%) for untreated mothers. In multivariate analysis transmission was lower: with ART (OR 0.01; p<0.001); caesarean section (OR 0.30; p= 0.022); greater birth weight (p = 0.003); and higher CD4 count (p = 0.039). These data which were collected at a time when HIV-RNA PCR assays were less sensitive than currently available suggest a protective effect of both ART and caesarean section even at very low viral loads. However, whether caesarean section has an additive effect at a delivery viral load of < 50 HIV RNA copies / ml is not known. Cost effectiveness analysis suggests that the vertical transmission rate would have to be less than 0.5% before caesarean section would be no longer cost effective[98].

The benefit of elective caesarean section in reducing the risk of vertical transmission is now clear, especially for women with detectable viral load. However possible surgical complications must be included in any discussion regarding mode of delivery. Some studies have suggested that post operative complications are increased in HIV infected women compared to the background population [99-101] others [52] found no difference. Not surprisingly, reported complication rates are related to the level of maternal immunocompromise.

Management of Delivery

A plan for delivery management should be made relatively early in pregnancy. Planned delivery by pre-labour section should be undertaken at 38 weeks[102] but there is some evidence that women infected with HIV do labour early and if there are signs that delivery is imminent the date for the caesarean section should be brought forward [26; 103]. If labour starts prior to the planned delivery date the woman should be assessed urgently to confirm the onset of labour. Intravenous zidovudine should be commenced if this is part of the planned anti-retroviral regime, but the caesarean section should not be delayed to complete the induction course of Zidovudine if labour is progressing rapidly or the membranes have ruptured (Table 4 scenario 7).

If there is premature rupture of membrane, with or without labour, then an assessment will have to be made as to the risk of HIV transmission compared to the risk of premature delivery, expert advice should be sought (Table 4 scenario 8). There is no known contra-indication to the use of short term steroids to promote fetal lung maturity in women with HIV.

Although an elective caesarean section is currently the recommended mode of delivery for women with HIV, some women may still wish for a vaginal delivery. This may be an important consideration for women who are planning to return to an African country

where subsequent caesarean section deliveries may not be possible or safe. If a vaginal birth is planned the membranes should be left intact until delivery is imminent. Fetal scalp electrodes and fetal blood sampling must be avoided. If there are signs of fetal distress on the cardiotocograph consideration should be given to performing an emergency caesarean section as the risk of vertical transmission of HIV is increased after emergency vaginal obstetric intervention.

Other Pregnancy issues

Prenatal diagnosis

HIV infected women contemplating invasive prenatal diagnosis for the diagnosis of Down's syndrome or other abnormalities should be counselled in a specialist fetal medicine unit. In order to assess the risk of any specific abnormality the best non-invasive screening tests available should be employed e.g. Nuchal Translucency screening combined with serum biochemistry to accurately assess the risk of Down's syndrome. Should a woman be at high risk or request invasive testing she should be offered an amniocentesis at 16 weeks when the risk of fetal contamination with maternal blood will be less. No data exist on the risk of vertical transmission in this situation. However extrapolation from Hepatitis B infection data suggests that a chorionic villus sample and fetal blood sampling has a higher risk attached to it and that the overall risk with amniocentesis is very low **(ref)**. Consideration to administration of antiretroviral therapy to cover the procedure should also be made.

Women who become unwell in the third trimester of pregnancy

Presentation in the third trimester with signs and symptoms of pre-eclampsia, cholestatis or other liver dysfunction may be due to these complications of pregnancy but may also be side effects of antiretroviral drugs (see section 6). Any women presenting with vomiting, malaise or oedema should be investigated for acidosis, liver function, pancreatic function, and disseminated intravascular coagulation whether or not she has hypertension or proteinuria. In cholestasis of pregnancy, the presenting symptom will be generalised itching and the bile acids will be raised. In pre-eclampsia there is likely to be proteinuria and a raised urate. Drug toxicity may be more common with stavudine and didanosine, but all the nucleoside analogues may disturb mitochondrial function and low levels of lactic acidaemia are not uncommon. However, if the lactate level is rising or associated with acidosis discontinuation of the ART even at this crucial time of pregnancy must be seriously considered.

8) Assement of HIV viral load in pregnancy

A number of commercial assays are currently available for quantification of HIV-1 RNA, the most widely used in the United Kingdom being the Bayer branched chain DNA assay and the Roche RT PCR assay. Studies have demonstrated that absolute HIV RNA copy number may vary depending on: the assay employed; biological variation of RNA; and

specimen handling [104]. The contribution of these variables to HIV RNA concentrations appears to be of the order of 0.3 to 0.6 $\log_{10}$ copies/ml, although in some instances it may be as high as 1.0 $\log_{10}$. The Bayer bDNA assay (version 3.0) generally gives lower HIV RNA copy numbers than the Roche RT PCR (version 1.5) but the two assays have been shown to be highly correlated [105]. In order to ensure reliable and accurate quantification of HIV-1 RNA the same assay should be used to monitor viral load. As the absolute copy number may vary, depending on the assay used, HIV-1 RNA thresholds for initiation of antiretroviral treatment in pregnancy should be based on a range rather than a single value. In cases where there are discrepancies between viral load, CD4 cell number and clinical status it is advisable to re-test with another assay in which different nucleotide sequences are used to bind or amplify target RNA.

Accurate quantification of non-B subtypes of HIV-1 is an important requirement for monitoring pregnant women. Mismatches between the probes used in commercial assays and RNA target sequences may result in falsely low or undetectable viral loads among women infected with divergent subtypes. In the United Kingdom, 78% of infections among women attending antenatal clinics are non-B with 61% being subtype A and 29% subtype C [106]. Commercial assays have been developed primarily using the B subtype of HIV-1 and their ability to quantify non B subtypes of the virus is variable [107; 108]. Failure to detect or accurately quantify non-B subtypes may be a particular problem with nucleic acid sequence based amplification (NASBA, Organon Teknika Ltd). The first version of the Roche assay (version 1.0) also failed to detect a high proportion of non-B subtypes but assay performance has been considerably improved by the addition of non- B primers in version 1.5 of the assay [109]. In contrast to these two PCR based assays the Bayer bDNA assay utilises multiple probes to detect a larger part of the genome and, as a consequence, may be more efficient in detection of genetically diverse variants.

Detection of antiretroviral drug resistance

Genotypic and phenotypic assays for detection of resistance to antiretroviral drugs are now becoming more widely available commercially and the value of resistance testing in therapeutic decision making is established. In general, sequence based genotyping assays require approximately 1000 HIV RNA copies/ml and samples with low viral loads may not be sequenced successfully. Current assays may also fail to detect minority species representing less than about 20% of the viral population. Drug resistant virus quickly reverts to wild type in the absence of drug pressure consequently use of resistance testing to monitor treatment during pregnancy should ideally be conducted while the woman is still on therapy or within a few weeks of stopping [110]. Sexual transmission of drug resistant HIV is now well documented with prevalence rates, following recent infection, of approximately 10-20% in Europe and North America [111-113]. Less information is available for the UK but a recent study has demonstrated a prevalence of 5% following primary HIV infection [114]. Transmission of drug resistant virus from mother to infant is also known to occur [115].

As with viral load assays, commercial resistance assays have been developed using the B subtype of HIV. Non-B subtypes may therefore be amplified and sequenced less efficiently than subtype B. However, there are data demonstrating successful resistance analysis of non B subtypes of the virus with generally similar drug resistance profiles to subtype B [116]. The protease gene of HIV is highly polymorphic and this may contribute to development of resistance to protease inhibitors. Naturally occurring accessory mutations within the protease gene have been demonstrated in 85% of individuals never treated with protease inhibitors and the frequency of these mutations was higher among non B (91%) than subtype B virus (75%) [117]. Individually these accessory mutations, which reflect natural polymorphisms, have limited effects on drug susceptibility, however, they may influence the rate at which resistant virus is selected during treatment with protease inhibitors[15]. The clinical significance of this, particularly for individuals infected with non-B subtypes of the virus, is unclear.
Any women presenting in pregnancy on a non-suppressive ART regimen should have resistance testing undertaken (ref Euro guidelines). Consideration should be given to testing ART naïve women, especially if there is an epidemiological risk of primary resistance (e.g. an ART exposed partner).

9) Interventions to reduce mother to child transmission of HIV

Table 4 details 9 clinical scenarios where a different approach to therapy in pregnancy may need to be considered and the issues relating to each scenario are discussed in this section as well as other sections of the text. Pre-labour caesarean section at 38 weeks is recommended as the mode of delivery in all scenarios. Consideration for vaginal delivery may be given for women on stable therapy with undetectable viral load at that time but there are insufficient data for this to be formally recommended at present.

Scenario 1: Women who do not yet require treatment for their HIV disease

Asymptomatic women with low plasma viral loads (less than 10 – 20,000 HIV RNA copies/ml) and good CD4 counts (> 200 – 350 cells/μl) do not require ART for their own health. AZT monotherapy with pre-labour caesarean section can still be advocated for them to reduce vertical transmission as well as ART exposure in pregnancy. An alternative regimen for those wishing to deliver with viral load < 50 HIV RNA copies / ml would be "START" (see below).

Scenario 2,3,4: Women who require treatment for their HIV disease

US [118] and UK[3] guidelines currently recommend that women with advanced HIV who would normally be treated with combination anti-retroviral 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 recommended. 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 have reduced transmission. However, there are now data for both ritonavir and nevirapine monotherapies which suggest equivalence with zidovudine (see section 5). Since protease inhibitors have limited placental transfer, reduction in maternal viraemia may be more important than had been thought for zidovudine. Since triple combinations reduce plasma viraemia to less than 50 copies/ml, vertical 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 still needs to be confirmed epidemiologically.

For treatment naïve mothers requiring combination therapy (scenarios 2 & 3), consideration should be given to safety and efficacy data, tolerability, and whether treatment is likely to be continued after delivery. The most extensive safety and prevention of transmission data are for zidovudine and lamivudine however the rapid development of lamivudine resistance precludes dual therapy and optimally suppressive therapy should be recommended. Limited experience with triple therapies including a PI or nevirapine have been reported (Section 5). If treatment discontinuation is planned, e.g. for a mother who has elected to take short term triple antiretroviral therapy (”START”) in pregnancy to prevent mother to child transmission (Table 4 scenario 2), a protease inhibitor such as nelfinavir might be preferred because the long half-live of nevirapine might result in the emergence of resistance. Alternatively the nucleoside backbone of the regimen may be continued for a few days after stopping nevirapine to avoid inadvertent ‘nevirapine monotherapy’. However there are no trial or observational data that address this issue.

Scenario 4,5: Women who conceive on therapy

Women who conceive whilst on antiretroviral therapy may wish to discontinue therapy during the first trimester. There are no data to support or refute this. 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 two to three weeks and ‘strategic treatment interruptions’ have been associated with significant CD4 lymphocyte decline. This may not only jeopardise maternal health but in theory result in reactivation of infections associated with congenital abnormalities e.g. CMV. Many women will not realise or report their pregnant state until well into the period of organogenesis. With the exception of efavirenz (see appendix) 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. Resistance testing can help to identify the best options. Only exceptionally should antiretroviral therapy be initiated in or changed during the first trimester. Reasonable exceptions include serious illness for which antiretrovirals are the only recognised therapy.

Scenario 6,7,8: Women who present late in pregnancy

For women who present very late in gestation or in labour, for whom no risk assessment has been possible it seems sensible to include compounds that rapidly cross the placenta and have reliable pharmacokinetics in the neonate. In this situation the most effective antiretroviral therapy is nevirapine. Protease inhibitors are not preferred because they have limited transplacental transfer. Given the high risk of resistance developing in the mother with even a single dose of nevirapine monotherapy[66; 77], two other compounds, usually nucleoside analogues such as zidovudine and lamivudine should be started. During labour zidovudine should preferably be infused IV and all treatment should be continued after delivery until the mother's clinical, immunological and virological status have been determined. Consideration should be given to continuing triple therapy until plasma viraemia has become undetectable and then discontinuing nevirapine a few days (no data available) prior to the nucleoside analogues to accommodate the long half-life of nevirapine.

Scenario 9: Presentation of the infant after delivery

Where it is only ascertained after delivery that an infant has been born to an HIV infected mother, where maternal interventions have been declined or when interventions were introduced after labour had started post exposure prophylaxis (PEP) should be offered as soon as possible. There is observational data that AZT can reduce transmission in this situation if given within 48 hours of delivery. Although there are no data, it would seem logical and consistent with other current PEP recommendations for high risk exposure to offer triple combination therapy for four weeks[119].

10) Management of infants born to HIV infected mothers

Exposure to Antiretrovirals (ART)

Most neonates born in the UK to mothers known to have HIV will be exposed to ART in utero, during delivery and after birth for the first 4-6 weeks of life. The range of different combinations of ART to which neonates are being exposed is constantly expanding. Neonatal drug metabolism is generally slower than that of older infants or children, and premature neonates have even less efficient metabolism. Neonatal dosing regimens have been developed for most of the nucleoside analogues and for Nevirapine both for the stat dosing in mother and infant regime and for longer term use (Table 5). Adequate neonatal blood levels are difficult to achieve with Nelfinavir and there is little experience of other PI's [120]. In Europe, the only ART available for intravenous (IV) use in sick and / or premature neonates, unable to take oral medication, is ZDV. Reduced oral and IV dosing schedules for premature infants have only been developed for ZDV. Neonatal metabolism of Nevirapine is induced where there is antenatal exposure, so if this drug is subsequently given to the neonate a different regime may be required .[121; 122]

When to Consider Combination ART in Neonates

There have been very few studies of combination therapy in neonates[84; 123 120]. Whether combination ART to the neonate has any additional benefit over single drug treatment is not known. Where a mother on combination therapy delivers with a viral load of < 50 copies / ml, our current practice is to use only single drug therapy for the neonate, as this is practically easier for the family and may reduce the incidence of adverse events in the neonate. The drug chosen from the maternal combination is usually the NRTI with the best-known infant pharmacokinetics (eg ZDV, 3TC etc). With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred, use of didanosine is avoided. Zidovudine should not be given to an infant born to a mother who is receiving stavudine because of their theoretical competitive interaction. There are two situations where combination treatment for neonates should be considered:

1) where the mother is only found to be HIV infected after delivery (Scenario 9);
2) where an unplanned delivery occurs, either prematurely prior to starting ART, or after a late presentation when details of maternal HIV parameters may not be available (Scenario 8)

In one observational US cohort study, where maternal diagnosis was made after delivery, infants commenced on ZDV monotherapy within 48 hours of birth still had a reduced risk of transmission (transmission risk: complete 076 treatment- antepartum (AP), intrapartum (IP), and postpartum (PP) – 6.1% (95%CI 4.1-8.9%), IP + PP – 10.0%(3.3-21.8%); PP <48hrs – 9.3%(4.1-17.5%); PP >48 hrs – 18.4% (7.7-34.3%); no Rx – 26.6% (21.1-32.7%) [48]. There have been no trials of combination treatment to infants in the above situations, but as combination ART is advised for other post-exposure prophylaxis cases it would seem logical to consider it for neonates. We have used ZDV, 3TC and NVP for infants born to drug naïve women, but for non-naïve mothers other combinations might be required if there is a possibility of resistance. Resistance testing should be carried out in the mother in such a situation and as early as possible in the infant as well, if infected.

Duration of Treatment for Neonates

In the PACTG 076 study[12] ZDV was administered for 6 weeks after birth and this subsequently became standard of care. However, in a recent Thai study, where a short course of three days of neonatal treatment was compared to one month there was no increased transmission where the mother received ZDV from 28 weeks gestation [43]. In the UK, neonates are currently treated for 4-6 weeks but it is worth remembering that current post-exposure-prophylaxis guidelines suggest treatment for 4 weeks only [119].

Side Effects of Treatment

Long term

Long term side effects of perinatal exposure to ART can be considered in four main categories: teratogenic; carcinogenic; developmental; and mitochondrial. Teratogenicity is most likely to be a problem with first trimester exposure to ART +/- other drugs. All currently licensed antiretroviral therapies are classified either B or C for use in pregnancy by the FDA (See Tables 6 and 8). All women who receive ART in pregnancy should be registered prospectively with the International Drug Registry (see below for details). To date, no increase in total number nor any specific fetal abnormality have been identified, but the voluntary reporting rate is disappointingly low (Appendix and Table 7). Detailed fetal anomaly scanning at 18-20 weeks is advised after first trimester exposure. NRTI exposure could theoretically lead to a longterm risk of carcinogenicity, no increased rate is currently identified [124]. In the UK, the register of cancer and deaths is linked anonymously to the register of infants born to mothers with HIV to high light any relationship. So far, no adverse developmental effects of ART exposure have been demonstrated in children [125]. Mitochondrial toxicity after perinatal ART exposure was first reported in 8/1760 infants from the prospectively followed French cohort [126]. In an updated analysis of the French cohort mitochondrial toxicity was suspected in 18/2547 (0.7%) (CROI8) Deaths have not been identified in other large cohorts [127]. One study did not demonstrate any evidence of later cardiomyopathy, but the cohort was small [128]. In the long term follow up of the infants from the 076 study, two ZDV exposed children were shown to have unexplained retinopathy and cardiomyopathy [125], which could potentially be related to mitochodrial dysfunction.

Short term

Short term, acute mitochondrial toxicity may also be a problem in the newborn period, exacerbating the metabolic stress of delivery. A small number of sick infants have been reported with severe lactic acidosis, multi-system failure and anaemia, not attributable to any other cause, all have recovered with supportive care [129; 130]. Elevated lactic acid levels have also been found in asymptomatic ART exposed infants [131]

Symptomatic neonatal anaemia is increasingly being reported in infants exposed to ART, and this may be worse where there is exposure to combination therapy [68]. Transfusion is rarely required and most children respond to discontinuation of marrow suppressive therapy. Abnormal liver function has been reported in infants exposed to zidovudine with lamivudine[68]. In a small study, infants exposed to PIs *in utero* had significantly higher γGT levels than therapy naïve or zidovudine monotherapy exposed infants [132]. In a study of the safety and tolerance of ritonavir in combination with lamivudine and zidovudine given to mothers, 3/6 infants were born prematurely, two with severe hypoglycaemia, whilst the third infant, delivered severely preterm, died. One infant had grade 3/4 hyperbilirubinaemia, one had neutropenia and two were significantly anaemia [84]. High

triglyceride levels were documented transiently in 2/6 infants treated with nelfinavir (combined with stavudine plus didanosine), despite the fact that inadequate plasma levels of nelfinavir were achieved [123]. Whether different combinations of ART may be more or less deleterious to the neonate is not known.

In view of the metabolic abnormalities increasingly reported with combination therapy neonates exposed to ART should have base line blood tests including: FBC; pH; lactate; glucose; U+E; LFT's; trigylcerides; and amylase; as well as diagnostic HIV PCR tests. It is our practise to repeat these tests with each set of HIV diagnostic samples.

Laboratory diagnosis of HIV infection in non-breast fed Infants

The gold standard test for HIV infection in infancy is HIV DNA PCR on peripheral blood lymphocytes [133]. As most infants are infected intrapartum and blood levels may still be very low, HIV DNA is not amplified from all infected infants at birth. Indeed a positive HIV PCR result within 72 hours of birth has been taken as evidence of intra-uterine transmission [91]. Within the first weeks of life the sensitivity of the test increases dramatically and by 3 months of age 95+% of non-breast fed HIV infected infants will be detected. In view of the genomic diversity of HIV a maternal sample should always be amplified with the first infant sample to confirm that the primers used can detect the maternal virus. If a maternal virus cannot be detected by the HIV DNA PCR used then a different primer set, or a different test e.g. HIV culture / HIV RNA PCR should be used [134]. Our current practice is to test infants at one day, one month, and three months of age. If all these tests are negative and the baby is not being breast fed, then we inform parents the child is not infected. Loss of maternal antibodies is subsequently confirmed at 18 months of age. It is not necessary to carry out other surrogate or less sensitive tests (eg CD4, Ig's, p24ag) unless there is a concern about the sensitivity of the HIV DNA PCR. Use of HIV RNA PCR ("viral load tests") for infant diagnosis has been increasingly reported, but this test may give false positive results of low copy number, which may cause unnecessary worry to families [135; 136].

There is no current evidence that perinatal ART exposure delays the detection of HIV infection in infants. If an infant is found to be HIV infected after perinatal ART exposure then the mother and infant should have urgent HIV resistance testing to delineate the reasons for treatment failure and to help guide further treatment.

Prophylaxis, Immunisations and Clinical Monitoring

Primary pneumocystis pneumonia in infants with HIV remains a disease with a high mortality and morbidity [137]. However as the risk of neonatal HIV infection has fallen to <1% where mothers have taken up interventions, the necessity for PCP prophylaxis has declined and in most European countries it is no longer prescribed. Co-trimoxazole as PCP prophylaxis should still be prescribed to infants born to mothers who decline any interventions (see table 5 for dose).

Infants born to HIV infected mothers should follow the routine immunisation schedule except that, BCG vaccine should not be given until the infant is confirmed un-infected.

The risk of live oral polio vaccination (OPV) to HIV infected infants and their carers has not proved significant, so it is not necessary to give killed injected polio vaccine in countries like the UK where the normal schedule contains OPV. The hepatitis status of the HIV infected mother should be ascertained, so that Hepatitis B vaccination can be carried out if necessary. PCR amplification is required for early diagnosis of HCV infection in infants born to HCV infected mothers.

Considering the importance of confidentiality, where possible families should be strongly encouraged to inform primary health carers, including midwives, health visitors and family doctors about maternal HIV and indeterminate infants. This will enable the local team to give appropriate support and advice, especially regarding infant feeding and where an infant or mother is unwell.

Reporting and long term follow up

It is the responsibility of clinicians caring for women with HIV and their children to report them to the UK National study of HIV in pregnancy, via the RCOG antenatally and the BPSU after birth, as well as the International Drug Registry (see below for details). BPSU follow up of HIV exposed uninfected infants will now extend beyond 18 months to at least 5 years of life to assess for longer term affects of ART exposure (personal communication, Pat Tookey).

Antiretroviral Pregnancy Registry (in Europe managed by GlaxoSmithKline) GlaxoSmithKline Ltd, Greenford Rd, Greenford, UB6 0HE Tel no: 020 8966 4500; Fax 0208 966 2338
National Survey of HIV in Pregnancy - Royal College of Obstetricians and Gynaecologists British Paediatric Surveillance of HIV in Children Co-ordinator for both Ms Pat Tookey 0171 829 8686, e-mail p.tookey@ich.ucl.ac.uk

11) Infant feeding

Breastfeeding is an important route of transmission. In the UK, where safe infant feeding alternatives are available, HIV-infected women are advised to refrain from breast feeding. HIV-1 can be detected in breast milk by virus culture, but it is unknown whether infection takes place through cell-free HIV or through HIV infected cells. Cell-free virus could penetrate the mucosal lining of the gastro-intestinal tract of infants by infecting cells, or by direct entry into the blood stream via mucosal breaches. It is unclear whether damage to the intestinal tract of the infant, caused for example by the early introduction of other foods, could increase its permeability and thus result in increased rates of acquisition of infection for the infant.

Where a mother acquires HIV infection after delivery, whilst breastfeeding, the risk of transmission through breastfeeding is about 30% [9]. In established infection, the additional risk of transmission through breastfeeding, over and above the intra-uterine and intra-partum contribution, is estimated to be between 7 and 22% [9]. These estimates agree with

those from prospective studies (in Europe, South Africa and Brazil), and from a randomised trial [138].

If a woman chooses to breast feed despite the evidence, then she should be advised to breastfeed exclusively as this may reduce the risk of transmission [139]. She should be advised to feed for a shorter rather than longer period. If she is taking antiretroviral medication it should be explained that currently there is no evidence that this will protect the infant. Although ART is likely to reduce free virus its effect on cell associated virus in the milk is not known.

12) Pregnancy in women with HIV-2 infection

HIV-2 is endemic in West Africa and other areas of high prevalence include parts of India and Portugal. Thirty two cases of HIV-2 infection had been reported in the UK and 11 of these infections were in women [140]. HIV-2 appears to be less pathogenic than HIV-1 with prolonged periods of asymptomatic infection and slower rates of disease progression reflecting a lower rate of viral replication. [141; 142]. Vertical transmission rates of HIV-2 are also low, 0-4% in breast fed infants, in the absence of any interventions [143-145]. Interventions to reduce transmission of HIV-2 in pregnant women have not been clearly defined. Treatment is indicated in pregnancy if the woman is symptomatic and CD4 cell numbers are <300 per cu mm as this is usually associated with a detectable plasma viral load [146]. Non nucleoside reverse transcriptase inhibitors have little inhibitory activity against HIV-2 and are therefore not recommended but the virus is susceptible to nucleoside reverse transcriptase inhibitors and protease inhibitors. Although currently there is no evidence to support interventions such as caesarean section or ART in women with HIV-2, they should probably be managed in a similar way to HIV-1 infected women with low level viraemia (e.g. AZT with caesarean section). The risk from breast milk is probably lower than for HIV-1 but it may be advisable to avoid this method of feeding. Although quantification of HIV-2 RNA is the preferred method for monitoring disease and responses to treatment no commercial assays are currently available, however, there is one laboratory in the UK which can provide this service (contact Dr Judy Brewer, Royal London Hospital and St Batholomew's). Infants born to infected women can be monitored for HIV-2 DNA PCR and loss of HIV-2 antibodies by 12-18 months of age.

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