

British HIV Association

Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV

31st March 2005

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1) HIV in pregnancy and risk of transmission - Background

The prevalence of HIV infection amongst women giving birth in England and Wales has increased every year since 1990. Results from the Unlinked Anonymous Surveys of HIV infection in pregnancy, show that in 2003, the prevalence reached one in 180 (0.56%) in inner London, one in 271 in outer London (0.37%) and one in 1282 (0.08%) in the rest of England¹. The majority of these women are from Sub-Saharan Africa. The Department of Health policy of recommending an HIV test to every pregnant woman² has resulted in an increase in the proportion of these women who are aware of their diagnosis prior to delivery (more than 80% in London in 2001) and a decrease in the absolute number of infants infected in the UK³.

In untreated women the risk of transmission is related to maternal health, obstetric factors and infant pre-maturity. Overall there is a close linear correlation between maternal viral load and risk of transmission but rare transmissions have been reported even at plasma viraemia less than 400 RNA copies/ml⁴. 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. 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.

There are still relatively few, and often conflicting data, 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 foetus. Newer data are reassuring with

regard to possible teratogenicity of ART but have produced new concerns over maternal and infant toxicity of some drugs or combinations.

The findings of the first RCT, published in 1994, showing that monotherapy with zidovudine (AZT) could reduce transmission from 25.5% to 8.3% in a non breast feeding population⁵ have been supported by numerous observational studies confirming this reduction in clinical practice⁶⁻⁸. More recent data continue to support the efficacy of monotherapy with elective caesarean section for certain women^{9;10}, and there are reassuring data on the risk of resistance¹¹.

As standard treatment for non-pregnant adults is now with at least three antiretrovirals more women are taking combination therapy in pregnancy³, although the evidence for the efficacy of this approach, in reducing mother to child transmission, comes from observational cohorts^{4;12} and from the ACTG316 study of the addition of Nevirapine to standard combination therapy¹³.

More women are now conceiving on ART and whilst it is not possible to produce evidence based guidelines that will address the management of every woman in this situation, sections 6 and 7 cover much of the background data on efficacy and toxicity needed to make decisions in these more complicated scenarios.

The protective role of caesarean section was demonstrated in both a meta-analysis¹⁴ and a RCT reported in 1999^{3;15}, prior to the widespread use of combination therapy in pregnancy. However mounting observational data demonstrating very low levels of transmission in women on therapy with undetectable viral loads who deliver vaginally, have led to changes in the advice on mode of delivery for these women (see sections 8 and 13)¹⁶.

Formula feeding has been advocated for positive women since breast feeding was reported to result in HIV transmission in 14% of at risk infants¹⁷ and this continues to be the BHIVA recommendation. Section 12 of these guidelines

covers this issue in some detail, as it is likely that further information about the risk of breast feeding when mothers are on combination therapy, and have undetectable viral loads, will become available, making guidance in this area more complex in the future.

Women with HIV are at a small increased risk of adverse pregnancy outcomes such as spontaneous abortion, stillbirth and intra-uterine growth retardation¹⁸. Furthermore, an increased risk of premature delivery, which has been reported with combination therapies¹⁹ has important implications for any treatment to reduce vertical transmission.

New sections have been added on pre-conception, fertility, management of CIN in pregnancy and the transmission of hepatitis viruses in women with HIV co-infection.

The Guidelines are based on a review of the literature and presentations at the major conferences. However, as with previous versions, many of the recommendations are based upon an understanding of HIV infection, data from non-pregnant women and expert opinion. Each section has a highlights box. The section on management of specific scenarios contains measures of the level of evidence and grades of recommendation.

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

- Self-insemination of partner's semen is recommended to protect the uninfected male partner of an HIV+ female and is easily performed by the couple
- Fertility assessment is indicated if conception has not occurred after 6-12 months of self-insemination
- Sperm-washing is recommended to protect the uninfected female partner of an HIV+ male, but is expensive, currently only provided by a few centres and patient-funded in over 50% of cases

There are three aspects to consider: interventions that can minimise transmission risk between discordant couples during conception, the management of any fertility issues and the state of health and medication of the infected partner pre-conceptually.

In discordant couples in which the male partner is infected with HIV, assisted conception with either sperm washing or donor insemination is significantly safer than timed unprotected intercourse and should be advised in all cases. In these couples, presuming a stable relationship, HIV transmission risk per act of unprotected intercourse is reported to be between 0.03% and 1%^{14;20}. The risk can be reduced, but not eliminated, by limiting exposure to the fertile period of the female cycle. In the only prospective study of couples actually trying to conceive through this method, 4% of women seroconverted²¹ which presents an unacceptable risk. However, a retrospective study in Spain of 77 discordant couples conceiving in which the infected partner had fully suppressed HIV replication on therapy for at least 6 months, reported no transmissions. The couples were instructed how to limit unprotected intercourse to the fertile period of each cycle²². No data were presented on seroconversion risk in discordant couples that did not conceive and the numbers are too small to comment on transmission rates but the study does reflect common practice. Donor insemination removes the possibility of genetic parenthood from the infected male but eliminates any risk of HIV transmission during conception. Sperm washing has the advantage of allowing genetic parenting and is a procedure

during which live sperm, which do not carry HIV, are separated from HIV contaminated seminal plasma and non-germinal cells by centrifugation before being used in an insemination or IVF procedure²³. The efficacy of the wash is then verified with a post wash HIV assay (e.g. PCR or NASBA) before being used in treatment^{24;25}. The treatment is relatively simple and significantly safer than timed unprotected intercourse, with no reported cases of seroconversion in either female partner or child born in over 3000 cycles of sperm washing combined with intrauterine insemination, IVF or intra-cytoplasmic sperm injection reported in the literature to date^{23;24;26-30}. Couples should have natural cycle insemination unless fertility factors are identified when fertility drugs for superovulation or IVF should be considered. The disadvantage of sperm washing is that the treatment is at present only provided by a limited number of fertility centres in the UK, Europe and Northern America. Until recently in the UK, the majority of cases had to be funded by the patient. National Institute of Clinical Excellence guidelines published February 2004 on fertility recommend sperm washing to be considered in serodiscordant couples³¹. This has led to a significant increase in the number of Primary Care Trusts willing to fund up to 3 cycles of sperm washing treatment on the basis of risk reduction (Gilling-Smith, personal communication). A letter of recommendation by the GU physician to the patient's Health Authority is usually required. Couples should be provided with information and counselling on donor insemination and sperm washing, including advice on how to access such treatment to allow them to make an informed choice.

Discordant couples in which the female partner is infected with HIV should avoid unprotected intercourse and instead be provided with quills, syringes and sterile containers and advised on the use of self-insemination during the fertile time of the cycle. Fertility investigations should be initiated when pregnancy is not achieved after 6 – 12 months of self-insemination, sooner in women over 35 years or those with irregular cycles or a history suggestive of tubal disease²⁵. Concordant couples should also avoid unprotected intercourse and be advised to

consider sperm washing to minimise the risk of transmitting a viral variant to the female partner and future child.

Although the ethics of offering fertility treatment to infected men and in particular women continues to be debated intensively³²⁻³⁶, the increased life expectancy and fall in vertical transmission risk noted over the last decade has prompted fertility centres to review their policy. A recent UK audit indicated that 16% of men and 4% of women attending HIV specialist clinics had enquired about fertility treatment³⁷ and 30% of fertility centres were planning to offer treatment to HIV positive males and 26% to positive females. In couples requiring reproductive assistance in the form of Human Fertilisation and Embryology Authority (HFEA) licensed treatment e.g. IVF, the HFEA Act (1990) requires treatment centres to take into account the state of health of both prospective parents in terms of the welfare of any child arising as a result of treatment. In ideal circumstances one would recommend an undetectable viral load and CD4 count > 400, no AIDS defining illness and, in the case of a positive female, a commitment to comply with interventions during pregnancy and post-natally to minimise vertical transmission risk. The referring HIV physician should be asked to sign the Welfare of the Child form in preference to the GP as he/she is likely to be best informed of ongoing high risk activity and medical issues that might affect long term health and viral transmission risk during pregnancy³⁸.

Assisted reproductive techniques for infertility such as IVF should at present only be offered within a research setting, as little is known of the impact of invasive procedures such as intrauterine insemination, oocyte retrieval and embryo transfer on the risk of vertical transmission³⁹. Centres electing to treat HIV infected patients should have separate laboratory facilities to eliminate the risk of cross contamination to uninfected samples^{25;35}.

Guidelines for the fertility management of HIV discordant couples have been published by the British Fertility Society⁴⁰.

3. Sexual Health of HIV positive pregnant women

- Routinely screen for genito-urinary tract infections at presentation and in the 3rd trimester
- Repeat Treponemal serology in the 3rd trimester

There are few data regarding the prevalence of genital infections in HIV positive women in the United Kingdom⁴¹. At present, the majority of pregnant HIV infected women in the United Kingdom come from, and mostly acquired HIV in, Sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV infected population, can be high⁴². In addition, recent figures from Communicable Disease Surveillance Centre (CDSC) show a small but significant increase in the number of patients of Afro-Caribbean origin testing positive for HIV-1 in the United Kingdom⁴³. The prevalence of genital infections is high in this ethnic group, and should these trends continue, women of Afro-Caribbean origin will form an increasing proportion of the antenatal HIV positive cohort⁴⁴. 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. However, apart from the recommendation that all pregnant women should be screened for HIV, Hepatitis B Virus and syphilis, asymptomatic pregnant women in the UK are not routinely screened for genital infections.

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth^{45 46}. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with mother-to-child transmission (MCT) of HIV and may be inter-linked⁴⁷⁻⁴⁹. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoea* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma urealyticum*^{45;46}. A strong association between BV and premature delivery has been reported^{46;50}. There are data from Malawi which suggest 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 HIV⁵¹. Further work is needed. A large meta-analysis assessing the effects of antibiotic treatment of BV in pregnancy, does not support the routine screening for and treatment of BV in pregnant HIV negative women⁵². However, the available evidence cannot rule out a small benefit in pregnancy outcome associated with the screening and treatment of BV. As the numbers of HIV-1 infected women are relatively small and the risk of screening and treating for BV is small, the potential for increased MTCT of HIV-1 in the presence of BV and the fact that HIV positive pregnant women are recommended to undergo STD screening, it seems reasonable to screen and treat for BV in this high risk group.

It has long been recognised that genital infections, in particular ulcerative diseases, are associated with sexual transmission of HIV^{53;54}. 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^{55;56}. Organisms associated with BV have been shown to stimulate HIV expression *in vitro*^{57;58}. A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis⁵⁹. Viral load in cervico-vaginal specimens has been shown to be correlated with MCT of HIV-1⁶⁰. Genital tract VL will usually mirror the plasma VL⁶¹, but there is increasing evidence of compartmentalisation of HIV-1 between the plasma and genital tract. Genital tract HIV-1 has been detected in women with an undetectable plasma VL^{62;63}, and genetic diversity of virus from the two compartments has been reported⁶⁴. A number of factors may be responsible for this, including, differential drug penetration into body compartments and the presence of genital infections. At present the majority of HIV infected pregnant women in the United Kingdom deliver by pre-labour caesarean section, but increasingly, those women with an undetectable plasma viral load are undergoing a trial of labour. In addition, women planning a pre-labour caesarean section may rupture their membranes prematurely which may result in a vaginal delivery. Thus, an increasing number of fetuses will be exposed to the cervico-vaginal secretions of HIV positive women.

In the absence of randomised controlled trials, but for the reasons outlined above, it would continue to 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. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the UK national guidelines, followed by a test of cure⁶⁵. Partner notification should take place where indicated, to avoid re-infection.

Management of cervical intraepithelial neoplasia (CIN) in pregnancy

An association between cervical intraepithelial neoplasia (CIN), cervical cancer and HIV related immunosuppression has been known for many years. Invasive cervical cancer has been an AIDS defining illness since 1993⁶⁶. HIV is known to cause systemic immune depletion which has been related to the development of CIN⁶⁷⁻⁷⁰ and local immunosuppression which has also been related to the development of CIN⁷¹. The presence of HIV infection allows permissive replication of human papillomavirus (HPV) which tends to behave more aggressively and to be more resistant on a background of HIV disease⁷². There may be an increased risk of rapid progression from CIN to cervical carcinoma⁷³. With highly active antiretroviral therapy (HAART) CIN tends to regress with rising CD4 count and falling viral load^{74;75}.

Cytology should be undertaken in pregnancy as for HIV seronegative women. If an abnormality is detected referral should be made for colposcopy, which can be undertaken irrespective of gestation. If CIN is seen at colposcopy, it is customary to repeat the colposcopy on one or two occasions during the pregnancy to ensure there are no signs of invasive cancer developing. Usually if any abnormality is detected, treatment is deferred until six weeks post-natal, unless invasive cervical cancer is suspected when biopsies will be required. Irrespective of HIV status, it is prudent to do these in the operating theatre, since bleeding may be brisk.

4. Psycho-Social Issues

- The minimum composition of the ante-natal multi-disciplinary team is: HIV specialist, Obstetrician, Specialist Midwife, Paediatrician
- A thorough early assessment of the social circumstances of a newly diagnosed HIV positive pregnant woman is essential
- Consider special, tailored antenatal classes where inappropriate emphasis on breast-feeding and vaginal delivery can be avoided
- All HIV positive pregnant women should be encouraged to disclose their HIV status to their partner but this may be viewed as a process rather than an event
- Testing any other children for HIV is recommended but can often be deferred until after delivery

Antenatal HIV testing of all pregnant women is clearly an extremely effective medical intervention allowing MTCT of HIV to be reduced to low rates. However the intervention has to be completed within a finite time period, the duration of which depends on the stage of pregnancy when the diagnosis is made. HIV diagnosis during pregnancy may be a profoundly shocking and life-changing experience for the newly diagnosed HIV positive woman. There may be a complex mix of emotional, psychosocial, relationship, economic and even legal issues that arise directly out of the HIV diagnosis. The newly diagnosed woman also has a relatively brief time in which she needs to be able to develop trust in her medical carers and attain sufficient medical knowledge of her situation to be able to make appropriate informed decisions that will affect the long term health of herself, her foetus and her male partner. For many pregnant women the psychological impact of an antenatal HIV diagnosis is similar to that of bereavement, with the additional anxiety about the possibility of the HIV being passed on to her child^{76;77}

The prevention of MTCT can only be achieved if the pregnant woman embraces the medical interventions appropriately, and in a number of cases the

psychosocial issues may threaten to impede or obstruct the medical process of reducing MTCT. These issues therefore need to be understood by those providing antenatal HIV care, so that potential problems may be identified and addressed early, and their impact minimised.

The Antenatal HIV team

Antenatal HIV care should be delivered by a multi-disciplinary team (MDT). The members of the team providing care for different HIV positive pregnant women will vary according to the needs of the individual women and her circumstances. The minimum team would comprise: HIV specialist, Obstetrician, Specialist Midwife, Paediatrician and the recommendation of peer and voluntary sector support. Frequently, it may be necessary to involve many others; including patient advocates, social workers, legal advocacy, clinical psychologists, psychiatrists, counsellors, health advisors, CAB (Citizens Advice Bureau) workers, interpreters, the voluntary sector, community midwives, clinical nurse specialists and health visitors⁷⁸. In addition to managing the clinical care of HIV positive women these MDT's are ideally placed to oversee the delivery of antenatal HIV care at a more strategic level, including the uptake and delivery of HIV antenatal testing protocols, training of antenatal staff, clinical governance and strategic development of antenatal HIV services. In settings with relatively few HIV positive pregnant women it is still important to develop robust pathways of care with identified members of an MDT. Regular links, formal or informal, could then also be established with a larger unit to provide advice and support as necessary. Good communication is vital in view of the complexity of the issues involved and care planning should be pro-active and instigated early so that any significant problems can be identified early and addressed in the limited time available. A rapid and thorough early assessment of the social circumstances of a newly diagnosed HIV positive woman is a critical part of this process. The likely nature of the adjustment to the HIV diagnosis and a woman's attitudes to the recommended interventions should also be assessed early. Clear referral pathways to relevant members of the multi-disciplinary team should be

established, ideally to identified individuals in the different specialties. This allows for the individuals of the team to develop the necessary expertise and improves communication and understanding within the team. Patients who initially refuse interventions or default from outpatient follow-up need to be identified and actively followed up with particular care. Efforts should be made to understand the reasons for these problems in order that they can be addressed in a supportive manner by the team, but with some urgency if that is required. The management of these women should be reviewed regularly, ideally in the context of regular team meetings.

Expectations of pregnant women.

These will obviously vary from individual to individual but pregnancy is frequently a time of high expectation, anxiety and concern. Pregnant women may report that their pregnancy is treated as though it is public property and feel closely scrutinised by those around them. They may also carry the burden of expectations of their partner, family and friends. Many of these shared expectations will revolve around 'natural birth' (i.e. vaginal delivery), breastfeeding and the avoidance of all medications during pregnancy. Levels of disclosure of their HIV status to those around them will vary enormously. Some women will not have disclosed their HIV positive status to anyone, including their partners, while others may have disclosed to a few key individuals only⁷⁹.

Many pregnant women engage in antenatal classes, but these generally concentrate on issues such as vaginal delivery and breastfeeding, and they seem to be rarely used by HIV positive women. In centres with sufficient levels of antenatal HIV activity, specially tailored antenatal classes may be worthwhile so that the particular issues around HIV and pregnancy can be discussed in an informed, safe and supportive environment.

Peer support

Peer support by trained peer support workers is an invaluable component of the management of HIV positive pregnant women. Many newly diagnosed HIV

positive pregnant women are initially reluctant to engage with peer support, whether one-to-one or in a group setting. However, the great majority of women who do engage with it find that peer support becomes one of the most highly valued of all the interventions that they undertake. Peer support is an integral component in the process of providing effective antenatal HIV care. It becomes particularly relevant in cases where the women have multiple psychosocial concerns, and fear or reluctance in agreeing to uptake of recommended MTCT interventions⁸⁰.

Peer support is also helpful in addressing issues around their HIV status, and helping to facilitate disclosure of HIV status. Some centres have established antenatal/perinatal support groups for HIV positive pregnant women and these have proved to be very popular and useful for those involved (Innovative Vision Organisation, London, UK– unpublished communication). Dedicated peer support workers can also pick up issues such as problems with adherence to medication. It is important to develop good working relationships with peer support workers so that appropriate training and governance can be maintained.

Disclosure of HIV status to Health Care workers

The importance of informing appropriate health care workers should be emphasized to each HIV positive pregnant woman and encouraged. This includes midwives, GP's, Health Visitors and Paediatricians. The process of in-patient care should be explained clearly so that the women can be helped to inform ward staff explicitly about levels of disclosure to visitors, and to reassure them that they will be treated in the same way as HIV negative women.

Disclosure of HIV status to partners.

Levels of disclosure of newly diagnosed pregnant women about their HIV status to their partners varies from 30 – 75% depending on the setting^{78;81;82}. This issue may cause considerable distress to newly diagnosed women and frequently requires time and support from services, including midwives, doctors, peer

support workers, counsellors and health advisors. Disclosure should be encouraged in all cases but may be viewed as a process that may take some time^{83;84}.

Different strategies may need to be developed to facilitate this process in individual cases. However, the situation in the UK is becoming more complex in the light of recent legal cases leading to criminal prosecutions following HIV transmission. One of the cases is currently under appeal and the legal status of HIV transmission is still uncertain. This is not the place to analyse this issue in detail as the legal framework is still developing. However clinicians are advised to keep up to date with developments in this area⁸⁵. Non-disclosure to a sexual partner, especially in the context of antenatal HIV testing, is important for several reasons. A significant number of the male partners of women testing HIV positive during antenatal testing will be HIV negative at the time of initial diagnosis. Some issues relating to HIV sero-discordant couples are discussed below. There are situations where a newly diagnosed HIV positive woman refuses to disclose to a current sexual partner, or appears to want to delay disclosure indefinitely. This can give rise to very complex professional, ethical, moral and potentially, legal situations. There is a conflict between the duty of confidentiality to the index patient and a duty to prevent harm to others. Breaking confidentiality in order to inform a sexual partner of the index patient's positive HIV status is sanctioned as a 'last resort' by both the WHO, GMC and BMA⁸⁶⁻⁸⁸. However it is not to be taken lightly as it could have the negative impact of deterring others from testing due to fear of forced disclosure and loss of trust by patients in the confidential doctor-patient relationship. This could then undermine the current successful high uptake of antenatal HIV testing. It is important to accurately record discussions and disclosure strategy in difficult cases.

Difficult disclosure cases should be managed by the MDT. This allows consideration of different approaches and a shared responsibility for the process. In practice it is usually possible to achieve disclosure without breaking confidentiality and there are a variety of potential approaches depending on the individual case. The first priority in these cases is to understand why the index

patient refuses to disclose. This may be due to a straightforward fear of HIV combined with a lack of acceptance and an inability to come to terms with their HIV diagnosis. They may fear rejection, violence, homelessness, and be dependent on their partner economically, or for their current legal status as a dependent⁸⁹. They may be more concerned about bringing shame on their family and/or themselves if their diagnosis becomes known more widely. HIV infection is still highly stigmatised in many communities. Index cases may also be concerned that the mere fact that they were diagnosed first means that they will be blamed for the infection by their partners, if they are also found to be HIV positive, regardless of the reality of the situation. These issues can be discussed with the patient and addressed supportively. It is accepted that this process may take some time and it is important that the patient is encouraged to protect their partner from infection while disclosure is being considered⁹⁰.

Simultaneous partner testing during the original antenatal HIV test should be encouraged wherever possible as couples will frequently choose to receive their HIV test results together, providing simultaneous disclosure. The term 'Reverse Discordance' has been used to describe the situation during antenatal HIV testing where the pregnant woman is HIV negative and her male partner is found (simultaneously) to be HIV positive⁷⁸. This knowledge clearly has a variety of benefits, especially giving the fact that acute HIV sero-conversion in pregnancy, or while breastfeeding, is likely to significantly increase the risk of vertical HIV transmission⁹¹. Disclosure of HIV status to a regular male partner in the context of the antenatal HIV testing of pregnant women is important for several reasons: the health of the male partner if he is HIV positive and unaware of his status, the prevention of ongoing HIV transmission, and to ensure that the male partner is aware of the medical and treatment issues concerning the foetus. Many of those initially reluctant to disclose feel relief once they have removed that burden. However, others may experience adverse results as a direct result of disclosure, including domestic violence, rejection and homelessness, and need to be supported through this⁹².

Disclosure of HIV status to others.

Reassurance about confidentiality is extremely important, especially regarding family members and friends who may not know the diagnosis but are intimately involved with the pregnancy. Women from communities with high levels of HIV awareness may be concerned about HIV “Disclosure-by-Association” when discussing certain interventions including: taking medication during pregnancy; having a caesarean section, and avoiding breast feeding. Possible reasons such as the need to “take vitamins”, or having “obstetric complications” and “mastitis” may help the women feel more confident in explaining the need for certain procedures to persistent enquiries⁹³.

HIV Serodiscordance and antenatal HIV testing.

Between 20-80% of newly diagnosed HIV positive pregnant women may have partners who are HIV negative, depending on the setting^{78;81;94}. This has significant long-term implications for the provision of care for these couples beyond the management of the pregnancy alone. It is important to help couples understand some of the possible biological reasons for HIV discordance and the importance of preventing subsequent infection of the negative partner⁹⁵⁻⁹⁸. Condom use should be discussed in detail but it should be recognized that there are relatively high levels of unprotected intercourse between HIV serodiscordant partners. Information concerning post sexual exposure prophylaxis should be discussed with the couples⁹⁹⁻¹⁰³. It is most likely to be appropriate for couples using condoms exclusively, who then have occasional condom “accidents”. However, detailed studies in this setting are lacking¹⁰⁴. (For further information see British Association for Sexual Health and HIV National Guidelines for the use of post exposure prophylaxis for HIV following sexual exposure: www.bashh.org/guidelines/ceguidelines.htm).

Welfare and Immigration.

Many HIV positive women will have issues relating to social support needs

and/or immigration issues. In both cases it is important to identify the issues as early as possible so that women can be referred for appropriate specialist advice and support. Dispersal is an issue that arises and is generally felt to be inappropriate in pregnant women, especially if they are late in pregnancy or are recently delivered¹⁰⁵.

Formula feeding support

Women with very limited funds should have access to supplementary formula feed¹⁰⁶.

HIV testing of existing children

This issue should be raised with all newly diagnosed pregnant women who have other children. The timing of testing may vary depending on the individual situation but the issues should be explored early and a strategy clearly identified and recorded.

Adherence to ART

This is of vital importance for the success of therapy and pregnant women may need extra support and planning in this area, especially if there are practical or psychosocial issues that may impact adversely on adherence. Referral to peer support workers, psychology support and telephone contact may all be considered.

Eligibility for treatment

Legislation concerning eligibility to Free NHS Health Care in the UK is currently changing, both in primary and secondary care. ([Proposals to Exclude Overseas Visitors from Eligibility to Free NHS Primary Medical Services](#)) ([Download Implementing the overseas visitors charging regulations guidance for NHS Trust Hospitals England \(PDF, 227K\)](#)) It is not yet clear how this will affect antenatal care generally (including access to routine antenatal HIV, STS and hepatitis

screening) as well as the antenatal care of identified HIV positive women. Clearly it would be regarded as unethical and undesirable to deny an HIV positive woman in the UK with the treatment and interventions that would preserve her own health as well as protect her child from becoming vertically infected. Indeed a recent unpublished letter from the Department of Health implies that full antenatal care should be given to all pregnant women presenting in the UK irrespective of their immigration status. In the absence of formal guidance it would seem inappropriate to withhold treatment and to deal with each case on a case-by-case basis. Of more concern is the fate of undiagnosed HIV positive pregnant women who are unable to access antenatal care and have their screening tests. These women may present in labour without knowing their HIV status. Rapid (e.g. point-of-care [POCT]) HIV testing in this setting should be encouraged¹⁰⁷. This is an area that is changing so it is necessary that people involved in antenatal HIV care stay up to date with developments. It may be advisable to get advice from colleagues, the GMC, BMA and Medical Defence Organizations in difficult cases. Legal advice can also be sought from organizations such as the THT (www.tht.org.uk)

Referral pathways

Women should be given the opportunity to discuss a care plan in detail and this should include referral pathways as appropriate.

Resistance to intervention

Some women may choose to refuse any intervention during pregnancy or declare their intention to breastfeed the baby against advice. These cases are best dealt with by a team approach. It is important to engage with these women as sensitively as possible as often the reasons for refusal may be obscure initially but will eventually turn out to have relatively straightforward solutions. Common reasons may include fear of accepting their HIV status, religious reasons, fear of

disclosure or partners and other family members, forbidding the woman from embracing interventions. Some women are afraid that treatment will lead to disclosure, either by HIV medications being found in their possession, or 'Disclosure –by-Association' as mentioned earlier. Exploring these issues at length will often lead to solutions that may need to be improvised somewhat to meet the needs of the individual case. In cases where the women still refuses intervention and threatens to breastfeed against advice it may become a child protection issue once the child is born. These cases are rare but would need to be discussed with Social Services pre-delivery so that a strategy can be developed.

Post-natal issues

Postnatal depression is relatively common in the general population and tends to be under-diagnosed. It is certainly a risk in HIV positive women and needs to be actively excluded as a diagnosis, especially where women may already be depressed, isolated, homeless or have economic, psychosocial and/or immigration and legal issues. Dispersal of HIV positive pregnant women, or those recently delivered, may also be a risk factor. Women with, or at risk of, antenatal depression should be assessed early and referred to: psychology/Mental health teams; peer support; 'Surestart' where available or other local projects (not necessarily HIV-related) available for new mothers and their children.

5. Viral Load and Resistance

HIV viral load

- Viral load is an important determinant of transmission
- Quantify HIV plasma load
 - at least every three months and at week 36 in women on established therapy
 - 2 weeks after starting or changing therapy
 - at delivery
- Use a second assay where there are discrepancies between viral load, CD4 count and clinical status

The risk of mother to child transmission correlates with maternal plasma viral load even among women receiving ART¹⁰⁸⁻¹¹⁰. Although the risk is greatest for those pregnant women with high viral loads, transmission can occur even when maternal viral loads are below the lower detection limit of the assay¹¹¹⁻¹¹³. Although there is no evidence for a threshold below which transmission will not occur, low or undetectable maternal viral loads are associated with very low rates of transmission to the infant. Studies have generally demonstrated correlation between viral load in plasma and cervicovaginal secretions^{61;114}, however, viral load may sometimes be higher in the genital tract than the blood and virus may even be shed in this compartment when plasma viral load is undetectable⁶³. Responses to ART and selection of drug resistant variants may differ between plasma and CVS¹¹⁵ and there is evidence of genetic diversity between viral populations in the blood and female genital tract which could account for this^{116;117}.

Consequently, plasma viral load may not always reflect activity of HIV in the genital tract and this could account for those rare cases of transmission in women with low or undetectable plasma viral load. More information is required to determine whether there is a need for monitoring genital tract viral load as part of routine clinical management¹¹².

Plasma viral load should be monitored at least every three months during pregnancy and at approximately 36 weeks gestation (depending on turn around time) in order to inform decisions on mode of delivery and treatment of the infant. Knowing that the viral load at delivery was undetectable will be reassuring to all concerned. A number of commercial assays are available for quantification of HIV-1 RNA, the most widely used in the United Kingdom being the Bayer HIV-1 RNA 3.0 branched chain DNA (bDNA) assay and the Ultrasensitive Roche Monitor RT PCR assay. Although the Bayer bDNA assay generally gives lower HIV RNA copy numbers than the Roche RT PCR (version 1.5) the two assays correlate well¹¹⁸.

Absolute HIV RNA copy number may vary not only with the assay employed but also with biological variation of RNA and specimen handling¹¹⁹. The contribution of these variables to HIV RNA concentrations appears to be of the order of 0.3 to 0.6 log₁₀ copies/ml. In order to ensure reliable and accurate quantification of HIV-1 RNA the same assay should be used to monitor viral load.

In the United Kingdom, 78% of HIV infections among women attending antenatal clinics are with non-B subtypes, 61% being subtype A and 29% subtype C¹²⁰. Accurate quantification of non-B subtypes of HIV-1 is therefore an important requirement for monitoring pregnant women. Mismatches between primers and probes used in some commercial assays and RNA target sequences may occasionally result in falsely low or undetectable viral loads among individuals infected with divergent subtypes¹²¹⁻¹²³. 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.

Antiretroviral drug resistance

- Determine HIV genotype (or phenotype):
 - Pre-therapy (at presentation)
 - If viraemic on established therapy
 - At delivery if on monotherapy
 - 2 – 3 weeks after stopping suppressive therapy

Antiretroviral drug resistance will develop when viral replication continues under the selective pressure of drug exposure, as can occur with sub-optimal treatment, and drug resistance is one of the major factors responsible for treatment failure. Genotypic and phenotypic assays for detection of resistance to antiretroviral drugs are available commercially. Conventional phenotyping assays involve culturing isolates of HIV in the presence of drug and determining the concentration of drug required to inhibit the virus. More rapid recombinant

assays are also available in which reverse transcriptase and protease sequences amplified from plasma RNA are inserted into a laboratory clone in which these genes have been deleted; the recombinant virus then being assayed for drug susceptibility. The most recent development in technology is the 'virtual phenotype'. This provides a quantitative prediction of phenotype from the genotypic sequence using a database containing paired genotypic and phenotypic data. Genotyping assays use PCR amplification of the reverse transcriptase and protease genes followed by automatic sequencing of the viral DNA. The antiretroviral drug resistance profile is obtained by identification of mutations known to be associated with resistance. However, the results generated are complex and expert interpretation is required.

Genotyping tends to be used more widely than phenotyping as it has a faster turnaround, is technically less demanding and is more cost effective. In general, sequence based genotyping assays require at least 1000 HIV RNA copies/ml and samples with low viral loads may not be sequenced successfully. Current commercial assays are based on population sequencing and will not detect minority species representing less than about 20% of the viral population. Such minority drug resistant variants may persist and impact on future treatment options. There is therefore a need for more widespread availability of single genome sequencing assays which are more sensitive than standard genotyping systems¹²⁴. Drug resistant virus quickly reverts to wild type in the absence of drug pressure consequently resistance testing should be conducted on samples obtained while the woman is still on treatment, including use of archived samples.

As with viral load assays, commercial resistance assays have been developed using the B subtype of HIV and non-B subtypes may therefore be amplified and sequenced less efficiently. Although information is more limited on patterns of drug resistance among non B subtypes, particularly among infected pregnant women, it has been demonstrated that the frequency and pattern of mutations

are generally similar to subtype B¹²⁵⁻¹²⁸. 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 has been shown to be higher among non B than subtype B virus¹²⁹. 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 inhibitors¹³⁰. The clinical significance of this, particularly for individuals infected with non-B subtypes of the virus, is unclear.

Transmission of drug resistant virus is well documented, with prevalence rates among newly infected drug naïve individuals, of 10-20% in Europe and North America¹³¹⁻¹³³. Among untreated individuals with chronic infection, prevalence rates are generally lower, reflecting earlier infection or reversion of drug resistant mutants to wild type in the months following transmission. BHIVA guidelines for the management of HIV in adults recommend HIV genotypic testing of all patients at presentation.

With more widespread use of antiretroviral treatment (ART), both before and during pregnancy, there is concern that drug resistance could limit its efficacy in reducing perinatal transmission risk as well as compromising the future treatment options for the woman. More information is now becoming available on development of anti-retroviral drug resistance during pregnancy¹³⁴. Although treatment with zidovudine monotherapy has been recommended during pregnancy since 1994 there has been concern that this may be more likely than combination treatment to lead to the emergence of drug resistant virus. A number of genotypic mutations within the reverse transcriptase gene (codons 41, 67, 70, 210, 215, 219) can occur within a few months of initiating zidovudine monotherapy and mutations at codon 215 are associated with high level resistance. In the ACTG 076 trial the prevalence of any mutations associated

with decreased susceptibility to zidovudine was only 3% and no mutations at codon 215 were detected¹³⁵. Similarly, no mutations were detected among women in the Cote d'Ivoire receiving short course zidovudine monotherapy initiated late in pregnancy¹³⁶. A more recent UK study¹¹ also demonstrated that resistance to zidovudine was uncommon (5%) and restricted only to those women treated before 1998 who had higher baseline viral loads than those treated between 1998 and 2001. Although other studies have demonstrated zidovudine associated resistance mutations in approximately 10-25% of pregnant women, with high level resistance at codon 215 in 6-12%¹³⁷⁻¹⁴⁰, maternal viral loads were generally higher and exposure to zidovudine more extensive than among women in whom prevalence rates were low. The risk of developing zidovudine resistance is therefore likely to be low if monotherapy is restricted to drug naïve asymptomatic women, with low viral loads and good CD4 cell numbers (see section 6).

Genotypic testing is recommended before starting zidovudine monotherapy and at delivery to confirm that the circulating virus has remained wild-type. In contrast to zidovudine, high level resistance to lamivudine can develop rapidly as only a single point mutation in the reverse transcriptase gene at codon 184 (M184V) is required. In a small UK study¹⁴¹ 4 of 5 women (80%) treated with ZDV and 3TC from the second trimester had developed the M184V mutation at the time of delivery or very shortly after. A larger French study¹²⁶, with samples from 132 women, demonstrated 3TC resistance in 52 (39%) when 3TC had been added to ZDV after 32 weeks gestation. There was no evidence of resistance to 3TC when treatment was for less than 4 weeks duration. A US study¹⁴², which tested 207 delivery samples, demonstrated 3TC resistance in 44% of drug experienced women receiving standard combination ART. Factors associated with development of the M184V mutation in all studies included higher viral load, low CD4 cell number and longer duration of therapy.

Rapid emergence of high level resistance to the NNRTI nevirapine can occur due to single point mutations in the reverse transcriptase gene most frequently at codons 103 (K103N) and 181 (Y181C) as well as at codons 106, 108, 188 and

190. The long half-life of nevirapine also contributes to development of resistance. In the Ugandan HIVNET 012 study¹⁴³ drug naïve women received a single dose of NVP at the onset of labour and their infants a single dose within 72 hours of delivery. NVP resistance was detected in 19% (21/111) of women at six weeks post partum and was associated with higher baseline viral loads and lower CD4 cell numbers¹⁴⁴. Detectable resistance appeared to be transient, with these mutations no longer found in plasma 12-24 months postpartum. More recent studies have demonstrated resistance in as many as 40% of women following single dose nevirapine¹⁴⁵. Following single dose nevirapine resistance is more frequently detected in women with subtype C HIV infection compared with subtypes A and D¹⁴⁶. Resistance to NVP can also occur when a single dose is given to women already receiving combination antiretroviral treatment, the prevalence of the K103N mutation being approximately 15%¹⁴². The implications of resistance following single-dose NVP are discussed in section 6.

Genotypic resistant mutations will affect the replicative capacity or fitness of the virus but the significance of this in terms of HIV transmission is still unclear. Transmission of drug resistant virus to the infant can occur¹⁴⁷. Among infected children the prevalence of zidovudine associated resistance mutations, as a result of perinatal transmission, has ranged from 9-17% in some studies^{139;140;148}, and between 30-40% in others^{126;149}. Similarly, nevirapine resistant virus was detected in 11 of 24 (46%) infected infants in the HIVNET 012 study¹⁴⁴. However, mutations were transient and no longer detected 4 to 12 months after delivery. The implications of these mutations and their subsequent 'fading' for the further management of these children is uncertain. Although some studies have indicated that drug resistance is not necessarily associated with an increased risk of perinatal transmission^{135;138;139;148} there is still insufficient information to define clearly the relationship between drug resistant mutants and mother to child transmission.

Any pregnant woman on non-suppressive ART should have a resistance test conducted^{150;151}. Following short-term antiretroviral therapy to prevent mother-to-child transmission (START) a genotypic analysis should be performed early in rebound.

6. Anti-Retroviral Therapy in Pregnancy: Efficacy

- See individual scenarios
- Balance the risk of HIV transmission with the toxicities of therapy
- Zidovudine monotherapy remains a valid option for women:
 - with <6-10,000 HIV RNA copies/ml plasma,
 - wild type virus,
 - not requiring HAART for maternal health,
 - not wishing to take HAART during pregnancy
 - and willing to deliver by PLCS
- Do not prescribe dual NRTI therapy
- Prescribe effective (≥ 3 drug) combination therapy whenever:
 - indicated for maternal health as per adult guidelines
 - baseline maternal viraemia $>10,000$ cps/ml
 - baseline maternal viraemia $<10,000$ cps/ml (as an alternative to ZDV monotherapy plus pre-labour Caesarian section)
 - drug resistance detected on genotype/phenotype
- Short Term HAART (START) for prevention of MtCT should:
 - Be discontinued after delivery when viral load <50 cps/ml
 - Carefully consider the half-life of each component to avoid unplanned monotherapy after stopping, especially drugs with a low genetic barrier to resistance
- Avoid Stavudine plus Didanosine as NRTI backbone when ever possible (and monitor lactate if unavoidable)
- HAART commenced prior to conception should usually be continued throughout pregnancy
- Consider a detailed anomaly ultrasound at 21 weeks for all fetuses exposed to ART during the first trimester

Twenty compounds are currently licensed by the Medicines Control Agency for the specific treatment of HIV-1 infection in the UK. Of these only zidovudine is specifically indicated for use in pregnancy (excluding the first trimester) to prevent mother to child transmission of HIV.

The introduction of recommending HIV testing to all pregnant women and the increasing number of women of child-bearing potential aware of their HIV infection who are on combination therapies and wishing to conceive has led to a significant increase in the number of women needing advice on the management of HIV in pregnancy. Between 2002 and 2003 19% of known HIV+ pregnant women in the UK and Ireland had conceived on combination ART¹⁵². At preconception consultation or some weeks into the first trimester of pregnancy such women 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. The Cochrane Systematic review which was restricted to interventions shown to be effective in randomised controlled trials, concludes that zidovudine monotherapy, nevirapine monotherapy and delivery by elective Caesarian section (PLCS) appear to be very effective in decreasing the risk of transmission¹⁵³. Whilst true this does not reflect current best care. In this section we will summarise key efficacy data from observational and controlled studies (Tables 1a and 1b). Section 13 described various scenarios and weighted recommendations on the use of ART in pregnancy that balance the needs of the mother and infant with the limitations of the available data are presented. The question of efficacy relates to reducing infections in the neonate, maintaining or improving maternal health and preserving maternal therapeutic options. Pre-clinical and clinical safety data can be found in the appendix.

Evidence of efficacy from monotherapy studies

Reduction of Mother to Child Transmission of HIV

Published studies are available for zidovudine, stavudine, didanosine, 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^{5;109;154} and supported by epidemiological surveys^{6-8;155}. The efficacy of zidovudine ranges from 67%, when started before the third trimester administered by iv infusion during labour and given to the neonate for the first 6 weeks of life 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^{156;157}. In a non-breast feeding population the transmission rate with addition of zidovudine has been reduced to 6-8%^{5;8}. 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 log₁₀ reduction in plasma viraemia at the time of delivery^{113;8}. In the Bangkok study zidovudine 300mg twice daily was commenced at week 36 resulting in a 0.57 log₁₀ reduction in plasma viraemia at delivery. This was considered to account for 80% of the efficacy of zidovudine to reduce transmission¹⁰⁹.

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 therefore 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 and probably for any mother with a viral load > 6 - 10,000 copies/ml. *(No transmissions occurred in the recent Thai short course zidovudine plus single dose nevirapine study if maternal viral load was less than 6,000 HIV RNA copies/ml plasma at the time of delivery [Communicated at 11th Conference on Retroviruses and Opportunistic Infections, Feb 8 -11, 2004, San Francisco, CA, USA, LB41] with only 1 transmission out of 387 exposed if maternal baseline HIV RNA copies <25,000 /ml¹⁵⁸).* Pre-labour caesarian section (PLCS) 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 with all levels of viral load, transmission was further reduced to <1 %¹⁵. In a South African randomised open-label study of 362 mother-infant formula-feeding pairs, (A1455-094), didanosine alone was compared with stavudine alone, zidovudine alone and with didanosine combined with stavudine. Although all three ddN arms resulted in greater viral load reductions than zidovudine only the combination arm (4.6%) had equivalent transmission rates to zidovudine monotherapy (5.6%)¹⁵⁹. Trans-placental transfer stavudine is similar to that of zidovudine and lamivudine with equivalent levels found in maternal plasma and cord blood after oral and IV dosing¹⁶⁰. Studies in pigtailed macaques show fetal blood levels of dideoxyinosine to be half the maternal plasma level¹⁶¹. Stavudine and Didanosine appear to accumulate in amniotic fluid^{160;161}.

Protease inhibitors (PIs)

PIs are highly protein bound and placental transfer in humans appears to be 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 log₁₀ and the transmission rate was 9.5% but twelve women discontinued treatment, ten because of elevated liver enzymes (see section 7) ¹⁶².

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 47% with nevirapine after 3 months follow-up¹⁴³. As with short-course (4 weeks) zidovudine in the same setting the transmission

rates at 18 months remain less than expected (15.7% cf 25.8%), the increased protection with nevirapine persisting even though the infants were breast-fed¹⁶³. 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%)¹⁶⁴. The efficacy, low cost and ease of use led to the widespread use of the two-dose nevirapine regimen in resource-restricted settings and its adoption by the World Health Organisation (although these have now changed).

Maternal Health

Monotherapy is used to reduce the risk of mother to child transmission of HIV. Although these and other guidelines do not recommend monotherapy when ART is required for maternal health in two studies a maternal survival benefit was seen following four weeks of zidovudine monotherapy compared with placebo^{165;166}.

Evidence from studies of combination therapy

Prevention of mother to child transmission

Dual nucleoside analogue therapy

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%)¹⁶⁷. In a large French prospective non-randomised cohort study of 440 women treated with initially with zidovudine, with lamivudine added from gestational week 32, maternal plasma HIV viraemia was reduced by 0.95 log₁₀ and the mother-to-child transmission rate was 2.6%. This compares favourably with a historical transmission rate of 6.5% in mothers in the same cohort receiving zidovudine monotherapy¹²⁶. 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 significance¹⁶⁸. Equivalent efficacy between short course stavudine combined with didanosine compared with zidovudine and between zidovudine combined with lamivudine compared with single dose nevirapine was noted above. The current practice, as advocated by the WHO in resource limited settings¹⁶⁹, of adding single dose nevirapine to short course zidovudine (from 34/40), which in practice constitutes serial monotherapy with a short overlap at the time of delivery, reduces transmission to 2% in formula-feeding mothers¹⁵⁸.

Combinations with more than two drugs

In the North American Women and Infants Transmission Study (WITS) cohort there has been 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 inhibitor⁴. In PACTG 367 the transmission rate among 3081 pregnant women delivering in N. America has fallen from 4.2% in 1998 to 0.5% in 2002. Among women who did not receive any ART transmission was 18.5%, falling to 5.1% with zidovudine monotherapy, 1.4% with dual NRTIs and 1.3% with three or more drugs. Of the 1736 women who had plasma viraemia of less than 1000 copies/ml at the time of last measurement prior to delivery the transmission rate was 0.7%. This includes an unspecified number of transmissions when maternal viraemia was less than 50 copies (data communicated at CROI 2004 [but not in the abstract]). 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 therapies⁴. In the ACTG 316 study nevirapine was added at labour to maternal therapy whether it was mono, dual or triple and a further dose was given to the neonate. 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 way¹³

Maternal Health

The development of mutations associated with resistance following monotherapy is considered in section 5 above. There is now evidence that single dose nevirapine does impact on the future response to NNRTI containing regimens. In the Thai PHPT-2 study, NNRTI-Resistance mutations were detected in 30.5% of women 12 days after single-dose nevirapine. Triple therapy with nevirapine, stavudine and lamivudine in a fixed dose combination pill was commenced a mean of 5.8 months later. After six months treatment 86% of women not previously exposed to nevirapine had suppressed viraemia to < 400 HIV RNA copies/ml plasma compared with 68% of women with a history of single dose nevirapine exposure. Using <50 copies/ml as a measure of therapeutic success 75% of nevirapine unexposed mothers had no detectable plasma viraemia at 6 months compared with 34% of mothers who had a history of detectable NNRTI mutation following single dose nevirapine exposure. Further more, mothers exposed to nevirapine in whom NNRTI mutations had not been found post-partum also fared less well than unexposed mothers with only 53% achieving < 50 copies at 6 months¹⁷⁰.

Efavirenz has not been used in this way, but has a plasma half-life that is at least as long as nevirapine and similar problems might be anticipated.

In London women starting triple ART following zidovudine monotherapy were no less likely to have fully suppressed viral replication during 30 months follow up post delivery than women treated with triple combinations during pregnancy¹⁷¹.

Where therapy is not required during pregnancy for maternal health, combinations of three or more drugs to suppress HIV replication may be

prescribed short term to reduce transmission and it is to be hoped to preserve future maternal therapeutic options. However different drug half-lives are being found to impact on combination therapy too. In the UK and elsewhere stopping nevirapine or efavirenz 5 – 7 days prior to nucleoside analogues or switching to a drug with a short clearance time is recommended. Following only a few weeks of drug exposure nevirapine plasma concentrations remain above the IC₅₀ of wild-type virus for up to 10 days with considerable individual variation¹⁷² and even out to 21 days¹⁷⁰ Similar drug persistence has been reported with efavirenz¹⁷³ with evidence of racial differences. This observation is supported by the discovery of higher efavirenz concentrations in patients of black African or Hispanic origin compared with those of white European origin. Different polymorphism frequencies in CYP2B6 at G516 seemingly underlie this association¹⁷⁴. However, nevirapine resistance mutations have been detected by population based sequencing in women post-partum despite full suppression of plasma viraemia, triple therapy and a tailored approach to discontinuing therapy¹⁷⁵.

7. Antiretroviral therapy in Pregnancy – Toxicity

Maternal Toxicity

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.

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 re-absorption 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. In the French cohort most of the adverse events seen in mothers taking zidovudine plus lamivudine were related to pregnancy or post-partum complications of pregnancy¹²⁶. 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 inhibitors¹⁷⁶. 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 γ polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion¹⁷⁷. The relative potency of the nucleoside analogues in inhibiting mitochondrial DNA γ polymerase in vitro is highest with zalcitabine (ddC), followed by didanosine (ddl), stavudine (d4T), lamivudine (3TC), zidovudine (AZT) and abacavir (ABC)¹⁷⁸. 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 combination¹⁷⁹. It is not clear whether the frequency of this recognised complication is higher in pregnant than 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 didanosine plus stavudine in pregnancy should be restricted to woman with resistance or intolerance to other nucleoside analogues and no reasonable alternatives.

Protease Inhibitors (PI)

Hyperglycaemia, new onset diabetes, exacerbation of existing diabetes mellitus and diabetic ketoacidosis have been reported with administration of protease inhibitors^{180;181}. Women taking ART that includes a PI reportedly 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)¹⁸².

In a study of 86 HIV-positive, treatment naïve women, ritonavir monotherapy 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)¹⁶²

The plasma concentrations of saquinavir when prescribed as unboosted soft-gel capsules are generally low¹⁸³ but when either the hard –gel capsules¹⁸⁴ or soft-gel capsules¹⁸⁵ are boosted by co-prescription with ritonavir plasma concentrations appear to be generally therapeutic and the combination well tolerated.

Ritonavir boosted lopinavir also appears well tolerated and clinically effective although a pharmacokinetic study showed significantly reduced drug exposure in pregnancy.(ref Stek A, Mirochnick M, Capparelli E, Best B, Burchett S K, Hu C, Gardella J, Elgie C, Schiffhauer J, Smith E, Read J, Tuomala R for the Pediatric AIDS Clinical Trials Group (PACTG) 1026 Team Reduced lopinavir exposure

during pregnancy: preliminary pharmacokinetic results from PACTG 1026 15th Int AIDS Conf Bangkok 2004)

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. Obstetric 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 pregnancy¹⁸⁶.

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)¹⁸⁷.

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 women developed GI symptoms, which were attributed to, and settled on changing, the nucleoside analogues¹⁸⁸. However a number of hepatitis related deaths have been reported in pregnant women taking regimens that include nevirapine¹⁸⁹. There has also been a change to the Summary of Product Characteristics (13th February 2004) which, along with other changes, now states that 'women and patients with higher CD4 counts are at increased risk of hepatic adverse events, often associated with rash, especially women with pre-treatment CD4 counts greater than 250 cells/mm³'. Although there is no specific mention of pregnancy, pregnant women are perhaps more likely to match this description than non-

pregnant women, especially those choosing short-course therapy. Whether the risk of hepatitis is the same in pregnancy is uncertain. Bershoff-Matcha and colleagues report no serious adverse events among 43 pregnant women compared with 23 among 227 non-pregnant women¹⁹⁰ whereas in PACTG 1022 4 of 17 women discontinued nevirapine due to toxicity compared with 1/21 randomised to nelfinavir. One patient treated with nevirapine, whose baseline ALT was 58 U/L, died of fulminant hepatic failure¹⁹¹. Mooney et al reported 'major' toxicities in 5/56 women (10.5%) taking nevirapine during pregnancy compared to 1 episode of renal calculi among 47 women taking a PI (2%)¹⁹². Natarajan found a relatively low rate (4.7%) of nevirapine complications among 189 pregnant women in London with most occurring when women started therapy with a CD4 count greater than 200 cells/mm³ but not above 250 cells/mm³¹⁹³. This could be explained by the lower CD4 counts seen with haemodilution in pregnancy. In a study of 126 women commencing NVP-based HAART in Thailand 8 (6.3%) developed hepatitis of whom 6 discontinued NVP and 9 (7.1%) developed a rash resulting in the discontinuation NVP in six. No statistically significant difference in frequency of complications was seen in the women commencing NVP based HAART with a CD4 count greater than 250 cells/mm³ (14.5%) compared with those starting at less than 250 (12%) but the treatment time was shorter in the later group who started therapy at 28 weeks of gestation¹⁹⁴. 9.4% of a Thai population (males, pregnant women and non-pregnant women) starting nevirapine as part of triple therapy developed liver or skin toxicities with not significantly higher rates in pregnant women with CD4 counts greater than 250 cells/mm³¹⁹⁵. These conflicting data are likely to be due to difference in populations, small sample size and reporting bias especially if the outcomes for patients starting therapy during pregnancy are mixed with patients continuing therapy during pregnancy. It is interesting that in the Kisumu study in Kenya in which ZDV, 3TC and nevirapine are started at 34 weeks gestation to prevent mother to child transmission in a breast-feeding population 13/155 (8.4%) mothers had to stop NVP with Grade 2 – 4 toxicities, but a CD4 count cut-off of 250 cells/mm³ did not discriminate between susceptibility states¹⁹⁶.

Nevirapine has been widely prescribed and effective in pregnancy. In terms of experience only nelfinavir (as the third drug on a dual NRTI backbone) has been used to a similar degree. There is very little experience with other triple therapies in pregnancy. 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. Prescribing in pregnancy, particularly when initiating therapy, should be with due caution. The pharmacokinetics in pregnancy of newer agents such as abacavir, emtricitabine, tenofovir, atazanavir and fos-amprenavir have not been described. A reduced dose of didanosine is usually prescribed with combined with tenofovir, but there is increased renal excretion of didanosine in pregnancy. Although not considered sufficient to merit dose amendment there are no data on didanosine in pregnancy when prescribed with tenofovir. However, the new European recommendations are that these compounds should not be co-administered, especially in patients with high viral load and low CD4 cell count (Letter to Health Care Professionals from Bristol-Myers Squibb and Gilead 02 March 2005). Total nelfinavir concentrations are commonly lower in pregnancy, dose adjustment may be necessary but studies of the protein-unbound concentration and a correlation of pregnancy PK data with efficacy are required. There is an urgent need for extensive investigation of the pharmacokinetics of antiretroviral therapy in pregnant women to ensure efficacy, reduce toxicity and to prevent the emergence of resistance through inadvertent under dosing. Consider TDM for all new agents and all PIs.

Pregnancy outcome

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 mothers had identifiable risk factors for PTD such as a history of PTD, smoking and substance misuse. HIV transmission had been excluded in the 34 babies with adequate follow-up¹⁹⁷. The possibility that protease inhibitor usage was associated with an increased risk of PTD had been suggested by Swiss

investigators in 1998¹⁷⁶ 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 abnormality¹⁹⁸. An increased rate of preterm delivery has also been reported in women on combination ART with PI's in Europe¹⁹⁹. In the latest analysis of this on-going study, a trend towards more pre-term deliveries (in women not delivering by PLCS) has been shown over time, correlating with increased use of combination therapies²⁰⁰. However this was not seen in a North American cohort²⁰¹ nor on analysis of data submitted voluntarily to the Antiretroviral Pregnancy Register, which mostly includes submissions from N. America. A trend to very low birth weight was however noted in babies exposed to three or more drugs in utero²⁰². Data from the UK and Ireland of 3807 pregnancies reported between 1990 and 2003 13% of deliveries were before 37 weeks with a 1.5 fold increase risk if the mother took HAART during pregnancy compared with zidovudine monotherapy¹⁵².

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 pneumonia prophylaxis combined with ART²⁰³. 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 risk²⁰⁴. An association between gestational diabetes (GD) and protease inhibitor using in pregnancy has also been proposed. In a Spanish cohort of 609 pregnant women with HIV infection the incidence of GD was 7% (higher than expected for the general population). Older age and use of protease inhibitor (OR 2.3 95% CI 1.0 – 5.3) were associated with GD in a multivariate analysis²⁰⁵.

8 Obstetric management of pregnancy and delivery

- In addition to any obstetric considerations PLCS is recommended for:
 - All women taking ZDV monotherapy
 - Women on combination therapy with detectable viraemia
 - Women with HIV/HCV coinfection
- PLCS to prevent MtCT should be planned for 38 weeks
- Elective Vaginal delivery is an option for:
 - Women with no detectable viraemia
- Maternal wishes should be considered
- Avoid invasive monitoring of foetus and artificial rupture of membranes
- Prescribe appropriate peri-operative antibiotics for all CS and immediately should membranes rupture during 1st stage of labour
- Give Corticosteroids for threatened pre-term delivery
- Communication between team members is essential and each delivery (by whatever mode) should be planned.
- Ensure provision of appropriate formulations of neonatal therapy on the delivery/post-natal ward.
- Give the mother a written care plan with contact details for emergency admissions.
- Advise ART for invasive genetic diagnostic tests
- IV zidovudine is NOT usually indicated for mothers not on ZDV or for mothers with <50 HIV RNA copies/ml plasma on HAART

The management of the HIV positive pregnant woman during the delivery of her baby aims to minimise the risk of mother to child transmission (MTCT) while not increasing maternal and neonatal morbidity.

A decision on mode of delivery will involve the mother and her physician in a detailed risk assessment. Discussion will take into account maternal plasma viral load, efficacy data on mode of delivery by pre-labour C-section (Table 2), the use of antiretroviral therapy in pregnancy and very importantly the wishes of the mother.

Viral Load.

Initial studies proposed that a pre labour caesarean section (PLCS) in the presence of intact membranes reduced the risk of vertical transmission. A trans-

Atlantic meta-analysis of 15 prospective cohort studies²⁰⁶ and a randomised controlled study of mode of delivery in Europe¹⁵ both supported the protective effect of PLCS, this effect continued even when ART was used. In the RCT, there was an overall reduction in transmission of 70%, in a cohort of women with all levels of CD4 and disease status. These studies showed however that caesarean sections performed in labour or after membrane rupture was not associated with the same reduction in MTCT. Indeed in a further meta-analysis of the 15 cohorts, the risk of transmission increased approximately 2% for every hour of rupture of the membranes up to 24 hours²⁰⁷. These studies, done before routine viral load testing and combination antiretroviral therapy, showed a consistent reduction in MTCT with a PLCS. Whether this protective effect continues when the maternal HIV 1 RNA is very low or undetectable has yet to be established.

Several studies have looked at MTCT rates according to maternal viral load. In a study of 480 mother child pairs there was no MTCT among 84 women with HIV-1 levels below 500 copies per mm³ at booking or among the 107 women with undetectable levels at delivery²⁰⁸. In a similar study there was no MTCT in 57 women with a viral load of less than 1000 copies per mm³¹⁰⁸. However transmission has been reported when maternal viraemia was not detected^{113;209}. A recent meta-analysis of seven prospective studies from the US and Europe revealed 44 transmissions in 1020 deliveries where plasma viral load was <1000 HIV RNA copies/ml at or around delivery. The rates were lowest for mothers on ART. In multivariate analysis transmission was lower with ART, caesarean section, greater birth weight and higher CD4 count. These data, collected when HIV-RNA PCR assays were less sensitive than currently suggest a protective effect of both ART and caesarean section even at very low viral loads¹¹². Whether caesarean section in the presence of combination ART and undetectable plasma viraemia (<50 HIV RNA copies/ml plasma) continues to offer a protective effect is unknown.

There have been several studies that have suggested that the complications from caesarean section are higher in HIV positive women, with the highest risk in those women undergoing emergency caesarean section. The main complication appears to be post partum fever and this was increased in women with low CD4 counts. However in at least one of these studies, 16% of the women had not been on any antiretroviral therapy, only 82% received “peri-operative” antibiotics (amoxicillin or mezlocillin plus a β -lactamase inhibitor), and the mean CD4:CD8 ratio was 0.49 in the patients who had postoperative complications²¹⁰⁻²¹². Many of these studies were performed before the recommendation that prophylactic antibiotics be prescribed to all women undergoing caesarean section to reduce infectious morbidity²¹³.

A more recent case controlled study from the UK where all the HIV positive women were treated with antiretroviral therapy in pregnancy and all received prophylactic antibiotics showed no difference in the incidence of post operative morbidity²¹⁴. Recent data from Latin America and the Caribbean revealed much lower rates of post-partum morbidity in HIV+ women, the majority of whom (73%) were taking HAART. Following vaginal delivery (265 cases) and pre-labour, pre-rupture of membranes elective Caesarean section (240 cases) the complication rates were 3.4 and 3.3% respectively²¹⁵.

In the standard pregnant population it is recommended that PLCS be performed at 39 weeks to reduce the frequency of transient tachypnoea of the newborn seen in babies delivered by PLCS²¹⁶. However in the HIV positive group of women, for whom delivery by caesarean section has been decided it is suggested that this be performed at 38 weeks to avoid the potential risk of labour or membrane rupture, the frequency of which will necessarily increase toward term.

Mode of delivery must be discussed with the woman and her wishes taken into account. In addition to factors such as the viral load and the use and duration of use of the ART obstetric factors should also be considered. Many units in the UK

now have caesarean section rates of 25%, if there are obstetric factors that make it seem likely that the HIV positive woman has an increased chance of an emergency caesarean section e.g. a large baby with an unengaged head it may be wise to plan a PLCS rather than risk the complications of an emergency caesarean section.

Intrapartum management in the HIV positive parturient is also complicated by the need to avoid fetal blood sampling, invasive fetal monitoring and rupture of the membranes. Scalp laceration has been reported with the ventouse, forceps should be the assisted delivery instrument of choice. The use of IV zidovudine, as per the ACTG076 regimen is not considered essential in women on triple therapy with <50 HIV RNA copies/ml plasma. Data from the French Perinatal Cohort show no additional benefit of intrapartum IV zidovudine if the viral load is less than 1000 HIV RNA copies/ml plasma²¹⁷.

Other pregnancy issues

Prenatal diagnosis.

HIV infected women completing invasive prenatal diagnosis should be counselled in a specialist fetal medicine unit and the best non invasive screening tests available should be employed in the first instance. In those women requiring genetic amniocentesis every effort should be made to avoid inserting the needle through the placenta. Administration of ART to cover the procedure is advised although there are no data on transmission rates with or without ART.

Women who become unwell during pregnancy with signs and symptoms of pre-eclampsia, obstetric cholestasis or other liver dysfunction may have a pregnancy related problem but consideration should be given to the adverse effects of the ART. Studies in UK²¹⁸ and Spain²¹⁹ but not Brazil or South Africa^{220;221} have reported low pre-eclampsia rates in HIV-1 infected women untreated or treated with monotherapy but normal rates when combination therapy is used. Any woman presenting with vomiting and malaise should be investigated for acidosis,

hepatitis and pancreatitis. If there is a lactic acidosis consideration should be given to discontinuing the ART even at this critical time.

Management of nausea and vomiting

Nausea and vomiting is common in early pregnancy. Symptoms occur between weeks 6 and 16 but may continue into the second and third trimester in about 20 % of patients. The incidence of nausea and vomiting may be increased in women taking ART. Most women are able to adjust the timing of their ART to avoid times of nausea. In most cases, the nausea and vomiting can be managed without any intervention. However, in some cases, the women may require anti-emetics to control severe vomiting. If oral preparations cannot be tolerated, injections or suppositories can be used. Anti-histamines such as promethazine and cyclizine have been widely used in pregnancy. There is no conclusive evidence to suggest that therapeutic doses of these drugs are associated with increased risk of congenital abnormalities above the background rate for the population^{222;223}. Prochlorperazine and metoclopramide should be considered as second line agents as there are less data on their use in pregnancy and, they have been associated with extrapyramidal reactions in some young women^{222;224}. There is very little information on the safety of ondansetron in pregnancy. Pyridoxine may be effective in reducing nausea in some cases, however, it is less effective in reducing vomiting. There are limited published data on efficacy and safety to recommend using ginger to control nausea and vomiting.

Hyperemesis gravidarum is a condition defined by intractable vomiting leading to fluid and electrolyte disturbances and nutritional deficiency. Symptoms usually occur during the first month of gestation and remit by the end of the first trimester. Most patients will require hospital admission for fluid, electrolyte and vitamin replacement. Controlled interruption of therapy may be the best option in some cases. There are no known interactions between anti-emetics and anti-retrovirals.

9. Pregnancy in women with HIV-2 infection

- If mother asymptomatic, good CD4 (>300), possibly manage as low viral load HIV-1
- If HIV-2 viral load known to be <50 cps/ml antenatal/peripartum/neonatal intervention may be unnecessary.
- If mother symptomatic, low CD4 (<300) manage as low CD4 HIV-1
- Do not prescribe NNRTIs
- Breast-feeding probably best avoided

HIV-2 is endemic in West Africa and other areas of high prevalence include parts of India and Portugal. Eighty-seven cases of HIV-2 infection had been reported in the UK; 72 diagnosed with HIV-2 infection only and 15 with HIV-1 and HIV-2 co-infection²²⁵. Thirty-nine of the 72 HIV-2 infections are in women. 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^{226;227}. Mother to child transmission rates of HIV-2 are also low, 0-4% in breast fed infants, in the absence of any interventions²²⁸⁻²³⁰. To date, 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 mm³ as this is usually associated with a detectable viraemia²³¹. NNRTIs have little inhibitory activity against HIV-2 and are therefore not recommended but the virus is susceptible to nucleoside reverse transcriptase inhibitors and some protease inhibitors. Decreased in vitro activity has been documented for amprenavir²³² but the clinical significance of polymorphisms in HIV-2 *pol* for other PIs requires clarification²³³. 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). If the mother has a high CD4 (> 300 /mm³) and a consistently undetectable HIV 2 viral load, even these interventions may not be necessary²³⁰ 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. Two laboratories in the UK can provide an HIV-2 viral load service:

Prof Judy Breuer/Tony Oliver
4th Floor Molecular Lab
St Bartholomew's Hospital
Department of Virology
51-53 Bartholomew Close
West Smithfield
London EC1A 7BE
Tel: 0207 601 7359
Fax: 0207 377 7259
Tel Judy Breuer: 0207 377 7141
Email j.breuer@gmul.ac.uk
Tel Tony Oliver: 0207 601 7359
Email tony.oliver@bartsandthelondon.nhs.uk

Prof Richard Tedder/ Dr Jeremy Garson
Department of Virology,
Royal Free & University College London Medical School,
Windeyer Bldg. 46, Cleveland St. London W1T 4JF. UK
Tel: 0207 679 9490 / 9483
Fax: 0207 580 5896
e-mail j.garson@ucl.ac.uk

The laboratory should be contacted first to discuss sample specimens and conditions for transporting.

Infants born to infected women should ideally be monitored for HIV-2 proviral DNA, - , samples should be referred to a specialist laboratory (see above). Determining loss of HIV-2 antibodies by 12-18 months of age is also recommended. In the absence of any studies on treatment of HIV-2 infection in children it is recommended that guidelines for paediatric HIV-1 infection are followed^{234;235}.

10. HIV and Hepatitis virus B and C co-infections

A. Mother to Child Transmission of HCV

- All HIV+ pregnant women should be tested for HCV
- HCV+ HIV+ women should be treated with combination ART
- PLCS should be offered to all co-infected mothers

All women with HIV should be screened for both hepatitis B and C infection.

Women with very low CD4 counts may not produce a serological response to hepatitis C virus (HCV) and molecular assays to detect HCV RNA is advised in this circumstance.

In women who are infected with the hepatitis C virus (HCV) there is a low rate of transmission of HCV from mother to infant and current estimates indicate that up to 6% of women will infect their child²³⁶⁻²³⁸. The timing and route of transmission is unclear and it is not known whether transmission is trans-placental or during delivery. HCV plasma viral load is associated with transmission; women with undetectable viraemia are highly unlikely to transmit. HCV viraemic mothers, (HCV+/HIV-) have an increased transmission rate of up to 10%^{237;239}. Some studies indicate that instrumental delivery may be associated with an increased rate of transmission and one study suggests that delivery by Caesarean section may reduce the rate of transmission^{236;240}. These data arise from relatively small scale, retrospective studies and the findings have not been confirmed. Breast feeding is not thought to increase the risk of infection^{236;238;240-242}.

In women who are HCV and HIV co-infected transmission is increased to up to 15%, with higher rates in those who are HCV viraemia^{237;237;238;241;243}. Pappalardo's meta-analysis shows an increased Odds Ratio for HCV transmission of 2.82 (95% CI 1.78 – 4.45) if the mother is co-infected with HIV²⁴⁴. Effective control of HIV is associated with a reduction in the rate of HCV transmission although the mechanisms of this improvement are unclear^{245;246}. No studies to assess the benefits of surgical, rather than vaginal delivery, have been performed in HIV/HCV co-infected women.

Guidelines on the management of adults with HIV/HCV co-infection per se can be obtained from the BHIVA website.

<http://www.bhiva.org/guidelines/2004/HCV/index.html>

Diagnosis of infected children

In view of the increased risk of HCV infection in children born to women who are co-infected with HIV testing for HCV is recommended for all infants born to dually infected mothers. The optimal timing and nature of the test that should be used is unclear. However transmission of maternal antibodies is almost invariable and therefore antibody testing is unreliable until the infant is 15 -18 months old. Testing for viraemia during the first few months of life may not reliably identify chronically infected children and some studies suggest that a proportion of infants who are originally HCV RNA positive will clear virus without intervention^{236;240}. To identify chronically infected children repeat PCR testing for HCV RNA should be performed during the first year of life. A proportion of infected children do become HCV RNA negative, so both serological and molecular tests are important^{247;248}.

B. Mother-to-child transmission of HBV

- All HIV+ pregnant women should be tested for HBV
- Infants born to women who are HBsAg positive should receive active vaccination
- Infants born to women who are HBsAg positive and HBeAg positive, as well as those with high levels of HBV viraemia should receive additional passive vaccination with HBIg
- ART for pregnant women with HIV/HBV co-infection should include drugs with activity against HRV

Maternal infection with the hepatitis B virus (HBV) is associated with a high incidence of transmission of HBV to their infants. Transmission can be effectively prevented by immunisation of the at-risk infant shortly after birth²⁴⁷ and materno-fetal transmission of HBV has been greatly reduced in developed countries by effective vaccination programs. Materno-fetal transmission of HBV is related to the level of HBV viraemia. In general women who are HBeAg positive have a high incidence of transmission of HBV to their infants (90%) and the risk is reduced in women who are HBeAg negative (40%)²⁴⁹. However women who are HBeAg negative with high level hepatitis B viraemia may have an increased incidence of materno-fetal transmission, although the magnitude of the increased risk and the precise level of viraemia at which the risk becomes significant is not known. Hepatitis B viral DNA quantification is therefore recommended for all HBsAg positive mothers. It is standard practice in the UK to offer active vaccination to all infants born to HBsAg positive mothers and to offer passive vaccination with HBIg to children born to mothers who are HBeAg positive. A Chinese study has demonstrated a reduction in vertical HBV transmission where mothers received either the antiretroviral lamivudine or hyper-immune globulin, compared to no treatment²⁵⁰. Further studies to define the optimal treatment of maternal disease as well as to prevent transmission are required.

HIV may increase the serum HBV DNA levels and it is plausible that co-infection will increase the rate of HBV transmission. To-date no studies have reported an increase in the prevalence of materno-fetal transmission of HBV in HIV/HBV co-infected patients. A single study from Tanzania suggested that co-infection did

not increase the risk of transmission but the study was small and an increase in the rate of transmission cannot be excluded²⁵¹.

Some antiretroviral agents (for example lamivudine and tenofovir) are active against both HBV and HIV and in pregnant women with HIV/HBV co-infection it may be appropriate to consider HAART regimes that include agents active against both HBV and HIV. Guidelines on the management of adults with HIV/HBV co-infection per se can be obtained from the BHIVA website.

<http://www.bhiva.org/guidelines/2004/HBV/index.html>

Diagnosis of HBV infection in children born to HBV positive mothers

Infants born to HBV positive mothers in the UK should receive active HBV vaccination at birth, 1 month, 2 months, and 12 months of age. Infants born to mothers with high risk of infectivity should also receive HB immunoglobulin at birth. At 15-18 months of age infants should be screened for: 1) HBsAg, to confirm they have not been infected and; 2) HBsAb to confirm that they have responded to their vaccination.

11. Management of infants born to HIV infected mothers

- Most infants should be given Zidovudine monotherapy for 4 weeks
- Alternative suitable ART monotherapy may be given if maternal therapy does not include ZDV
- Triple therapy should be considered for PEP for infants born to untreated mothers or mothers with detectable viraemia despite combination therapy

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

metabolism²⁵². Neonatal dosing regimens have been developed for most of the nucleoside analogues, for the NNRTI Nevirapine, and for the PI Nelfinavir. Studies of dosing regimens for other drugs (e.g. Lopinavir/ritonavir and tenofovir) are planned or underway (Table 3). Adequate neonatal blood levels are difficult to achieve with Nelfinavir and there is little experience of other PI's²⁵³⁻²⁵⁵. The only ART available for intravenous (IV) use in sick and / or premature neonates, unable to take oral medication, is ZDV^{256;257}. Reduced oral and IV dosing schedules for premature infants have only been developed for ZDV and these have been recently reviewed with a new lower ZDV dosing regime for premature babies²⁵⁷. A new simplified, dosing regime for neonatal nevirapine use is suggested in these guidelines, pharmacokinetic studies have demonstrated adequate infant plasma levels with this regime²⁵⁸. This regime is based on infant weight rather than surface area, and was used in the study of prophylaxis of breast fed infants once daily, for up to 6 months²⁵⁹. Neonatal metabolism of Nevirapine is induced where there is antenatal in-utero exposure^{260;261}, so if this drug is given to the neonate, when the mother has taken it for more than a three days, then the full dose of 4mg/kg per day should be started at birth, rather than the induction dose (Table 4). In view of the long half-life of nevirapine, if this is used in combination therapy for the infant, it should be stopped two-week before the other drugs to reduce the risk of monotherapy exposure and development of resistance¹⁷².

When to Consider Monotherapy ART for the infant after birth

Where a low transmission risk mother chooses ZDV monotherapy with Caesarean section delivery, then the infant should also receive ZDV monotherapy. Where a mother on triple combination therapy delivers with a viral load of < 50 copies / ml, our current practice is to use 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 and didanosine is avoided. Although in a recent study with a higher neonatal dose of didanosine high plasma levels were found²⁶². Zidovudine should not be given to an infant born to a mother who is receiving stavudine because of the theoretical negative competitive interaction. Development of resistance mutations in women treated with Zidovudine monotherapy is rare in those on short-term treatment, with low viral load and less advanced disease^{11;263}. Transmission of Zidovudine resistant mutants to infants has been reported, but is most common in mothers with: more advanced disease; higher viral loads; and previous and /or longer treatment with ZDV monotherapy^{140;264-266}. Most of these transmissions occurred before the use of combination therapy for such higher risk mothers. Monotherapy with nevirapine either to mother or infant should be avoided because of the high rate of development of resistance even with a single dose to mother and / or infant¹⁴⁴.

When to Consider Combination ART in Neonates

There have been very few studies of combination therapy in neonates and most are of only two drugs. There are no published studies of efficacy of triple therapy in neonates. Dual combination ART to the neonate (AZT+3TC v AZT) had additional benefit over single drug treatment (in historical controls) in terms of reduction of transmission when mothers were also receiving dual ART¹²⁶. A randomised African study which compared short course (1 week) treatment to the infant with either AZT+NVP or NVP also demonstrated superiority of two drugs (see below)²⁶⁷. However, in the randomised African "SAINT" study, no significant difference in transmission rate was demonstrated in short course treatment with either AZT+3TC or NVP after perinatal treatment to the mother¹⁶⁴.

There are three situations where triple combination treatment for neonates should be considered:

- 1) **Post delivery prophylaxis:** where the mother is only found to be HIV infected after delivery (Scenario 6);
- 2) **Unplanned delivery:** e.g. prematurely prior to starting ART; or after a late presentation when details of maternal HIV parameters may not be available (Scenario 7)
- 3) **Persistent maternal viraemia on HAART** (Scenarios 3 and 4)

Two studies have examined the first situation where due to late diagnosis of the mother treatment could only be given to the infant after birth. In a US cohort study a reduced risk of transmission, compared with no intervention, was observed in infants commenced on ZDV monotherapy provided this was started within 48 hours of birth (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%)¹⁵⁵. In a randomised African study of after birth prophylaxis, babies born to mothers presenting at delivery received either single dose nevirapine or single dose nevirapine + a week of ZDV²⁶⁷. At 6-8 weeks after delivery, the overall mother to children transmission rate was 15.3% in 484 babies who received nevirapine+ ZDV and 20.9% in 468 babies who received nevirapine alone (p=0.03). Of the babies who were HIV negative on testing at birth, 34 (7.7%) who received nevirapine+ ZDV and 51 (12.1%) who received nevirapine alone were subsequently infected (p=0.03) – a protective efficacy of 36% for the dual combination.

There have been no randomised studies of combination infant treatment after emergency delivery. Despite this, it is logical to consider it appropriate for neonates, as it is standard of care for any other post-exposure prophylaxis cases, where the level of blood/body fluid exposure is likely to be much less.ref 264

We have used ZDV, 3TC and NVP as combination therapy for infants born to drug naïve women, but for non-naïve mothers other combinations might be required if there is a possibility of resistance, (see above for details on stopping

NVP). Resistance testing should be carried out in the mother in such a situation and on the first positive sample of any infected infant.

Duration of Antiretroviral Treatment for Neonates

In the PACTG 076 study ZDV was administered for 6 weeks after birth and this subsequently became standard of care⁵. However, in a Thai study, where a short course of three days of neonatal treatment was compared to six weeks there was no increased transmission where the mother received ZDV from 28 weeks gestation¹⁵⁴. In the UK, neonates are currently treated for 4-6 weeks but it is of note that current post-exposure-prophylaxis guidelines in other situations suggest treatment for 4 weeks only²⁶⁸.

Side Effects of Treatment

- No evidence of any increase in congenital malformations in humans with first trimester exposure to any antiretroviral therapy (including Efavirenz) to date
- Inadequate data to exclude a teratogenic risk for most individual drugs and for all combinations
- Laboratory evidence of mitochondrial depletion in infants exposed to ART perinatally but clinical importance uncertain.
- Prolonged haematological (but not clinical) effects of ZDV in exposed uninfected infants

Long term

Long term side effects of perinatal exposure to ART can be considered in four main categories: teratogenic; carcinogenic; developmental; mitochondrial, but there may be others not yet recognised²⁶⁹. Teratogenicity is most likely to be a problem with first trimester exposure to ART +/- other drugs. All currently licensed antiretroviral therapies (except efavirenz which has recently been re-classified D) are classified either B or C for use in pregnancy by the FDA (See Tables XXXX). 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, or any specific foetal abnormalities have been identified, but the voluntary reporting rate is disappointingly low. Detailed foetal anomaly scanning at 18-21 weeks is advised after first trimester exposure to any combination of ART. NRTI exposure could theoretically lead to a long-term risk of carcinogenicity, although no increased rate has yet been identified²⁷⁰. So far, no adverse growth or developmental effects of ART exposure have been demonstrated in children^{271;272}. Mitochondrial toxicity after perinatal ART exposure, with two deaths from encephalopathy, was first reported in uninfected infants from the prospectively followed French cohort²⁷³. Deaths have not been identified in other large cohorts²⁷⁴⁻²⁷⁷. However, laboratory analysis of mitochondrial DNA has demonstrated abnormalities in infants born to ART treated mothers, and this is an area of ongoing investigation²⁷⁸. 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, which could potentially be related to mitochondrial dysfunction²⁷². A long-term follow up study of health and development in ART exposed children, by annual parental questionnaire, is underway in the UK²⁷⁹.

Short term

Short term, acute mitochondrial toxicity may rarely present 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 care²⁸⁰. Elevated lactic acid levels have also been found in asymptomatic ART exposed infants²⁸¹. Neonatal anaemia and neutropaenia is reported in infants exposed to NRTI's, this may be worse where there is exposure to combination therapy, or more prolonged treatment¹²⁶. Transfusion is rarely required and most children appear to respond to discontinuation of marrow suppressive therapy. However, a more recent study of over 4,000 infants from the French cohort has

demonstrated that perinatal zidovudine may exert a small but significant, durable negative effect on hematopoiesis up to the age of 18 months²⁸². The mechanism and longer-term significance of this bone marrow suppression is not known. An increased rate of febrile seizures in antiretroviral exposed infants has also been reported from the French perinatal cohort²⁸³. Whether different combinations of ART may be more or less deleterious to the neonate is not known.

In view of the potential metabolic abnormalities reported with antiretroviral therapy neonates exposed to ART should have base line blood tests including: FBC; glucose; U+E; and LFT's; as well as diagnostic HIV PCR tests. It is our practise to repeat these tests with each set of HIV diagnostic samples. Lactate and pH monitoring for mitochondrial toxicity should be undertaken in any symptomatic new born but does not appear to be necessary in otherwise well infants.

Laboratory diagnosis of HIV infection in non-breast fed Infants

- DNA PCR on at least two occasions off therapy
- Using primers known to amplify maternal virus
- Triple therapy in neonates can delay diagnosis of infection
- Document loss of maternal antibody at 18 months

The gold standard test for HIV infection in infancy is HIV DNA PCR on peripheral blood lymphocytes²⁸⁴, although some studies are now demonstrating equal / increased early sensitivity with other amplification methods for viral RNA²⁸⁵. 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 previously been taken as evidence of intra-uterine transmission²⁸⁶. 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 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 RNA PCR / NASBA / HIV culture) should be used^{287;288}. It is recommended to test infants at one day, 6 weeks, and 12 weeks of age. If all these tests are negative and the baby is not being breast-fed, then parents can be informed that the child is not HIV infected. Loss of maternal antibodies is subsequently confirmed at 18 months of age. Evidence from the French perinatal cohort has demonstrated that neonatal ART, especially if more than one drug, can delay the detection of both HIV DNA and RNA in the infant²⁸⁹. For this reason, the second HIV DNA PCR is collected at 6 weeks of age, after 2 weeks off treatment. 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.

A Managed Network for Children with HIV in the UK

Where an infant is found to be HIV infected, an urgent referral to the local specialist clinic should be made so that early commencement of combination ART can be considered. HIV services for children in the UK are now being organised in managed networks, Perinatal HIV care in London is managed within three clinical networks North West, North East and South London. Outside London there is a regional network for perinatal and paediatric HIV with each region linked to one of the three London lead centres. The details of the CHIN Networks and contact details of the paediatricians can be found in the CHINN report at www.bhiva.org/chiva²⁹⁰.

Prophylaxis, Immunisations and Clinical Monitoring

Primary pneumocystis pneumonia (PCP) in infants with HIV remains a disease with a high mortality and morbidity²⁹¹. 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 routinely. However, Co-trimoxazole as PCP prophylaxis should still be prescribed for infants born to mothers at high risk of transmission (see table 4 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, with two negative HIV DNA PCRs after one month of age. Killed OPV is now recommended for all polio vaccination in the UK regardless of HIV exposure. HBV see section 10.

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.

Child Protection

Rarely, pregnant mothers refuse treatment for their own HIV as well as interventions to reduce the risk of transmission to their unborn infant. Where the multi-disciplinary team is unable to influence a mother's views, then a pre-birth planning meeting with social services should be held. The mother should be informed that court permission will be sought at birth to treat the infant for 4 weeks with combination post exposure prophylaxis and in addition breast-feeding will be strongly discouraged.

On a practical note – it has been found that dealing with each aspect of interventions to reduce mother-to-child transmission separately and at the appropriate time has been helpful in some circumstances where for social or religious reasons mothers have been reluctant to accept interventions for the prevention of MTCT.

Reporting and long term follow up

It is the responsibility of clinicians caring for women with HIV and their children to report women prospectively to the UK National study of HIV in Pregnancy and the International Drug Registry antenatally, and infants to the British Paediatric Surveillance Unit (BPSU) after birth (see below for details). Long term follow up of ART exposed infants is being undertaken via the Children exposed to ART (CHART) study²⁷⁹.

National Study of HIV in Pregnancy and Childhood (NSHPC)

This is the UK surveillance system for obstetric and paediatric HIV, based at the Institute of Child Health, London. Diagnosed pregnant women are mainly reported through a parallel reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists. HIV infected children and children born to HIV infected women are mainly reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health. For further information contact the co-ordinator of the NSHPC: Dr Pat Tookey 0207 829 8686, email p.tookey@ich.ucl.ac.uk

Antiretroviral Pregnancy Registry (in Europe managed by

GlaxoSmithKline)

GlaxoSmithKline Ltd, Greenford Rd, Greenford, UB6 0HE

Tel no: 020 8966 4500; Fax 0208 966 2338 www.apregistry.com

12. Infant feeding and HIV transmission during breastfeeding

- Recommend exclusive formula-feeding to all HIV positive mothers

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. If she is taking antiretroviral medication it should be

explained that currently there is no evidence that this will protect the infant²⁹². Although ART is likely to reduce free virus in the plasma its effect on free and cell-associated virus in the milk is not known.

Mechanisms of breastfeeding transmission

The level of HIV RNA in milk has only been studied on a limited number of samples from HIV infected mothers. Generally, RNA viral load in milk appears to be lower than in plasma, and frequently below the detection limit of current assays. In a study in South Africa^{293;294}, RNA viral load was quantified three times in the first 3 months after delivery, in samples taken from both left and right breasts from 145 lactating women. RNA shedding varied between breasts and over time²⁹³. Milk viral load was below the limit of detection of the HIV RNA polymerase chain reaction (PCR) assay (<200 copies/ml) in a substantial proportion of samples, and milk viral load in the first 14 weeks was highly variable and difficult to predict by maternal or infant factors. Low blood CD4 count (<200/ μ L) during pregnancy and raised Na/K ratio (a marker of sub-clinical mastitis) were significantly associated with increased milk RNA viral load at all times, but there were no consistent associations between infant feeding mode (whether exclusive or mixed breastfeeding) and RNA viral load in milk²⁹⁴. Together, the results of these studies indicate the random nature of virus shedding into breast milk.

Sub-clinical mastitis in the mother is hypothesised to increase 'leakiness' in the breast duct cell lining and therefore increase the amount of virus to which an infant is exposed^{294;295}. Intestinal permeability of the young infant has been suggested as a possible site of entry for the virus, but evidence to date is limited^{295;296}; it seems biologically plausible that mixed feeding increases the risk of HIV transmission by making the gut more susceptible through mechanical or inflammatory mechanisms.

Risk of MTCT through breastfeeding

More recent and reliable data, including the results of a randomised clinical trial, confirm the substantial risk of transmission through breastfeeding first highlighted

in the late 1980s and early 1990s. In the randomised clinical trial, in Nairobi, HIV infected pregnant women, none of whom had received antiretroviral prophylaxis during pregnancy, were allocated to either breast (n=212) or artificial (n=213) feeding²⁹⁷. Compliance with assigned feeding modality was 96% in the breastfeeding arm and 70% in the formula arm. Median duration of breastfeeding was 17 months. The cumulative probability of HIV infection at 2 years of age was 36.7% in the breastfeeding arm and 20.5% in the formula feeding arm. The estimated absolute rate of transmission through breastfeeding over two years was thus 16.2%, approximately doubling the overall rate of mother to child transmission (MTCT) to 39% at 2 years of age.

The rates of transmission through breastfeeding inferred from the cumulative rates over age in trials in which a peri-partum intervention to reduce MTCT risk was evaluated, are broadly in line with the results from the randomised trial, with an increase in the estimated percentage of infants infected between 4-6 weeks of age and 18-24 months of 10-14%^{163;164;168;298}. Differences between studies could be due to methodology used to assess rate of transmission²⁹⁹, variation in the duration of breastfeeding between populations, as well as to differences in maternal or other factors possibly associated with increased risk. In particular, there are considerable differences in maternal CD4 cell counts near the time of delivery.

Late postnatal transmission

The risk associated with breastfeeding can best be estimated starting with young infants born to infected mothers who tested negative for HIV early in life, and to follow these children until after they cease breastfeeding to determine their rate of acquisition of HIV infection through breastfeeding.

In a recent meta-analysis, including data from more than 4300 children enrolled in randomised controlled trials of peri-partum interventions in sub-Saharan Africa, early transmission was defined by a positive HIV test before 4 weeks, and late postnatal transmission (LPT) by a negative diagnostic test at or after 4 weeks of age, followed by a subsequent positive test result. The overall rate of

transmission was 24% and of the 993 infected children, the timing of acquisition was early in 314 (31.4%), late in 225 (23.1%) and unknown in 454 (45.4%). The mean duration of breastfeeding was nearly 7 months, and the median 4 months. Results show a continued risk of LPT throughout the breastfeeding period, which was approximately constant over time³⁰⁰. The cumulative probability of acquiring HIV infection after 4 weeks of age was 1.6% at 3 months, 4.2% at 6 months, 7.0% at 12 months and 9.3% (95% CI 3.8-14.8) at 18 months.

Section 13

Interventions to reduce mother-to child transmission of HIV – Clinical Scenarios

Table 5 summarises 8 clinical scenarios, where a different approach to therapy in pregnancy may need to be considered. The issues relating to each scenario are discussed in this section as well as other sections of the text. The classification of levels of evidence and grades of recommendations are summarised in Table 6.

Pre-labour caesarean section at 38 weeks is recommended as the mode of delivery in all scenarios where the most recent viral load is detectable at >50 copies per ml or where the viral load is unknown. Vaginal delivery may be considered for women on stable therapy with an undetectable viral load (<50 copies per ml) prior to delivery as the risk of transmission is very low (<1%). However, it is unclear from currently available data whether caesarean section might lead to any additional benefit in reduction of HIV transmission from this low level. These uncertainties need to be discussed between the patient and the medical and obstetric team in deciding on the individual birth plan.

Scenario 1- where mothers do not yet require treatment for their HIV disease.

Asymptomatic women who do not require antiretroviral treatment for their own health, according to current BHIVA Guidelines (CD4 count is >200 per mm³, any viral load) may be treated with a short-term antiretroviral therapy (START) commencing in the 2nd trimester with standard HAART regimens with the intention to achieve undetectable viral loads of <50 copies per ml prior to delivery. A protease-inhibitor based combination is recommended. PIs have a greater barrier to resistance development than NNRTIs and can be stopped concurrently with the nucleoside backbone. In addition PI pill burden and tolerance is improving with newer formulations and there is a low incidence of

severe short-term side-effects. If non-nucleosides are used, these must be discontinued 1-2 weeks prior to the nucleoside backbone to reduce the likelihood of the emergence of NNRTI resistance (see BHIVA Treatment Guidelines).

An alternative approach, in women who do not require treatment for themselves, and who have a viral load of less than 10000c/ml, is to use AZT monotherapy, combined with an elective caesarean section. The risk of vertical transmission is low, and this reduces antiretroviral exposure to the foetus in pregnancy. Maternal toxicity is reduced and the risk of the development of resistance in the mother, when used at this level of viral load, appears minimal.

Scenarios 2, 3 and 4 - women who required treatment for HIV disease

It is recommended that women with any viral load should be treated with antiretroviral regimens considered appropriated by BHIVA Guidelines for established HIV infection. The pros and cons of these drugs are discussed above.

In treatment naive mothers requiring HIV therapy (scenario 2), consideration should be given to safety and efficacy data available in pregnancy, tolerability and whether treatment is likely to be continued after delivery. There is most experience in pregnancy with zidovudine and lamivudine as the nucleoside backbone, which is therefore usually recommended in combination with either a protease inhibitor or a non-nucleoside drug (see Section 5).

Scenario 3 and 4 – women who conceive on antiretroviral therapy

We now advise that these patients continue their current treatment. Antiretroviral databases do not show an additional risk with this approach and there is also a theoretical concern that viral rebound will occur with this 'structured treatment interruption' which might be associated with a significant CD4 lymphocyte

decline. This may not only jeopardise maternal health but in theory result in reactivation of infections associated with congenital abnormalities - for example CMV. Furthermore many women will not realise or report their pregnant status until well into the period of organogenesis. It is also recommended to continue with efavirenz as there are no human data to suggest an increased risk of neural tube abnormalities. Furthermore switching to nevirapine as an alternative NNRTI may risk additional toxicity in the form of hepatitis or skin rash, particularly if the mother's CD4 count has been increased due to her prior antiretroviral therapy.

If the mother's treatment is failing, then this should be changed appropriately to ensure the lowest possible viral load at the time of delivery. Resistance testing can help to identify the best options. Only exceptionally should antiretroviral therapy be initiated or changed during the 1st trimester. Reasonable exceptions include serious illness for which antiretrovirals are the only recognised therapy.

Scenario 5 – women who present late in pregnancy

With 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 is nevirapine. Protease inhibitors are not preferred because they have limited trans-placental transfer. As always, combination antiretroviral therapy with at least 2 other drugs is recommended to reduce the likelihood of resistance development as has been shown with single-dose nevirapine monotherapy during labour. Zidovudine should preferably be infused I.V., and all treatments should be continued after delivery until the mother's clinical, immunological and virological status has been determined. Consideration should be given to continuing triple therapy until plasma viraemia has become undetectable. Therapy should subsequently be discontinued in the manner recommended in guidelines for non-nucleoside regimens (see BHIVA Guidelines).

Scenario 6– threatened premature delivery

Here, management would depend on optimum obstetric management (for example use of antibiotics and steroids where indicated) along with appropriate antiretroviral therapy to the mother and infant, according to the situation.

Scenario 7 – presentation of women 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 PEP regimens recommendations for high-risk exposure to offer triple-combination therapy for 4 weeks.

Scenario 8 – mother of unknown status presenting (re-presenting) in labour

Attempts must be made to (re) discuss the HIV test and if agreed perform a rapid test to determine the status. Where results are delayed (or unknown) PEP (triple) should be given to the infant according to standard risk assessment procedures²⁶⁸ www.bashh.org – CEG Guidelines reference.

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Table 1. Evidence of the efficacy of antiretroviral therapy to reduce the risk of mother-to-child transmission of HIV infection

A Studies of anti-retroviral therapy to prevent mother-to-child transmission in non-breast feeding populations

Study Name	Countries	Study size	Treatment Components				Age HIV assessed	Transmission Rates %	% Reduction (p)
			Pre-partum (Initial Gestation Week)	Intra-partum (IV/Oral)	Post-Partum (wks)				
ACTG 076/ ANRS 024 ⁵	France USA	402	14 – 34 Zidovudine 100mg 5 x daily	IV Zidovudine	6 Zidovudine	18 months (antibody)	22.6 placebo 7.6 ZDV	66.3 % (0.00006)	
Bangkok Trial ¹⁰⁹	Thailand	392	36 Zidovudine 300mg bd	Oral Zidovudine	Nil	6 months DNA PCR	18.9 placebo 9.4 ZDV	50% (0.006)	
PHPT ¹⁵⁴ Long/Long arm	Thailand	1437	Zidovudine 300mg bd 28	Zidovudine Oral	Zidovudine 6	180 days DNA PCR	6.7	57.6% cf short/short interim (0.004)	
Short/Long arm			35	Oral	6		5.7		
Long/Short arm			28	Oral	3 days		8.4		
Short/Short arm			35	Oral	3 days		10.6 *discontinued		
AI455-094 ³⁰¹	Soweto	197	34 – 36	Zidovudine 300mg bd	6 weeks Zidovudine Stavudine	6 weeks DNA PCR	6.3 4.2	Equivalence between ZDV and D4T combined with	

			Stavudine 40mg bd Didanosine 200mg bd D4T & DDI	Didanosine D4T & DDI	Didanosine D4T & DDI		1.9 2.0	DDI
PMCT-2 ¹⁵⁸	Thailand	1844	28 wk Zidovudine	Oral ZDV SD NVP SD NVP Placebo	1 wk ZDV SD NVP v placebo		1.9 2.8 6.5	

B Studies of anti-retroviral therapy to prevent mother-to-child transmission in breast feeding populations

Study Name	Countries	Study size	Treatment Components			Age HIV assessed	Transmission Rates %	% Reduction (p)
			Pre-partum (Initial Gestation Week)	Intra-partum (IV/Oral)	Post-Partum (wks)			
RetroCl ¹⁵⁶	Côte D'Ivoire	280	36 Zidovudine 300mg bd	Oral	Nil	DNA PCR	Placebo v ZDV	
						3 months 6 months 12 months 18 months 24 months	26.1 v 16.5 26.1 v 16.9 28.5 v 18.5 30.1 v 21.6 30.1 v 22.1	37 % (0.07) 35% 35% 28% 27% (<0.5)
DITRAME ³⁰²	Burkina Faso, Côte d'Ivoire	431	36 Zidovudine 300mg bd	Oral	1 week maternal	6 months 15 months	27.5 v 18 30.6 v 21.5	35% 30%

PETRA ³⁰³	RSA, Tanzania Uganda	1802	36 Zidovudine 300mg bd Lamivudine 150mg bd	Oral	Yes	6 weeks 18 months	17.2 v 8.6 26.6 v 20.7	50% 22%	(0.001) (0.07)
			Nil	Oral	Yes	6 weeks 18 months	17.2 v 10.8 26.6 v 24.4	37% 8%	(0.02) (0.5)
			Nil	Oral	Nil	6 weeks 18 months	17.2 v 17.7 26.6 v 25.7	- 3% 3%	(0.8) (0.8)
HIVNET 012 ³⁰⁴	Uganda	626	Nil	Zidovudine 300mg stat + 3hrly v Nevirapine 200mg stat	Zidovudine 7 days v Nevirapine stat 48 <72 hrs	6-8 weeks 12 months	ZDV v NVP 20.0 v 11.8 24.1 v 15.7	41% (0.006) 35%	
SAINT ¹⁶⁴	RSA	1307	Nil	Oral ZDV + 3TC v NVP	One week	8 weeks	ZDV+3TC v NVP 10.8 v 14	Equivalence	

Table 2

Evidence of the efficacy of pre-labour caesarean section to reduce the risk of mother-to-child transmission of HIV

	Transmission Rate %		OR (95% CI)	Transmission Rate %		OR (95% CI)	Transmission Rate %		OR (95% CI)
	PLCS	SVD & other MOD		PLCS & AZT *	SVD, other MOD & AZT*		PLCS & advanced maternal disease **	SVD, other MOD & advanced maternal disease**	
Relative efficacy of PLCS									
Meta-analysis 15 cohorts pre 1997 US & Europe N = 8533 ²⁰⁶	8.4 (72/857)	16.7 (1280/7676)	0.43 (0.33-0.56)	2 (4/196)	7.3 (92/1255)	0.13 (0.09-0.19)	13 (18/138)	21.4 (206/963)	Not given
European Mode of Delivery study ECLS at 38 weeks ¹⁵	1.8 (3/170)	10.5 (21/200)	0.2 (0.1-0.6)	0.8 (1/119)	4.3 (5/117)	0.2 (0-1.7)	0 (0/16)	14.3 (2/14)	NS

1993-98 N = 436	Actual CS (ELCS +EMCS)	Actual SVD	OR (95% CI)	Actual CS +AZT (ELCS +EMCS)	Actual SVD + AZT	OR (95% CI)	Actual CS + CD4 <200 (ELCS +EMCS)	Actual SVD + CD4 <200
	3.4 (7/203)	10.2 (17/167)	0.4 (0.2-0.9)	2.1 (3/144)	3.3 (3/92)	0.6 (0.1-3.2)	0 (0/20)	20 (2/10)
								NS

PLCS Pre-labour caesarian section, SVD spontaneous vaginal delivery, MOD mode of delivery

* Full 076 protocol with antepartum, intrapartum, and postpartum AZT.

** advanced maternal disease – an AIDS diagnosis and / or CD4 < 200 / < 14%

NS not significant by Fisher's exact test

Table 3: Antiretroviral Studies in Infants with Doses and Combinations. (* change of dose from previous BHIVA guidelines)

Drug	Dose	Mono/Combo	Study	New dose	Comments / Side effects
Zidovudine (AZT / ZDV) (Retrovir)	Oral <u>Term (> 34 wks)</u> 4mg/kg BD 2mg/kg QDS <u>Prem (30 - 34 wks)</u> 2mg/kg BD for 2 weeks then 2mg/kg TDS for 2 weeks. <u>Prem (<30wks)</u> 2mg/kg BD for 4 weeks Intravenous <u>Term</u> 1.5mg/kg QDS <u>Prem</u> 1.5mg/kg BD	Combo (+ 3TC) Mono Mono Mono Mono Mono	Moodley 2001 Boucher 1993 Capparelli 2003 Capparelli 2003 Boucher 1993 Capparelli 2003	* new * new * new	Anaemia, neutropaenia, more common with combination therapy in mother and infant. In French Study of AZT+3TC small proportion of infants either required transfusions or early stop of therapy AZT and D4T should not be administered together in view of theoretical risk of negative interaction
Lamivudine (3TC) (Epivir)	2mg/kg BD	Combo (all with ZDV)	Moodley 2001 Mandelbrot 2001 Moodley 2003		Anaemia, neutropaenia (but less common than with ZDV), more common with combination therapy in mother and infant.
Didanosine (DDI) (Videx)	60mg/m ² BD 100mg/m ² OD	Mono Combo (with D4T + NEL)	Wang et al, 1999 Rongkavilit, 2001	* new * new	Difficult to separate dosing from feeding, and DDI much better absorbed on an empty stomach. May cause GI symptoms. Variable absorption in neonate
Stavudine (D4T) (Zerit)	1mg/kg BD	Combo (with DDI + NEL)	Rongkavilit, 2001		AZT and D4T should not be administered together in view of theoretical risk of negative interaction
Abacavir (ABAC) (Ziagen)	2mg/kg BD	Mono	Johnson, 2000		Hypersensitivity reaction not been noted in infants (only small numbers treated)
Nevirapine (NVP / NEV) (Viramune)	Daily Dosing Regime 200mg to mother in labour, then 2mg/kg OD for 1 st week, then 4 mg/kg OD for 2 nd week (see table 4)	Mono	Shetty JAclimmDsynd 2003	* new	<u>Daily Dosing Regime</u> from HIVNET 023 (breast feeding prophylaxis study).
	Single Dose Regime	Mono	Guay, 1999		Single Dose Regime should be avoided as high risk of development of resistance in mother and

	200mg to mother in labour, then one 2mg/kg dose at 48-72 hrs from birth	50-75mg/kg BD 15 /30/45mg/kg BD 90 mg/kg/day (total dose)	Combo (with ZDV+3TC) Combo (with DDI+D4T) Combo (with DDI+D4T)	NICHD/HPTN 040/P1043 Bryson, 2000 Rongkavilit, 2002 Faye, 2002	* new	infant Ongoing, RCT of different regimens for PEP for infants born to mothers with antenatally untreated HIV In this study, insufficient dosing at all 3 doses If considering Nelfinavir use 75mg/kg BD (PENTA 7). PENTA 7 Study in HIV pos young infants, highly variable PK, with poor viral suppression May cause rash, bone marrow suppression. Give to infants born to mothers with a higher risk of transmission
Co-trimoxazole (septrin)	900mg/ m ² OD Mon/Wed/Fri <6 months 120mg OD Mon/Wed/Fri 6-12 months 240mg OD Mon/Wed/Fri	PCP prophylaxis	Simmonds, 1995			

Table 4: Suggested treatment for newborn infants as PEP for HIV

Scenario	Infant Treatment	Duration	Comments / Suggested doses
Mother on ZDV monotherapy + PLCS+IV ZDV in labour	Monotherapy ZDV	4 weeks	Well term infant, ZDV 4mg/kg BD (see table 3 for prem / sick infant doses)
Mother on combination ART VL<50: Combination contains ZDV Combination does not contain ZDV	Monotherapy ZDV Use the NRTI with most experience in mother's regime: 3TC>D4T>ABAC>DDI	4 weeks 4 weeks	Well term infant, ZDV 4mg/kg BD (see table 3 for prem / sick infant doses) May use ZDV , if no history of maternal resistance, or mother not on D4T . 3TC 2mg/kg BD; D4T 1mg/kg BD; ABAC 2mg/kg BD; DDI 100mg/m ² OD. If possible, avoid DDI due to feeding restriction
Mother presents with non-suppressed HIV and no previous ART exposure (e.g. premature labour / ROM; presentation at term with no ART etc)	Combination Therapy ZDV+3TC+NVP	4 weeks	Well term infant, ZDV 4mg/kg BD (see table 3 for prem / sick infant doses) + 3TC 2mg/kg BD + NVP 2mg/kg OD 1 st week and NVP 4mg/kg OD 2 nd week (use NVP 4mg/kg OD for 2 weeks if the mother has received > 3days NVP). Stop NVP after two weeks, in view of long half-life. Continue other NRTI's for full 4 weeks.
Mother presents with non-suppressed HIV and previous ART exposure (e.g. premature labour / ROM; presentation at term)	Combination Therapy Seek expert advice	4 weeks	Will require to tailor therapy according to maternal resistance pattern / ART exposure
Maternal HIV diagnosis ascertained after delivery (no previous ART)	Combination Therapy ZDV+3TC+NVP, start as soon as possible after delivery, but if presents after 48-72 hours maybe too late for PEP, unless mother is breast feeding.	4 weeks	Well term infant, ZDV 4mg/kg BD (see table 3 for prem / sick infant doses) + 3TC 2mg/kg BD + NVP 2mg/kg OD 1 st week and NVP 4mg/kg OD 2 nd week (use NVP 4mg/kg OD for 2 weeks if the mother has received > 3days NVP). Stop NVP after two weeks, in view of long half-life. Continue other NRTI's for full 4 weeks.
Mother with history of multiple ART exposure and resistance	Seek expert advice	4 weeks	Will require to tailor therapy according to maternal resistance pattern / ART exposure

Table 5 Clinical Scenarios

Scenario	Viral Load at Presentation	Antepartum Antiretroviral	Viral Load at 36/40	Mode of Delivery and Intrapartum Antiretrovirals	Postpartum to Child	Postpartum to Mother	Level of Evidence & Grade of Recommendation
<p>1a</p> <p>Mother does not need HAART according to BHIVA Guidelines.</p> <p>< 32/40 gestation</p> <p>Naive</p>	<p><10,000 copies per ml</p>	<p>AZT monotherapy starting between 20 - 32/40</p> <p>or</p>	<p>Unlikely to be <50 copies per ml</p>	<p>PLCS at 38/40 + I.V. AZT</p> <p>or</p>	<p>AZT for 4 weeks</p>	<p>Stop</p>	<p>1b</p> <p>A</p>
		<p>START (PI based) commencing between 20 - 32/40</p>	<p><50 copies per ml</p>	<p>PLCS at 38/40 + oral HAART or SVD + oral HAART</p>	<p>AZT for 4 weeks</p>	<p>Stop</p>	<p>III</p> <p>B</p>
			<p>>50 copies per ml</p>	<p>See Scenario 4</p>	<p>See Scenario 4</p>	<p>Stop when undetectable</p>	

1b	>10,000 copies per ml	START (PI based) commencing between 20 - 32/40	<50 copies per ml	PLCS at 38/40 + oral HAART or SVD + oral HAART	AZT for 4 weeks	Stop	III B
			>50 copies per ml	See Scenario 4	See Scenario 4	Stop when undetectable	
2	Mother needs HAART according to BHIVA Guidelines. < 32/40 gestation Naive	Any	<50 copies per ml	PLCS at 38/40 + oral HAART or SVD + oral HAART	AZT for 4 weeks (or other monotherapy component of HAART regimen)	Continue	III B
			>50 copies per ml	See Scenario 4	See Scenario 4		

3a		<50 copies per ml	Continue	<50 copies per ml	PLCS at 38/40 + oral HAART or SVD + oral HAART	Monotherapy component of Mother's HAART for 4/52		III B
3b	Mother presents on HAART	>50 copies per ml	Genotype and change to best option (expert advice)	<50 copies per ml			Continue	IV C
4	On HAART or START + viral load >50 copies per ml at 36/40	N/A	Genotype and change to best option if possible (expert advice)	>50 copies per ml	See Scenario 4	See Scenario 4		IV C
5	Late presentation before onset of labour	Any	Commence HAART	<50 copies	Scenario 2	AZT 4/52	If on START – discontinue If on HAART – continue	IV C

	>32/40 Naive			>50 copies per ml or no result	PLCS at 38/40 + oral HAART	Scenario 4	suggests mother needs HAART – continue	
6	Threatened unplanned delivery				Start Antibiotics early if ROM			IV
6a	Mother drug naive	>50 copies per ml	Commence Combivir + NVP NVP if CD4 <250		Optimum obstetric management	CBV/NVP But seek expert advice	If baseline CD4 suggests mother needs HAART – Continue	C
6b	Mother on HAART	>50 copies per ml	Expert advice Add NVP and optimise HAART		Optimum obstetric management	Seek expert advice	Continue HAART but ensure cover NNRTI	
6c	Mother on HAART	<50 copies per ml	Continue prescription		Optimum obstetric management	(monotherapy component of mother's regimen) for 4 weeks		

7	Mother diagnosed after delivery	Any	N/A	N/A	N/A	Combination PEP for 4	Manage as non-pregnant	IV C
8	Presentation in labour. HIV status unknown. Point of care HIV Test Unconfirmed HIV+ Treatment Naïve	Unknown	Combivir/ Nevirapine	N/A	Active management of labour Antibiotics stat if ROM Emerg CS if not about to deliver	Combination PEP for 4 weeks	As per BHIVA Guidelines for established infection if mother HIV positive. Cover NNRTI stop if CD4 >250	IV C

Table 6 Classification of levels of evidence and grades of recommendations**Classification of Evidence Levels**

- Ia Evidence obtained from meta-analysis of randomised clinical trials
- Ib Evidence obtained from at least one randomised clinical trial
- IIa Evidence obtained from at least one well-designed controlled study without randomisation
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Classification of Grades of Recommendations

- A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (*Evidence levels I*)
- B Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (*Evidence levels II and III*)
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (*Evidence level IV*)