2005

Guidelines for the Management of HIV Infection in Pregnant Women and the Prevention of Mother-to-Child Transmission of HIV

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Published in *HIV Medicine* (2005) 6 (Supplement 2): 107-148.

Guidelines for the Management of HIV Infection in Pregnant Women and the Prevention of Mother-to-Child Transmission of HIV

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1.0 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 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 1,282 (0.08%) in the rest of England [1]. The majority of these women are from sub-Saharan Africa. The Department of Health policy of recommending an HIV test to every pregnant woman [2] 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 UK [3].

In untreated women the risk of transmission is related to maternal health, obstetric factors and infant prematurity. Overall there is a close linear correlation between maternal viral load and risk of transmission but rare transmissions have been reported even at plasma viremia less than 400 RNA copies/mL [4]. 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 labor 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 fetus. 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 HIV combinations.

The findings of the first RCT, published in 1994, showing that monotherapy with zidovudine (LDV) could reduce transmission from 25.5% to 8.3% in a non-breastfeeding population [5] have been supported by numerous observational studies confirming this reduction in clinical practice [6–8]. 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 resistance [11].

As standard treatment for non-pregnant adults is now with at least three antiretrovirals, more women are taking combination therapy in pregnancy [3], although the evidence for the efficacy of this approach, in reducing mother-to-child transmission (MCT), comes from observational cohorts [4,10] and from the ACTG316 study of the addition of nevirapine to standard combination therapy [12].

More women are now conceiving on antiretroviral therapy (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-analysis [13] and a RCT reported in 1999 [3,14], 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 Sec-

tions 8 and 13) [15].

Formula feeding has been advocated for positive women since breast-feeding was reported to result in HIV transmission in 14% of at risk infants [16] 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, still-birth and intrauterine growth retardation [17]. Furthermore, an increased risk of premature delivery, which has been reported with combination therapies [18] has important implications for any treatment to reduce vertical transmission.

New sections have been added on preconception, fertility, management of CIN in pregnancy and the transmission of hepatitis viruses in women with HIV coinfection.

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 nonpregnant 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.

2.0 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-positive 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-positive male, but is expensive, currently only provided by a few centers and patient-funded in over 50% of cases.

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

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% [13,19]. 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 seroconverted [20] 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 cycle [21]. 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 procedure [22]. The efficacy of the wash is then verified with a post-wash HIV assay [*e.g.* polymerase chain reaction (PCR) or NASBA] before being used in treatment [23,24]. 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 3,000 cycles of sperm washing combined with intrauterine insemination, IVF or intracytoplasmic sperm injection reported in the literature to date [22,23,25–29]. 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 centers 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 in February 2004 on fertility recommend sperm washing to be considered in serodiscordant couples [30]. This has led to a significant increase in the number of Primary Care Trusts willing to fund up to three 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 disease [24]. Concordant couples should also avoid unprotected intercourse and be advised to consider sperm washing to minimize 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 intensively [31–35], the increased life expectancy and fall in vertical transmission risk noted over the last decade has prompted fertility centers 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 treatment [36] and 30% of fertility centers were planning to offer treatment to HIV-positive males and 26% to positive females. In couples requiring reproductive assistance in the form of Human Fertilization and Embryology Authority (HFEA) licensed treatment, *e.g.* IVF, the HFEA Act (1990) requires treatment centers 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 4,400, no AIDS defining illness and, in the case of a positive female, a commitment to comply with interventions during pregnancy and postnatally to minimize 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 pregnancy [37].

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 transmission [38]. Centers electing to treat HIV-infected patients should have separate laboratory facilities to eliminate the risk of cross contamination to uninfected samples [24,34].

Guidelines for the fertility management of HIV discordant couples have been published by the British Fertility Society [39].

3.0 Sexual health of HIV-positive pregnant women

- Routinely screen for genito-urinary tract infections at presentation and in the third trimester.
- Repeat treponemal serology in the third trimester.

There are few data regarding the prevalence of genital infections in HIV-positive women in the UK [40]. At present, the majority of pregnant HIV-infected women in the UK come from, and mostly acquired HIV in, sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV-infected population, can be high [41]. In addition, recent figures from the 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 UK [42]. 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 cohort [43]. 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 [44,45]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with MCT of HIV and may be interlinked [46–48]. Although both *Chlamydia trachomatis* and *Neisseria gonorrhea* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma urealyticum* [44,45]. A strong association between BV and premature delivery has been reported [45,49]. There are data from Malawi that suggest that BV may be associated with an increased risk of maternal HIV infection in pregnancy as well as premature delivery and MCT of HIV [50]. 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 women [51]. 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 MCT 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 recognized that genital infections, in particular ulcerative diseases, are associated with sexual transmission of HIV [52,53]. 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 [54,55]. Organisms associated with BV have been shown to stimulate HIV expression *in vitro* [56,57]. A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis [58]. Viral load in cervico-vaginal specimens has been shown to be correlated with MCT of HIV-1 [59]. Genital tract VL will usually mirror the plasma VL [60], but there is increasing evidence of compartmentalization of HIV-1 between the plasma and genital tract. Genital tract HIV-1 has been detected in women with an undetectable plasma VL [61,62], and genetic diversity of virus from the two compartments has been reported [63]. 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 UK deliver by pre-labor Caesarean section, but increasingly those women with an undetectable plasma viral load are undergoing a trial of labor. In addition, women planning a pre-labor 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 randomized 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 cure [64]. Partner notification should take place where indicated, to avoid re-infection.

3.1 Management of cervical intraepithelial neoplasia (CIN) in pregnancy

An association between CIN, cervical cancer and HIV-related immunosuppression has been known for many years. Invasive cervical cancer has been an AIDS defining illness since 1993 [65]. HIV is known to cause systemic immune depletion which has been related to the development of CIN [66–69] and local immunosuppression, which has also been related to the development of CIN [70]. 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 disease [71]. There may be an increased risk of rapid progression from CIN to cervical carcinoma [72].

With highly active antiretroviral therapy (HAART) CIN tends to regress with rising CD4 count and falling viral load [73,74].

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 6 weeks postnatal, 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.

4.0 Psycho-social issues

- 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 MCT 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 fetus 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 [75,76].

The prevention of MCT 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 MCT. 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 minimized.

4.1 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 an HIV specialist, an obstetrician, a specialist midwife, a pediatrician 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 visitors [77]. In addition to managing the clinical care of HIV-positive women these MDTs 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 multidisciplinary 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.

4.2 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 scrutinized 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), breast-feeding 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 only [78].

Many pregnant women engage in antenatal classes, but these generally concentrate on issues such as vaginal delivery and breast-feeding, and they seem to be rarely used by HIV-positive women. In centers 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.

4.3 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 MCT interventions [79].

Peer support is also helpful in addressing issues around their HIV status, and helping to facilitate disclosure of HIV status. Some centers 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 Organization, 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.

4.4 Disclosure of HIV status to healthcare workers

The importance of informing appropriate healthcare workers should be emphasized to each HIV-positive pregnant woman and encouraged. This includes midwives, GPs, health visitors and pediatricians. 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.

4.5 Disclosure of HIV status to partners

Levels of disclosure of newly diagnosed pregnant women about their HIV status to their partners varies from 30% to 75% depending on the setting [77,80,81]. 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 [82,83].

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 area [84]. 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 serodiscordant 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 BMA [85–87]. 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 dependent [88]. 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 stigmatized 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 considered [89].

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-positive [77]. This knowledge clearly has a variety of benefits, especially giving the fact that acute HIV sero-conversion in pregnancy, or while breast-feeding, is likely to significantly increase the risk of vertical HIV transmission [90]. 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 fetus. 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 this [91].

4.6 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 enquiries [92].

4.7 HIV serodiscordance and antenatal HIV testing

Between 20% and 80% of newly diagnosed HIV-positive pregnant women may have partners who are HIV-negative, depending on the setting [77,80,93]. 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 partner [94–97]. 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 couples [98–102]. 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 lacking [103]. (For further information see the 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).

4.8 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 delivered [104].

4.9 Formula feeding support

Women with very limited funds should have access to supplementary formula feed [105].

4.10 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.

4.11 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.

4.12 Eligibility for treatment

Legislation concerning eligibility to Free NHS Health Care in the UK is currently changing, both in primary and secondary care. 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 labor without knowing their HIV status. Rapid [*e.g.* point-of-care (POCT)] HIV testing in this setting should be encouraged [106]. 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 (http://www.tht.org.uk).

4.13 Referral pathways

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

4.14 Resistance to intervention

Some women may choose to refuse any intervention during pregnancy or declare their intention to breast-feed 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 breast feed 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 predelivery so that a strategy can be developed.

4.15 Postnatal 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.

5.0 Viral load and resistance

- Viral load is an important determinant of transmission.
- Quantify HIV plasma load (i) at least every 3 months and at week 36 in women on established therapy, (ii) 2 weeks after starting or changing therapy, (iii) at delivery.
- Use a second assay where there are discrepancies between viral load, CD4 count and clinical status.

5.1 HIV viral load

The risk of MCT correlates with maternal plasma viral load even among women receiving ART [107–109]. 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 assay [110–112]. 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 [60,113]; 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 undetectable [62]. Responses to ART and selection of drug-resistant variants may differ between plasma and CVS [114] and there is evidence of genetic diversity between viral populations in the blood and female genital tract that could account for this [115,116].

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 management [111].

Plasma viral load should be monitored at least every 3 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 UK 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 well [117].

Absolute HIV RNA copy number may vary not only with the assay employed but also with biological varia-

tion of RNA and specimen handling [118]. The contribution of these variables to HIV RNA concentrations appears to be of the order of 0.3–0.6 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 UK, 78% of HIV infections among women attending antenatal clinics are with non-B subtypes, 61% being subtype A and 29% subtype C [119]. 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 subtypes [120–122]. 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.

5.2 Antiretroviral drug resistance

- Determine HIV genotype (or phenotype):
- pre-therapy (at presentation)
- if *viremic* 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 suboptimal 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 1,000 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 that are more sensitive than standard genotyping systems [123]. 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 B [124–127]. The protease gene of HIV is highly polymorphic and this may contribute to development of resistance to protease inhibitors (PIs). Naturally occurring accessory mutations within the protease gene have been demonstrated in 85% of individuals never treated with PIs and the frequency of these mutations has been shown to be higher among non-B than subtype B virus [128]. 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 PIs [129]. 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-naive individuals of 10–20% in Europe and North America [130–132]. 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 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 op-

tions for the woman. More information is now becoming available on development of antiretroviral drug resistance during pregnancy [133]. 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 detected [134]. Similarly, no mutations were detected among women in the Côte d'Ivoire receiving short course zidovudine monotherapy initiated late in pregnancy [135]. A more recent UK study [11] 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% [136–139], 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 naive 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 con.rm 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 (M184 V) is required. In a small UK study [140] four of five women (80%) treated with zidovudine and lamivudine from the second trimester had developed the M184 V mutation at the time of delivery or very shortly after. A larger French study [125], with samples from 132 women, demonstrated lamivudine resistance in 52 (39%) when lamivudine had been added to zidovudine after 32 weeks gestation. There was no evidence of resistance to lamivudine when treatment was for less than 4 weeks duration. A US study [141], which tested 207 delivery samples, demonstrated lamivudine resistance in 44% of drug experienced women receiving standard combination ART. Factors associated with development of the M184 V 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 non-nucleoside reverse transcriptase inhibitor (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 study [142] drug-naive women received a single dose of nevirapine at the onset of labor and their infants a single dose within 72 hours of delivery. Nevirapine resistance was detected in 19% (21/111) of women at 6 weeks post partum and was associated with higher baseline viral loads and lower CD4 cell numbers [143]. Detectable resistance appeared to be transient, with these mutations no longer found in plasma 12–24 months post-partum. More recent studies have demonstrated resistance in as many as 40% of women following single dose nevirapine [144]. Following single-dose nevirapine resistance is more frequently detected in women with subtype C HIV infection compared with subtypes A and D [145]. Resistance to nevirapine 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% [141]. The implications of resistance following single-dose nevirapine 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 occur [146]. Among infected children the prevalence of zidovudine associated resistance mutations, as a result of perinatal transmission, has ranged from 9% to 17% in some studies [138,139,147], and between 30% and 40% in others [125,148]. Similarly, nevirapine-resistant virus was detected in 11 of 24 (46%) infected infants in the HIVNET 012 study [143]. However, mutations were transient and no longer detected 4–12 months after delivery. The implications of these mutations and there 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 [134,137,138,147], there is still insufficient information to define clearly the relationship between drug-resistant mutants and MCT.

Any pregnant woman on non-suppressive antiretroviral therapy (ART) should have a resistance test conducted [149,150]. Following short-term ART to prevent MCT (START), a genotypic analysis should be performed early in rebound.

6.0 ART 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: (i) with <6–10 000 HIV RNA copies/mL plasma; (ii) wild-type virus; (iii) not requiring HAART for maternal health; (iv) not wishing to take HAART during pregnancy; (v) and willing to deliver by PLCS.
- Do not prescribe dual NRTI therapy.
- Prescribe effective (.3 drug) combination therapy whenever: (i) indicated for maternal health as per adult guidelines; (ii) baseline maternal viremia 410,000 cp/mL; (iii) baseline maternal viremia <10,000 cp/mL (as an alternative to ZDV mono-therapy plus pre-labor Caesarean section).
- Drug resistance detected on genotype/phenotype.
- Short-term HAART (START) for prevention of MCT should: (i) be discontinued after delivery when viral load <50 cp/mL; (ii) 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 MCT 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-positive pregnant women in the UK and Ireland had conceived on combination ART [151]. 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 randomized 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 transmission [152]. Whilst true this does not reflect current best care. In this section we will summarize 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.

6.1 Nucleoside analog reverse transcriptase inhibitors (NRTIs)

The efficacy of zidovudine to reduce MCT of HIV-1 has been demonstrated in several large randomized controlled studies [5,108,153] and supported by epidemiological surveys [6–8,154]. The efficacy of zidovudine ranges from 67%, when started before the third trimester administered by IV infusion during labor 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 [155,156]. 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 viremia and increases CD4-positive lymphocyte counts. In ACTG 076, in which mothers commenced zidovudine 100 mg five times daily between weeks 14 and 28 of gestation, therapy was associated with a 0.24 log10 reduction in plasma viremia at the time of delivery [8,112]. In the Bangkok study, zidovudine 300 mg twice daily was commenced at week 36 resulting in a 0.57 log10 reduction in plasma viremia at delivery. This was considered to account for 80% of the efficacy of zidovudine to reduce transmission [108].

Viral load is an important predictor of transmission and zidovudine reduces transmission at all levels of maternal viremia. However, in mothers with very high viral load (4,100,000 RNA copies/mL) the transmission rate may be 460% and, therefore, even with a two-thirds reduction in transmission the risk to the infant would still be around 20%. Additional measures are, therefore, re-

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

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

			Treatment Components					
Study Name	**Countries**	**Study size**	**Pre-partum (Initial Gestation Week)**	**Intra-partum (IV/Oral)**	**Post-Partum (wks)**	**Age HIV assessed**	**Transmission Rates %**	**% Reduction (p)**
ACTG 076/ANRS 024 [5]	France USA	402	14–34 Zidovudine 100 mg 5 × 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 300 mg 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 300 mg bd Stavudine 40 mg bd Didanosine 200 mg bd D4T & DDI	Zidovudine Stavudine Didanosine D4T & DDI	6 weeks Zidovudine Stavudine Didanosine D4T & DDI	6 weeks DNA PCR	6.3 4.2 1.9 2.0	Equivalence between ZDV and D4T combined with 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 antiretroviral therapy to prevent mother-to-child transmission in breast feeding populations

			Treatment Components					
Study Name	**Countries**	**Study size**	**Pre-partum (Initial Gestation Week)**	**Intra-partum (IV/Oral)**	**Post-Partum (wks)**	**Age HIV assessed DNA PCR**	**Transmission Rates % Placebo v ZDV**	**% Reduction (p)**
RetroCI [156]	Côte D'Ivoire	280	36 Zidovudine 300 mg bd	Oral	Nil	3 months	26.1 v 16.5	37%
						6 months	26.1 v 16.9	(0.07)
						12 months	28.5 v 18.5	35%
						18 months	30.1 v 21.6	35%
						24 months	30.1 v 22.1	28% 27% (<0.5)
DITRAME [302]	Burkino Faso, Côte d'Ivoire	431	36 Zidovudine 300 mg bd	Oral	1 week maternal	6 months	27.5 v 18	35%
						15 months	30.6 v 21.5	30%
PETRA [303]	RSA, Tanzania Uganda	1802	36 Zidovudine 300 mg bd Lamivudine 150 mg bd	Oral	Yes	6 weeks	17.2 v 8.6	50% (0.001)
						18 months	26.6 v 20.7	22% (0.07)
			Nil	Oral	Yes	6 weeks	17.2 v 10.8	37% (0.02)
						18 months	26.6 v 24.4	8% (0.5)
			Nil	Oral	Nil	6 weeks	17.2 v 17.7	−3% (0.8)
						18 months	26.6 v 25.7	3% (0.8)
HIVNET 012 [304]	Uganda	626		Zidovudine 300 mg stat + 3hrly v Nevirapine 200 mg stat	Zidovudine 7 days v Nevirapine stat 48 <72 hrs	6–8 weeks	ZDV v NVP 20.0 v 11.8	41% (0.006)
			Nil			12 months	24.1 v 15.7	35%
SAINT [164]	RSA	1307	Nil	Oral ZDV + 3TC v NVP	One week	8 weeks	ZDV + 3TC v NVP 10.8 v 14	Equivalence

quired for these and probably for any mother with a viral load 46–10,000 copies/mL (no transmissions occurred in the recent Thai short course zidovudine plus single dose nevirapine study when 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*, February 8–11, 2004, San Francisco, CA, USA, LB41] with only one transmission out of 387 exposed if maternal baseline HIV RNA copies <25,000/mL [157]). 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% [14]. In a South African randomized 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%) [158]. Transplacental transfer stavudine is similar to that of zidovudine and lamivudine with equivalent levels found in maternal plasma and cord blood after oral and IV dosing [159]. Studies in pig-tailed macaques show fetal blood levels of dideoxyinosine to be half the maternal plasma level [160]. Stavudine and didanosine appear to accumulate in amniotic fluid [159,160].

6.2 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 mono-therapy was initiated at gestation week 36 at a dose of 300 mg bd increased incrementally to 600 mg 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 12 women discontinued treatment, 10 because of elevated liver enzymes (see Section 7) [161].

6.3 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 MCT of HIV. In HIVNET 012 two doses of nevirapine, the first given to the mother in labor and the second to the neonate age 48–72 hours, were compared with zidovudine initiated in labor and prescribed to the neonate for 1 week. Transmission was reduced by 47% with nevirapine after 3 months follow-up [142]. 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-fed [162]. In the SAINT study transmission rates at 8 weeks with the HIVNET 012 study regimen (14%) were not significantly different from the rate of transmission in mother-infant pairs receiving zidovudine 300 mg plus lamivudine 150 mg in labor and twice daily to mother and infant for 1 week post-partum (10.8%) [163]. The efficacy, low cost and ease of use led to the widespread use of the two-dose nevirapine regimen in resource-restricted settings and it's adoption by the World Health Organization (WHO), although these have now changed.

6.4 Maternal health

Monotherapy is used to reduce the risk of MCT 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 4 weeks of zidovudine monotherapy compared with placebo [164,165].

In a multicenter 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%) [166]. In a large French prospective non-randomized cohort study of 440 women treated with initially with zidovudine, with lamivudine added from gestational week 32, maternal plasma HIV viremia was reduced by 0.95 log10 and the MCT rate was 2.6%. This compares favorably with a historical transmission rate of 6.5% in mothers in the same cohort receiving zidovudine monotherapy [125]. In an international randomized controlled study in breast-feeding women there was a 22% reduction in transmission at 18 months follow-up compared with placebo in children perinatally exposed to zidovudine plus lamivudine from 36 weeks gestation to 1 week post-partum, although this did not quite reach statistical significance [167]. 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 settings [168], 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 mothers [157].

6.5 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 PI [4]. In PACTG 367 the transmission rate among 3081 pregnant women delivering in North 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 1,736 women who had plasma viremia 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 viremia was less than 50 copies (data communicated at *11th Conference on Retroviruses and Opportunistic Infections* 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 therapies [4]. In the ACTG 316 study nevirapine was added at labor 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 1,174 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 viremia at delivery. The study was closed when it became clear that it was not powered to demonstrate any benefit from nevirapine used in this way [12].

6.6 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 6 months treatment 86% of women not previously exposed to nevirapine had suppressed viremia 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 viremia at 6 months compared with 34% of mothers who had a history of detectable NNRTI mutation following single dose nevirapine exposure. Furthermore, mothers exposed to nevirapine in whom NNRTI mutations had not been found post-partum also faired less well than unexposed mothers with only 53% achieving <50 copies at 6 months [169].

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 pregnancy [170].

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 analogs 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 variation [171] and even out to 21 days [169]. Similar drug persistence has been reported with efavirenz [172] 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 association [173]. However, nevirapine resistance mutations have been detected by population-based sequencing in women post-partum despite full suppression of plasma viremia, triple therapy and a tailored approach to discontinuing therapy [174].

7.0 ART in pregnancy: toxicity

7.1 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 summarize 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, gastrointestinal (GI) transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood

flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in metabolic enzyme pathway in the liver.

7.2 NRTIs

Nucleoside analog 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 pregnancy [125]. 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 PIs [175]. Almost 80% of women developed one or more typical adverse effects of the drugs such as anemia, nausea/vomiting, raised transaminases, or hyperglycemia.

Nucleoside analogs may cause mitochondrial dysfunction as they have varying affinity for mitochondrial DNA g polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion [176]. The relative potency of the nucleoside analogs in inhibiting mitochondrial DNA g polymerase *in vitro* is highest with zalcitabine, followed by didanosine, stavudine, lamivudine, zidovudine and abacavir [177]. Toxicity related to mitochondrial dysfunction has been reported in patients receiving long-term treatment with nucleoside analogs 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 (FDA) 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 four cases of lactic acidosis in pregnancy with this combination [178]. It is not clear whether the frequency of this recognized complication is higher in pregnant than non-pregnant women. In one London center lactic acidemia (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 analogs and no reasonable alternatives.

7.3 PIs

Hyperglycemia, new onset diabetes, exacerbation of existing diabetes mellitus and diabetic ketoacidosis have been reported with administration of PIs [179,180]. 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) [181].

In a study of 86 HIV-positive, treatment-naive 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; one due to severe vomiting, diarrhrea, headache and fever; one an inability to take the capsule). The most frequently reported maternal adverse events included diarrhrea (30), nausea (22), altered taste (15) and vomiting (10). There were 51 maternal grade 3/4 laboratory abnormalities (mostly elevated liver enzymes) [161].

The plasma concentrations of saquinavir when prescribed as unboosted soft-gel capsules are generally low [182] but when either the hard-gel capsules [183] or soft-gel capusles [184] are boosted by coprescription 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.

The use of PIs in combination therapy has been reviewed in 89 pregnancies, from six sites in the USA. 36 women received nelfinavir, 33 saquinavir, 23 indinavir and five ritonavir. Obstetric complications reported were one full placenta previa, two abruptions, four oligohydramnios, three pre-eclampsia and one spontaneous abortion. PIs were generally reported to be well tolerated and appeared safe in pregnancy [185].

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 (three), hepatitis (one); PI: vomiting (two), ureteral obstruction (one) [186].

7.4 Nevirapine

The use of nevirapine as part of combination ART was retrospectively reviewed in a London cohort of 46 HIV-

infected pregnant women. Thirty initiated nevirapine 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 nevirapine were rash (two) and biochemical hepatitis (two). Six women developed GI symptoms, which were attributed to, and settled on changing, the nucleoside analogs [187]. However, a number of hepatitis-related deaths have been reported in pregnant women taking regimens that include nevirapine [188]. There has also been a change to the Summary of Product Characteristics (February 13, 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 pretreatment CD4 counts greater than 250 cells/mm' [3]. 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 women [189], whereas in PACTG 1022 four of 17 women discontinued nevirapine due to toxicity compared with one of 21 randomized to nelfinavir. One patient treated with nevirapine, whose baseline ALT was 58 U/L, died of fulminant hepatic failure [190]. Mooney *et al.* reported 'major' toxicities in five of 56 women (10.5%) taking nevirapine during pregnancy compared to one episode of renal calculi among 47 women taking a PI (2%) [191]. 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/mm [3] but not above 250 cells/mm [3,192]. This could be explained by the lower CD4 counts seen with hemodilution in pregnancy. In a study of 126 women commencing nevirapine-based HAART in Thailand, eight (6.3%) developed hepatitis of whom six discontinued nevirapine and nine (7.1%) developed a rash resulting in the discontinuation nevirapine in six. No statistically significant difference in frequency of complications was seen in the women commencing nevirapine-based HAART with a CD4 count greater than 250 cells/mm^3 (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 gestation [193]. 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/mm [3,194]. 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 zidovudine, lamivudine and nevirapine are started at 34 weeks gestation to prevent MCT in a breast-feeding population, 13 of 155 (8.4%) mothers had to stop nevirapine with Grade 2–4 toxicities, but a CD4 count cut-off of 250 cells/mm [3] did not discriminate between susceptibility states [195].

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 MCT 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 fosamprenavir 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, March 2, 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 pharmacokinetics 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 therapeutic drug monitoring (TDM) for all new agents and all PIs.

7.4.1 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) (o37 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-up [196].

The possibility that PI usage was associated with an increased risk of PTD had been suggested by Swiss investigators in 1998 [175] following which recruitment of women to studies of PIs 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). Nineteen of 462 (4.1%) babies were born with a structural abnormality [197]. An increased rate of PTD has also been reported in women on combination ART with PIs in Europe [198]. In the latest analysis of this ongoing study, a trend towards more preterm deliveries (in women not delivering by PLCS) has been shown over time, correlating with increased use of combination therapies [199]. However, this was not seen in a North American cohort [200] nor on analysis of data submitted voluntarily to the Antiretroviral Pregnancy Register, which mostly includes submissions from North America. A trend to very low birth weight was, however, noted in babies exposed to three or more drugs in utero [201]. Data from the UK and Ireland of 3,807 pregnancies reported between 1990 and 2003, show that 13% of deliveries were before 37 weeks with a 1.5-fold increased risk if the mother took HAART during pregnancy compared with zidovudine monotherapy [151].

7.5 Other drug treatments

Women on ART are commonly on other therapies. In a multicenter retrospective study of 148 infants exposed to ART 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 ART [202]. In addition to neural tube defects, first trimester exposure to folate antagonists has been associated with an increased frequency of cardiac and renal tract malformations. The therapeutic needs of all women of child-bearing potential should be regularly reviewed particularly now that PCP and other prophylactic therapies can be safely discontinued as immune function recovers. Regular administration of even small doses of folic acid (such as found in some multivitamin preparations) appears to negate this additional risk [203]. An association between gestational diabetes (GD) and PI used 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 PI (OR 2.3 95% CI 1.0–5.3) were associated with GD in a multivariate analysis [204].

8.0 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 detect able viremia,
  - women with HIV/HCV coinfection.
- PLCS to prevent MCT should be planned for 38 weeks. Elective vaginal delivery is an option for:
  - women with no detectable viremia.
- Maternal wishes should be considered.
- Avoid invasive monitoring of fetus and artificial rupture of membranes.
- Prescribe appropriate peri-operative antibiotics for all CS and immediately should membranes rupture during first stage of labor.
- Give corticosteroids for threatened preterm 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/postnatal 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.

8.1 Management of pregnancy and delivery-obstetric issues

The management of the HIV-positive pregnant woman during the delivery of her baby aims to minimize the risk of MCT 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-labor C-section (Table 2), the use of ART in pregnancy and very importantly the wishes of the mother.

8.2 Viral load

Initial studies proposed that a pre-labor Caesarean section (PLCS) in the presence of intact membranes reduced the risk of vertical transmission. A trans-Atlantic meta-analysis of 15 prospective cohort studies [205] and a randomized controlled study of mode of delivery in Europe.

Table 2 Evidence of the efficacy of pre-labour Caesarean section to reduce the risk of mother-to-child transmission of HIV

	Relative efficacy of PLCS	Transmission Rate %			Transmission Rate %			Transmission Rate %		
		PLCS	SVD & other MOD	OR (95% CI)	PLCS & AZT*	SVD, other MOD & AZT*	OR (95% CI)	PLCS & advanced maternal disease**	SVD, other MOD & advanced maternal disease**	OR (95% CI)
Meta-analysis 15 cohorts pre 1997 US & Europe N = 8533 [206]	50%	**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 ELCS at 38 weeks [15] 1993–98 N = 436	70%	Allocated to PLCS	Allocated to SVD	OR (95% CI)	Allocated to PLCS + AZT*	Allocated to SVD + AZT	OR (95% CI)	Allocated to PLCS + CD4 <200	Allocated to SVD + CD4 <200	
		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
		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

Pre-labour Caesarean section (PLCS), spontaneous vaginal delivery (SVD), mode of delivery (MOD).
*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.

[14] 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 labor or after membrane rupture were not associated with the same reduction in MCT. 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 hours [206]. These studies, done before routine viral load testing and combination ART, showed a consistent reduction in MCT 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 MCT rates according to maternal viral load. In a study of 480 mother-child pairs there was no MCT among 84 women with HIV-1 levels below 500 copies/mm [3] at booking or among the 107 women with undetectable levels at delivery [207]. In a similar study there was no MCT in 57 women with a viral load of less than 1,000 copies/mm [3,107]. However, transmission has been reported when maternal viremia was not detected [112,208]. A recent meta-analysis of seven prospective studies from the USA and Europe revealed 44 transmissions in 1020 deliveries where plasma viral load was <1,000 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 loads [111]. Whether Caesarean section in the presence of combination ART and undetectable plasma viremia (<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 ART, only 82% received 'peri-operative' antibiotics (amoxicillin or mezloxicillin plus a b-lactamase inhibitor), and the mean CD4:CD8 ratio was 0.49 in the patients who had postoperative complications [209–211]. Many of these studies were performed before the recommendation that prophylactic antibiotics be prescribed to all women undergoing Caesarean section to reduce infectious morbidity [212].

A more recent case-controlled study from the UK where all the HIV-positive women were treated with ART therapy in pregnancy and all received prophylactic antibiotics showed no difference in the incidence of post-operative morbidity [213]. Recent data from Latin America and the Caribbean revealed much lower rates of postpartum morbidity in HIV-positive women, the majority of whom (73%) were taking HAART. Following vaginal delivery (265 cases) and pre-labor, prerupture of membranes elective Caesarean section (240 cases) the complication rates were 3.4 and 3.3%, respectively [214].

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 PLCS [215]. 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 labor 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 1,000 HIV RNA copies/mL plasma [216].

8.3 Other pregnancy issues

8.3.1 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 the UK [217] and Spain [218] but not Brazil or South Africa [219,220] 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.

8.3.2 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 antiemetics 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 [221,222]. 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 [221,222]. There is very little information on the safety of ondansetron in pregnancy. Pyridoxine may be effective at reducing nausea, however, in some cases it is less effective at 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 antiemetics and antiretrovirals.

9.0 Pregnancy in women with HIV-2 infection

- If mother asymptomatic, good CD4 (4300), possibly manage as low viral load HIV-1.
- If HIV-2 viral load known to be <50 cp/mL antenatal/peripartum/neonatal intervention may be unnecessary.
- If mother symptomatic, low CD4 (o300) 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 coinfection [223]. 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 [224,225]. MCT rates of HIV-2 are also low, 0–4% in breast-fed infants, in the absence of any interventions [226–228]. 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 mm [3] as this is usually associated with a detectable viremia [229]. NNRTIs have little inhibitory activity against HIV-2 and are, therefore, not recommended but the virus is susceptible to NRTIs and some PIs. Decreased *in vitro* activity has been documented for amprenavir [230] but the clinical significance of polymorphisms in HIV-2 pol for other PIs requires clarification [231]. 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 viremia (*e.g.* zidovudine with Caesarean section). If the mother has a high CD4 (4,300 cells/mm^3) and a consistently undetectable HIV-2 viral load, even these interventions may not be necessary [228]. 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:

Professor Judy Breuer/Tony Oliver
4th Floor Molecular Laboratory
St. Bartholomew's Hospital
Department of Virology
51–53 Bartholomew Close
West Smithfield
London EC1A 7BE, UK
Tel. 0207 6017359
Fax: 0207 3777259
Tel. Judy Breuer: 0207 3777141
E-mail: j.breuer@qmul.ac.uk
Tel. Tony Oliver: 0207 6017359
E-mail: tony.oliver@bartsandthelondon.nhs.uk

Professor 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 6799490/9483
Fax: 0207 5805896
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 pediatric HIV-1 infection are followed [232,233].

10.0 HIV and hepatitis virus B and C coinfections

10.1 MCT of HCV

- All HIV-positive pregnant women should be tested for HCV.
- HCV-positive HIV-positive women should be treated with combination ART.
- PLCS should be offered to all coinfected 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

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				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
	Term (>34 wks) 4 mg/kg BD	Combo (+ 3TC)	Moodley, 2001		
		Mono	Boucher 1993		
	2 mg/kg QDS	Mono			
			Capparelli, 2003	*new	
	Prem (30–34 wks) 2 mg/kg BD for 2 weeks then 2 mg/kg TDS for 2 weeks.	Mono	Capparelli, 2003	*new	AZT and D4T should not be administered together in view of theoretical risk of negative interation
	Prem (<30wks) 2 mg/kg BD for 4 weeks				
		Mono	Boucher, 1993		
	Intravenous	Mono	Capparelli, 2003	*new	
	Term 1.5 mg/kg QDS				
	Prem 1.5 mg/kg BD				
Lamivudine (3TC) (Epivir)	2 mg/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)	60 mg/m^2 BD	Mono	Wang et al., 1999	*new	Difficult to separate dosing from feeding, and DDI much better absorbed on an empty stomach. May cause GI symptoms. Variable absorption in neonate
	100 mg/m^2 OD	Combo (with D4T + NFV)	Rongkavilit, 2001	*new	
Stavudine (D4T) (Zerit)	1 mg/kg BD	Combo (with DDI + NFV)	Rongkavilit, 2001		AZT and D4T should not be administered together in view of theoritical risk of negative interaction
Abacavir (ABAC) (Ziagen)	2 mg/kg BD	Mono	Johnson, 2000		Hypersensitivity reaction not been noted in infants (only small numbers treated)
Nevirapine (NVP/NEV) (Viramune)	Daily Dosing Regime 200 mg to mother in labour, than 2 mg/kg OD for 1st week, then 4 mg/kg OD for 2nd week (see Table 4)	Mono Mono	Shetty JAclmmDsynd, 2003	*new	Daily Dosing Regime form HIVNET 023 (breast feeding prophylaxis study).
	Single Dose Regime		Gauy, 1999		**Single Dose Regime should be avoided as high risk of development of resistance in mother and infant**
	200mg to mother in labour, then one 2 mg/kg dose at 48–72 hrs from birth				
Nefinavir (NEL/NFV) (Viracept)	50–75 mg/kg BD	Combo (with ZDV + 3TC)	NICHD/HPTN 040/P1043 Bryson, 2000	*new	Ongoing, RCT of different regimes for PEP for infants born to mothers with antenatally untreated HIV
	15/30/45 mg/kg BD	Combo (with DDI + D4T)	Rongkavilit, 2002		In this study, insufficient dosing at all 3 doses **If considering Nelfinavir use 75 mg/kg BD (PENTA 7).**
	90 mg/kg/day (total dose)	Combo (with DDI + D4T)	Faye, 2002		PENTA 7 Study in HIV pos young infants, highly variable PK, with poor viral suppression
Co-trimoxazole (septrin)	900 mg/m^2 OD Mon/Wed/Fri <6 months 120 mg OD Mon/Wed/Fri 6–12 months 240 mg OD Mon/Wed/Fri	PCP prophylaxis	Simmonds, 1995		May cause rash, bone marrow suppression. Give to infants born to mothers with a higher risk of transmission

mother to infant and current estimates indicate that up to 6% of women will infect their child [234–236]. 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 viremia are highly unlikely to transmit. HCV viremic mothers (HCV +/ HIV -) have an increased transmission rate of up to 10% [235,237]. 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 [234,238]. 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 [234,236,238–240].

In women who are HCV and HIV coinfected, transmission is increased to up to 15%, with higher rates in those who are HCV viremia [235,236,239,241]. 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 coinfected with HIV [242]. Effective control of HIV is associated with a reduction in the rate of HCV transmission although the mechanisms of this improvement are unclear [243,244]. No studies to assess the benefits of surgical, rather than vaginal delivery, have been performed in HIV-HCV-coinfected women.

Guidelines on the management of adults with HIV/ HCV coinfection per se can be obtained from the BHIVA website (http://www.bhiva.org/guidelines/2004/ HCV/index.html).

10.1.1 Diagnosis of infected children

In view of the increased risk of HCV infection in children born to women who are coinfected 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 viremia 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 [234,238]. 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 [245,246].

10.2 MCT of HBV

- All HIV-positive 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 viremia should receive additional passive vaccination with HBIg.
- ART for pregnant women with HIV/HBV coinfection should include drugs with activity against HBV.

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 immunization of the at-risk infant shortly after birth [245] 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 viremia. 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%) [247]. However, women who are HBeAg negative with high level hepatitis B viremia may have an increased incidence of materno-fetal transmission, although the magnitude of the increased risk and the precise level of viremia 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 reductioninvertical HBV transmission wheremothers received either the antiretroviral lamivudine or hyper-immune globulin, compared with no treatment [248]. 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 coinfection 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 coinfected patients. A single study from Tanzania suggested that coinfection did not increase the risk of transmission but the study was small and an increase in the rate of transmission cannot be excluded [249].

Some antiretroviral agents (*e.g.* lamivudine and tenofovir) are active against both HBV and HIV and in pregnant women with HIV/HBV coinfection it may be appropriate to consider HAART regimes that include agents ac-

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** 4 mg/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 > ABC > DDI	4 weeks 4 weeks	Well term infant, **ZDV** 4 mg/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** 2 mg/kg BD; **D4T** 1 mg/kg BD; **ABAC** 2 mg/kg BD; **DDI** 100 mg/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** 4 mg/kg BD (see Table 3 for prem/sick infant doses) + **3TC** 2 mg/kg BD + **NVP** 2 mg/kg OD 1st week and **NVP** 4 mg/kg OD 2nd week (use **NVP** 4 mg/kg OD for 2 weeks if the mother has received >3 days **NVP**). Stop **NVP** after 2 weeks, in view of long half-life. Continue other NRTIs 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** 4 mg/kg BD (see Table 3 for prem/sick infant doses) + **3TC** 2 mg/kg BD + **NVP** 2 mg/kg OD 1st week and **NVP** 4 mg/kg OD 2nd week (use **NVP** 4 mg/kg OD for 2 weeks if the mother has received >3 days **NVP**). Stop **NVP** after 2 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

tive against both HBV and HIV. Guidelines on the management of adults with HIV/HBV coinfection per se can be obtained from the BHIVA website (http://www.bhiva.org/guidelines/ 2004/HBV/index.html).

10.2.1 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 and at 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 screened for: (1) HBsAg, to confirm they have not been infected; and (2) HBsAb to confirm that they have responded to their vaccination.

11.0 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 viremia 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 metabolism [250]. Neonatal dosing regimens have been developed for most of the nucleoside analogs, 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 PIs [251– 253]. The only ART available for IV use in sick and/or premature neonates, unable to take oral medication, is zidovudine [254,255]. 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 zidovudine dosing regime for premature babies [255]. A new simplified, dosing regime for neonatal nevirapine use is suggested in these guidelines, pharmacokinetic studies have demonstrated adequate infant plasma levels with this regime [256]. 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 months [257]. Neonatal metabolism of nevirapine is induced where there is antenatal in utero exposure [258,259], so if this drug is given to the neonate, when the mother has taken it for more than 3 days, then the full dose of 4 mg/kg/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 2 weeks before the other drugs to reduce the risk of monotherapy exposure and development of resistance [171].

11.1 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 zidovudine 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 (*e.g.* 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 found [260]. 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 [11,261]. 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 zidovudine monotherapy [139,262–264]. 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 infant [143].

11.2 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 (zidovudine + lamivudine vs. zidovudine) had additional benefits over single drug treatment (in historical controls) in terms of reduction of transmission when mothers were also receiving dual ART [125]. A randomized African study which compared short course (1 week) treatment to the infant with either zidovudine + nevirapine or NVP also demonstrated superiority of two drugs (see below) [265]. However, in the randomized African 'SAINT' study, no significant difference in transmission rate was demonstrated in short course treatment with either zidovudine + lamivudine or nevirapine after perinatal treatment to the mother [163].

There are three situations where triple combination treatment for neonates should be considered: (i) post-delivery prophylaxis, where the mother is only found to be HIV infected after delivery (Scenario 6); (ii) unplanned delivery, *e.g.* prematurely prior to starting ART; or (iii) after a late presentation when details of maternal HIV parameters may not be available (Scenario 7). 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 zidovudine monotherapy provided this was started within 48 hours of birth [transmission risk: complete 076 treatment – antepartum (AP), intrapartum (IP), and post-partum (PP), 6.1% (95%CI 4.1–8.9%); IP + PP, 10.0% (3.3–21.8%); PP <48 hours, 9.3% (4.1–17.5%); PP >48 hours, 18.4% (7.7–34.3%); no Rx, 26.6% (21.1–32.7%)] [154]. In a randomized 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 zidovudine [265]. At 6–8 weeks after delivery, the overall MCT rate was 15.3% in 484 babies who received nevirapine + zidovudine and 20.9% in 468 babies who received nevirapine alone (P 5 0.03). Of the babies who were HIV-negative on testing at birth, 34 (7.7%) who received nevirapine + zidovudine and 51 (12.1%) who received nevirapine alone were subsequently infected (P 5 0.03) – a protective efficacy of 36% for the dual combination.

There have been no randomized 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 postexposure prophylaxis cases, where the level of blood/body fluid exposure is likely to be much less [262].

We have used zidovudine, lamivudine and nevirapine as combination therapy for infants born to drug naive women, but for non-naive mothers other combinations might be required if there is a possibility of resistance (see above for details on stopping nevirapine). Resistance testing should be carried out in the mother in such a situation and on the first positive sample of any infected infant.

11.3 Duration of antiretroviral treatment for neonates

In the PACTG 076 study zidovudine was administered for 6 weeks after birth and this subsequently became

standard of care [5]. However, in a Thai study, where a short course of 3 days of neonatal treatment was compared to 6 weeks there was no increased transmission where the mother received zidovudine from 28 weeks gestation [153]. In the UK, neonates are currently treated for 4–6 weeks but it is of note that current postexposure-prophylaxis guidelines in other situations suggest treatment for 4 weeks only [266].

11.4 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 hematological (but not clinical) effects of ZDV in exposed uninfected infants.

11.4.1 Long term

Long-term side-effects of perinatal exposure to ART can be considered in four main categories: teratogenic, carcinogenic, developmental, and mitochondrial, but there may be others not yet recognized [267]. Teratogenicity is most likely to be a problem with first trimester exposure to ART1 -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. 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 fetal abnormalities have been identified, but the voluntary reporting rate is disappointingly low. Detailed fetal 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 identified [268]. So far, no adverse growth or developmental effects of ART exposure have been demonstrated in children [269,270]. Mitochondrial toxicity after perinatal ART exposure, with two deaths from encephalopathy, was first reported in uninfected infants from the prospectively followed French cohort [271]. Deaths have not been identified in other large cohorts [272–275]. However, laboratory analysis of mitochondrial DNA has demonstrated abnormalities in infants born to ART treated mothers, and this is an area of ongoing investigation [276]. In the long-term follow-up of the infants from the 076 study, two zidovudine exposed children were shown to have unexplained retinopathy and cardiomyopathy, which could potentially be related to mitochondrial dysfunction [270]. A long-term follow-up study of health and development in ART-exposed children, by annual parental questionnaire, is underway in the UK [277].

11.4.2 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, multisystem failure and anemia, not attributable to any other cause; all have recovered with supportive care [278]. Elevated lactic acid levels have also been found in asymptomatic ART exposed infants [279]. Neonatal anemia and neutropenia is reported in infants exposed to NRTIs, this may be worse where there is exposure to combination therapy, or more prolonged treatment [125]. 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 months [280]. 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 cohort [281]. 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 ART neonates exposed to ART should have base line blood tests including: FBC, glucose, U + E, and LFTs, as well as diagnostic HIV PCR tests. It is our practice to repeat these tests with each set of HIV diagnostic samples. Lactate and pH monitoring for mitochondrial toxicity should be undertaken in any symptomatic newborn but does not appear to be necessary in otherwise well infants.

11.5 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 lymphocytes [282],

although some studies are now demonstrating equal/increased early sensitivity with other amplification methods for viral RNA [283]. 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 intrauterine transmission [284]. Within the first weeks of life the sensitivity of the test increases dramatically and by 3 months of age 95% 1 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 [285,286]. It is recommended to test infants at 1 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 infant [287]. 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.

11.6 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 organized in managed networks. Perinatal HIV care in London is managed within three clinical networks: Northwest, Northeast and South London. Outside London there is a regional network for perinatal and pediatric HIV with each region linked to one of the three London lead centers. The details of the CHIN Networks and contact details of the pediatricians can be found in the CHINN report at http://www.bhiva.org/chiva [288].

11.7 Prophylaxis, immunizations and clinical monitoring

Primary pneumocystis pneumonia (PCP) in infants with HIV remains a disease with a high mortality and morbidity [289]. 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 immunization schedule except that BCG vaccine should not be given until the infant is confirmed uninfected, with two negative HIV DNA PCRs after 1 month of age. Killed OPV is now recommended for all polio vaccination in the UK regardless of HIV exposure.

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.

11.8 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 multidisciplinary team is unable to influence a mother's views, then a prebirth 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 MCT 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 MCT.

11.9 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) study [277]. The National Study of HIV in Pregnancy and Childhood (NSHPC) is the UK surveillance system for obstetric and pediatric 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 re-

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
1a	Mother does not need HAART according to BHIVA Guidelines.	<10,000 copies per ml	AZT monotherapy starting between 20–32/40	Unlikely to be <50 copies per ml	PLCS at 38/40 + I.V. AZT	AZT for 4 weeks	Stop	1b A
	<32/40 gestation naive		or		or			
			START (PI based) commencing between	<50 copies per ml	PLCS at 38/40 + oral HAART or SVD + oral HAART	AZT for 4 weeks	Stop	III B
			20–32/40	>50 copies per ml	See Scenario 4	See Scenario 4	Stop when undetectable	
1b		>10,000 copies per ml	START (PI based) commencing between	<50 copies per ml	PLCS at 38/40 + oral HAART or SVD + oral HAART	AZT for 4 weeks	Stop	III B
			20–32/40	>50 copies per ml	See Scenario 4	See Scenario 4	Stop when undetectable	
2	Mother needs HAART according to BHIVA Guidelines.	Any	HAART after 1st trimester (usually AZT containing)	<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
	<32/40 gestation Naive			>50 copies per ml	See Scenario 4	See Scenario 4		
3a	Mother presents on HAART	<50 copies per ml	Continue	<50 copies per ml	PLCS at 38/40 + oral HAART or	Monotherapy	Continue	III B
3b		>50 copies per ml	Genotype and change to best option (expert advice)	<50 copies per ml	SVD + oral HAART	component of mother's HAART for 4/52		IV C
				>50 copies per ml	See Scenario 4	See Scenario 4		
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	PLCS 38/40 + I.V. AZT if no AZT resistance on most recent genotype	Combination PEP therapy	If on START – discontinue If on HAART – continue	IV C
5	Late presentation before onset of labour >32/40 Naive	Any	Commence HAART	<50 copies >50 copies per ml or no result	Scenario 2 PLCS at 38/40 + oral HAART	AZT 4/52 Scenario 4	If baseline CD4 suggests mother needs HAART – continue	IV C
6	Threatened unplanned delivery				Start antibiotics early if ROM			IV C
6a	Mother drug naive	>50 copies per ml	Commence Combivir + NVP NVP if CD4 <250		Optimum obstetric management	CBV/NVP But seek expert advise	If baseline CD4 suggests mother needs HAART – Continue	
6b	Mother on HAART	>50 copies per ml	Expert advice Add NVP and optimise HAART		Optimum obstetric management	Seek expert advice		
6C	Mother on HAART	<50 copies per ml	Continue prescription		Optimum obstetric management	(monotherapy component of mother's regimen) for 4 weeks	Continue HAART but ensure cover NNRTI	
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 Naive	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

ported 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 8298686, E-mail: p.tookey@ich.ucl.ac.uk Antiretroviral Pregnancy Registry (in Europe managed by GlaxoSmithKline), GlaxoSmithKline Ltd, Green-ford Road, Greenford, UB6 0HE, UK. Tel. no: 020 89664500; Fax: 0208 9662338 http://www.apregistry.com

12.0 Infant feeding and HIV transmission during breast-feeding

- Recommend exclusive formula-feeding to all HIV-positive mothers.

Breast-feeding 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 infant [290]. 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.

12.1 Mechanisms of breast-feeding 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, USA, and frequently below the detection limit of current assays. In a study in South Africa [291,292], 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 time [291]. Milk viral load was below the limit of detection of the HIV RNA 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/mL) during pregnancy and raised Na/K ratio (a marker of subclinical 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 breast-feeding) and RNA viral load in milk [292]. Together, the results of these studies indicate the random nature of virus shedding into breast milk.

Sub-clinical mastitis in the mother is hypothesized to increase 'leakiness' in the breast duct cell lining and therefore increase the amount of virus to which an infant is exposed [292,293]. Intestinal permeability of the young infant has been suggested as a possible site of entry for the virus, but evidence to date is limited [293,294]; it seems biologically plausible that mixed feeding increases the risk of HIV transmission by making the gut more susceptible through mechanical or inflammatory mechanisms.

12.2 Risk of MCT through breast-feeding

More recent and reliable data, including the results of a randomized clinical trial, confirm the substantial risk of transmission through breast-feeding first highlighted in the late 1980s and early 1990s. In the randomized 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) feeding [295]. Compliance with assigned feeding modality was 96% in the breast-feeding arm and 70% in the formula arm. Median duration of breast-feeding was 17 months. The cumulative probability of HIV infection at 2 years of age was 36.7% in the breast-feeding arm and 20.5% in the formula-feeding arm. The estimated absolute rate of transmission through breast-feeding over 2 years was thus 16.2%, approximately doubling the overall rate of MCT to 39% at 2 years of age.

The rates of transmission through breast-feeding inferred from the cumulative rates over age in trials in which a peripartum intervention to reduce MCT risk was evaluated, are broadly in line with the results from the randomized trial, with an increase in the estimated percentage of infants infected between 4 and 6 weeks of age and 18–24 months of 10–14% [162,163,167,296]. Differences between studies could be due to methodology used to assess rate of transmission [297], variation in the duration of breast-feeding 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.

12.3 Late postnatal transmission

The risk associated with breast-feeding 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 breast-feeding to determine their rate of acquisition of HIV infection through breast-feeding.

In a recent meta-analysis, including data from more than 4300 children enrolled in randomized controlled trials of peripartum interventions in sub-Saharan Africa, early transmission was defined by a positive HIV test before 4 weeks, and late postnatal transmission (LPT) by

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)*

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 breast-feeding was nearly 7 months, and the median 4 months. Results show a continued risk of LPT throughout the breast-feeding period, which was approximately constant over time [298]. 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.

13.0 Interventions to reduce MCT of HIV–clinical scenarios

Table 5 summarizes eight 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 summarized in Table 6.

Pre-labor Caesarean section at 38 weeks is recommended as the mode of delivery in all scenarios where the most recent viral load is detectable at 450 copies/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/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.

13.1 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 4,200/mm [3], any viral load) may be treated with a short-term ART (START) commencing in the second trimester with standard HAART regimens with the intention to achieve undetectable viral loads of <50 copies/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–or switch the NNRTI to a short-acting PI before stopping the whole regimen–to reduce the likelihood of the emergence of NNRTI resistance (see Section 7.2.3, p. 23, BHIVA Adult Treatment Guidelines).

An alternative approach, in women who do not require treatment for themselves, and who have a viral load of less than 10,000 c/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 fetus 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.

13.2 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-naïve 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 PI or a non-nucleoside drug (see Section 5).

13.3 Scenarios 3 and 4–women who conceive on ART

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 jeopardize maternal health but in theory result in reactivation of infections associated with congenital abnormalities, *e.g.* cytomegalovirus. Furthermore, many women will not realize 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 ART.

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 first trimester. Reasonable exceptions include serious illness for which antiretrovirals are the only recognized therapy.

13.4 Scenario 5–women who present late in pregnancy

With women who present very late in gestation or in labor, 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. PIs are not preferred because they have limited trans-placental transfer. As always, combination ART with at least two other drugs is recommended to reduce the likelihood of resistance development as has been shown with single-dose nevirapine monotherapy during labor. Zidovudine should preferably be infused IV, 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 viremia has become undetectable. Therapy should subsequently be discontinued in the manner recommended in guidelines for non-nucleoside regimens (see BHIVA Adult Treatment Guidelines).

13.5 Scenario 6–threatened premature delivery

Here, management would depend on optimum obstetric management (*e.g.* use of antibiotics and steroids where indicated) along with appropriate ART to the mother and infant, according to the situation.

13.6 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 labor had started, post-exposure prophylaxis (PEP) should be offered as soon as possible. There are observational data that zidovudine 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.

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

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 procedures [265] (http://www.bashh.org – Clinical Effectiveness Guidelines (CEG) for post exposure prophylaxis following sexual exposure).

References

1 Health Protection Agency. *Focus on Prevention–HIV and Other Sexually Transmitted Infections in the UK in 2003: An Update.* November 2004. http://www.hpa.org.uk (accessed on May 25, 2005).
2 UK Health Departments. *Reducing Mother to Baby Transmission of HIV.* London: NHS Executive, 1999.
3 Tookey P. *National Study of HIV in Pregnancy.* Newsletter 59, 2004.
4 Cooper ER, Charurat M, Mofenson LM *et al.* Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immun Defic Syndr* 2002; 29: 484–494.
5 Connor EM, Sperling RS, Gelber R *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New Engl J Med* 1994; 331: 1,173–1,180.

6 Therapeutic and other interventions to reduce the risk of mother-to-child transmission of HIV-1 in Europe. The European Collaborative Study. *Br J Obstet Gynaecol* 1998; 105: 704–709.
7 Cooper ER, Nugent R, Diaz C *et al.* After AIDS Clinical Trial 076: the changing pattern of zidovudine use during pregnancy, and subsequent reduction in the vertical transmission of human immunodeficiency virus in a cohort of infected women and their infants. *J Inf Dis* 1996; 174: 1,207–1,211.
8 Mayaux MJ, Teglas J-P, Mandelbrot L *et al.* Acceptability and impact of zidovudine for prevention of mother-to-child human immunodeficiency virus type-1 transmission in France. *J Pediatr* 1997; 131: 857–862.
9 Mandelbrot L, Le Chenadec J, Berrebi A *et al.* Perinatal HIV–1 transmission: interaction between zidovudine prophylaxis and mode of delivery in the French perinatal cohort. *JAMA* 1998; 280: 55–60.
10 Taylor GP, Khan W, Navaratne L *et al.* Pregancy outcome of HIV-positive women in London 1998–2002. *HIV Med* 2004; 5: 11.
11 Larbalestier N, Mullen J, O'Shea S *et al.* Drug Resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS* 2003; 17: 2,665–2,667.
12 Dorenbaum A, Cunningham CK, Gelber RD *et al.* Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002; 288: 189–198.
13 International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1–a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999; 340: 977–987.
14 European Mode of Delivery Collaboration. Elective Caesarian-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; 353: 1,035–1,039.
15 Browne R, Lyall EGH, Penn Z, Hawkins D. Outcomes of planned vaginal delivery of HIV-positive women managed in a multi-disciplinary setting. *BHIVA/BASSH*, Dublin, April 2005 [Abstract P45].
16 Dunn DT, Newell M-L, Ades AE, Peckham C. Estimates of the risk of HIV-1 transmission through breast-feeding. *Lancet* 1992; 340: 585–588.
17 Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome. A systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol* 1998; 105: 836–848.
18 European Collaborative Study, Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000; 14: 2,913–2,930.
19 De Vincenzi I. The European Study Group on Heterosexual Transmission of HIV. A Longitudinal study of human immunodeficiency virus transmission by heterosexual partners. *N Engl J Med* 1994; 331: 341–346.
20 Mandelbrot L, Heard I, Henrion-Geant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. *Lancet* 1997; 349: 850–851.
21 Barreiro P, Soriano V, Nunez M, Gonzalez-Lanoz J. Benefit of antiretroviral therapy for serodiscordant couples willing to be parents. *7th International Congress on Drug Therapy in HIV Infection*, November 14-18, 2004, Glasgow, UK, 2004 [Abstract PL13.3].
22 Semprini AE, Levi-Setti P, Bozzo M *et al.* Insemination of HIV-negative women with processed semen of HIV-positive partners. *Lancet* 1992; 340: 1,317–1,319.
23 Gilling-Smith C. HIV prevention. Assisted reproduction in HIV-discordant couples. *AIDS Reader* 2000; 10: 581–587.
24 Gilling-Smith C, Almeida P. Practice and Policy Committee of the British Fertility Society. HIV, hepatitis B and hepatitis C and infertility: reducing risk. *Hum Fertil* (Camb) 2003; 6: 106–112.
25 Weigel M, Gentilit M, Beichert M, Friese K, Sonnenberg-Schwan U. Reproductive assistance to HIV-discordant couples–the German approach. *Eur J Med Res* 2001; 6: 259–262.
26 Sauer MV, Chang PL. Establishing a clinical program for human immunodeficiency virus 1-seropositive men to father seronegative children by means of *in vitro* fertilization with intracytoplasmic sperm injection. *Am J Obstet Gynae* 2002; 186: 627–633.
27 Marina S, Marina F, Alcolea R, Nadal J, Exposito R, Huguet J. Pregnancy following intracytoplasmic sperm injection from an HIV-1-seropositive man. *Hum Reprod* 1998; 13: 3,247–3,249.
28 Marina F, Marina S, Alcolea R *et al.* Human immunodeficiency virus type 1–serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril* 1998; 70: 35–39.
29 Tur R, Veiga A, Busquets A& *et al.* Artificial insemination with processed sperm samples from serodiscordant couples for HIV-1. *Hum Reprod* 1999; 14: 208.
30 National Institute for Clinical Excellence. NICE Guidelines. Management of couples with viral infections. *Fertility Assessment and Treatment for People with Fertility Problems*, 2004.
31 Gilling-Smith C, Smith RJ, Semprini AE. HIV and infertility: time to treat. *BMJ* 2001; 322: 566–567.
32 Eshre Ethics and Law Task Force. Taskforce 8: Ethics of medically assisted fertility treatment for HIV-positive men and women. *Hum Reprod* 2004; 19: 2,454–2,456.
33 Sharma S, Gilling-Smith C, Semprini AE, Barton SE, Smith JR. View 1: Assisted conception in couples with HIV infection. *Sex Transm Infect* 2003; 79: 185.
34 Englert Y, Van Vooren JP, Place I, Liesnard C, Laruelle C, Delbaere A. ART in HIV-infected couples: Has the time come for a change of attitude? *Hum Reprod* 2001; 16: 1,309–1,315.

35 Sauer MV. Providing fertility care to those with HIV time to re-examine healthcare policy. *Am J Bioeth* 2003; 3: 33–40.
36 Frodsham LCG, Boag F, Barton S, Gilling-Smith C. An estimation of the UK demand for fertility services in HIV-positive couples. *BHIVA Conference.* April 24-26, 2003 [Abstract 9:04].
37 Frodsham LC, Smith JR, Gilling-Smith C. Assessment of welfare of the child in HIV-positive couples. *Human Reprod* 2004; 19: 2,420–2,423.
38 Frodsham LC, Cox AD, Almeida P, Rozis G, Gilling-Smith C. *In vitro* fertilization in HIV-positive women: potential mother to embryo viral transmission risk. *Human Reprod* (Suppl.) 2004.
39 Gilling-Smith C, Almeida P. HIV, hepatitis B & hepatitis C and infertility: reducing risk. Educational bulletin sponsored by the Practice & Policy Committee of the BFS. *Human Fertil* 2003; 6: 106–122.
40 Madge S, Phillips AN, Griffioen A, Olaitan A, Johnson MA. Demographic, clinical and social factors associated with human immunodeficiency virus infection and other sexually transmitted diseases in a cohort of women from the United Kingdom and Ireland. MRC Collaborative Study of women with HIV. *Int J Epidemiol* 1998; 27: 1,068–1,071.
41 Leroy V, De Clerq A, Ladner J, Bogaerts J, Van der Perre P, Dabis F. Should screening of genital infections be part of antenatal care in areas of high HIV prevalence? A prospective cohort study from Kigali, Rwanda, 1992–1993. The pregnancy and HIV (EGE) Group. *Genitourin Medical* 1995; 71: 207–211.
42 Dougan S, Payne LJC, Brown AE *et al.* Black Caribbean adults with HIV in England, Wales, and Northern Ireland: an emerging epidemic? *Sex Transm Infect* 2004; 80: 18–23.
43 Low N, Sterne JAC, Barlow D. Inequalities in rates of gonorrhoea and chlamydia between black ethnic groups in south east London: cross sectional study. *Sex Transm Infect* 2001; 77: 15–20.
44 Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *New Engl J Med* 1988; 319: 972–978.
45 Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *New Engl J Med* 2000; 342: 1,500–1,507.
46 Landesman SH, Kalish LA, Burns DN *et al.* Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. *New Engl J Med* 1996; 334: 1,617–1,623.
47 European Collaborative Study. Vertical transmission of HIV-1: maternal immune status and obstetric factors. *AIDS* 1996; 10: 1,675–1,681.
48 Van Dyke RB, Korber BT, Popek E *et al.* The Ariel Project: a prospective cohort study of maternal-child transmission of human immunodeficiency virus type 1 in the era of maternal antiretroviral therapy. *J Inf Dis* 1999; 179: 319–328.
49 Hillier SL, Nugent RP, Eschenbach DA *et al.* Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. *New Engl J Med* 1995; 333: 1,737–1,742.
50 Taha TE, Gray RH. Genital tract infections and perinatal transmission of HIV. *Ann NY Acad Sci* 2000; 918: 84–98.
51 Mcdonald H, Brocklehurst P, Parsons J, Vigneswaran R. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2003: 2.
52 Cameron DW, Simonsen JN, D'Costa LJ *et al.* Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; 2: 403–407.
53 Dickerson MC, Johnston J, Delea TE, White A, Andrews E. The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. An application of the Bradford Hill criteria. *Sex Transm Dis* 1996; 23: 429–440.
54 Ghys PD, Fransen K, Diallo MO *et al.* The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS* 1997; 11: F–5–F93.
55 Lawn SD, Subbarao S, Wright JTC *et al.* Correlation between human immunodeficiency virus type 1 RNA levels in the female genital tract and Immune activation associated with ulceration of the cervix. *J Inf Dis* 2000; 181: 1,950–1,956.
56 Hashemi FB, Ghassemi M, Roebuck KA, Spear GT. Activation of human immunodeficiency virus type 1 expression by Gardnerella vaginalis. *J Inf Dis* 1999; 179: 924–930.
57 Hashemi FB, Ghassemi M, Faro S, Aroutcheva A, Spear GT. Induction of human immunodeficiency virus type 1 expression by anaerobes associated with bacterial vaginosis. *J Inf Dis* 2000; 181: 1,574–1,580.
58 Mcclelland RS, Wang CC, Mandaliya K *et al.* Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. *AIDS* 2001; 15: 105–110.
59 Chuachoowong R, Shaffer N, Siriwasin W *et al.* Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. Bangkok Collaborative Perinatal HIV Transmission Study Group. *J Inf Dis* 2000; 181: 99–106.
60 Hart CE, Lennox JL, Pratt-Palmore M *et al.* Correlation of human immunodeficiency virus type 1 RNA levels in blood and female genital tract. *J Inf Dis* 2000; 179: 871–882.
61 Fiore JR, Suligoi B, Saracino A *et al.* Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. *AIDS* 2003; 17: 169–176.
62 Kovacs A, Wasserman SS, Burns D *et al.* Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001; 358: 1,593–1,601.
63 de Pasquale MP, Leigh-Brown AJ, Cu-Uvin S *et al.* Differences in HIV-1 pol sequences from female genital tract and blood during antiretroviral therapy. *J Acquir Immun Defic Syndr* 2003; 34: 37–44.

64 UK National Guidelines on Sexually Transmitted Infections and Closely Related Conditions. *Sex Transm Inf* 1999: 75.

65 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recommendations Reports* 1992; 41: 1–19.

66 Massad LS, Reister KA, Anastros KM *et al.* Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immun Defic Syndr* 1999; 21: 33–41.

67 Delmas MC, Larsen C, Van Bethem B *et al.* Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. *AIDS* 2000; 14: 1,775–1,784.

68 Wright TC, Ellerbrock TV, Chiasson MA, USA, Van Devanter N, Sun X. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol* 1994; 84: 591–597.

69 Smith JR, Kitchen VS, Botcherby M *et al.* Is HIV infection associated with an increase in the prevalence of cervical neoplasia? *Br J Obstet Gynaecol* 1993; 100: 149–153.

70 Olaitan A, Johnson MA, USA, Maclean A, Poulter LW. The distribution of immunocompetent cells in the genital tract of HIV-positive women. *AIDS* 1996; 10: 759–764.

71 Heard ISAB, Tassie JM, Schmitz VALE, Mandelbrot LAUR, Kazatchkine MD, Orth GERA. Increased risk of cervical disease among human immunodeficiency virus-infected women with severe immunosuppression and high human papillomavirus load. *Obstetrics Gynecol* 2000; 96: 403–409.

72 Holcomb K, Maiman M, Dimaio T, Gates J. Rapid progression to invasive cervix cancer in a woman infected with the human immunodeficiency virus. *Obstetrics Gynecol* 1998; 91: 848–850.

73 Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* 1998; 12: 1,459–1,464.

74 Heard I, Tassie JM, Kazatchkine MD, Orth G. Highly active antiretroviral therapy enhances regression of cervical intraepithelial neoplasia in HIV-seropositive women. *AIDS* 2002; 16: 1,799–1,802.

75 HIV-infected women and their families. *Psychosocial support and related issues: a literature review.* http:// www.who.international/reproductive-health/publications/rhr_03–07/2003 (accessed on May 25, 2005).

76 Manopaiboon C, Shaffer N, Clark L *et al.* Impact on families of HIV-infected women who have recently given birth, Bangkok, Thailand. *J AIDS Human Retrovirol* 1998; 8: 54–63.

77 Wood C, Kumalo P, Ainsworth J, Govind A, Meates M. Disclosure, discordance and decisions – the psychosocial impact of antenatal HIV testing 2002. *6th International Congress on Drug Therapy in HIV Infection.* Glasgow, UK., November 17-21, 2002 (Abstract P319).

78 Simoni JM, Pantalone DW. Secrets and safety in the age of AIDS: does HIV disclosure lead to safer sex? *Top HIV Med* 2004; 12: 109–118.

79 Wood C, Ellison G. What have clinicians learnt from working with HIV/AIDS? A medical perspective from London, *In:* Ellison G, Parker M, Campbell C, eds. *Learning from HIV/AIDS.* Cambridge: Cambridge University Press, 2003, pp. 105–137.

80 Siriwasin W, Shaffer N, Roongpisuthipong A *et al.* HIV prevalence, risk, and partner discordance among pregnant women in Bangkok. *JAMA* 1998; 280: 49–54.

81 Lurie M, Williams B, Zuma K *et al.* Who infects Whom? HIV-1 concordance and discordance among migrant and non-migrant couples in South Africa. *AIDS* 2003; 17: 2,245–2,252.

82 Guilen AC, Fogarty L, O'Campo P, Anderson J, Keller J, Faden R. Women living with HIV. Disclosure, violence, and social support. *J Urban Health* 2000; 77: 480–491.

83 Stein MD, Freedberg KA, Sullivan LM *et al.* Sexual ethics. Disclosure of HIV-positive status to partners. *Arch Int Med* 1998; 158: 253–257.

84 Chalmers J. Crime and punishment. AIDS Treatment Update 131: 1–7.

85 Potterat JJ. Partner notification for HIV. Running out of excuses. *Sex Trans Dis* 2003: 75–90.

86 Opening up the HIV epidemic. *Guidance on encouraging beneficial disclosure.* http://www.who.international/entity/hiv/pub/vct/en/opening-E%5B1%5D.pdf. WHO, 2005.

87 *Serious Communicable Diseases.* General Medical Council, 2005.

88 Murray D. Presentation, characteristics, family belief systems and HIV disclosure patterns amongst asylum seeking Ugandan men and women attending a central London hospital. *Int J STD AIDS* 1998; 10: 639.

89 Ciccarone D, Kanouse D, Collins P *et al.* Sex without disclosure of positive HIV serostatus in a US probability sample of persons receiving medical care for HIV infection. *Am J Public Health* 2003; 93: 949–954.

90 Embree JE, Njenga S, Datta P *et al.* Risk factors for postnatal mother-child transmission of HIV-1. *AIDS* 2000; 14: 2,535–2,541.

91 Medley A, Garcia-Moreno C, Mcgill S, Maman S. Rates, barriers and outcomes of HIV serostatus disclosure among women in developing countries: implications for prevention of mother-to-child transmission programmes. *Bull WHO* 2004; 82: 299–307.

92 Serovich J. Helping HIV-positive persons to negotiate the disclosure process to partners, family members, and friends. *J Marital Family Ther* 2000; 26: 365–372.

93 Freeman E, Glynn J for the Study Group on Heterogeneity of HIV epidemics in African Cities. Factors affecting HIV concordancy in married couples in four African cities. *AIDS* 2004; 18: 1,715–1,720.
94 Kalichman SC, Rompa D, Luke W, Austin J. HIV transmission risk behaviors among HIV-positive persons in serodiscordant relationships. *Int J STD AIDS* 2002; 13: 677–682.
95 Lo Caputo S, Tabattoni D, Vivhi F *et al.* Mucosal and systemic HIV-1-specific immunity in HIV-1-exposed but uninfected heterosexual men. *AIDS* 2003; 17: 531–539.
96 Van Devanter N, Thacker S, Bass G, Arnold M. Heterosexual couples confronting the challenges of HIV infection. *AIDS Care* 1999; 11: 181–193.
97 Bernard E. Undetectable does not equal uninfectious. *AIDS Treatment Update.*
98 Cohen MS, Kashuba ADM. Antiretroviral drugs and the prevention of sexual tansmission of HIV. *Medscape Clinical Update 2003.* http://www.medscape.com (accessed on May 25, 2005).
99 van der Straten A, Vernon K, Knight K, Gomez C, Padian N. Managing HIV among serodiscordant heterosexual couples: serostatus, stigma and sex. *AIDS Care* 1998; 10: 533–548.
100 Buchacz K, van der Straten A, Saul J, Shiboski SC, Gomez CA, Padian N. Sociodemographic, behavioral and clinical correlates of inconsistent condom use in HIV-serodiscordant heterosexual couples. *J AIDS* 2001; 28: 289–297.
101 Skurnik JH, Kennedy AJ, Valentine SN, Cordell JR. Maintainence of safe sex behavior by HIV-serodiscordant heterosexual couples. *AIDS Education Prevention* 1998; 10: 493–505.
102 Allen S, Meinzen-Derr J, Kautzman M *et al.* Sexual behavior of HIV discordant couples after HIV counselling and testing. *AIDS* 2003; 17: 733–740.
103 Cairns G. Prevention Matters (PEP). *AIDS Treatment Update* 134: 1–9.
104 Creighton S, Sethi G, Edwards SG, Miller R. Dispersal of HIV-positive asylum seekers: national survey of UK healthcare providers. *BMJ* 2004; 329: 322–323.
105 Department of Health. *HIV and infant feeding.* Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS, Department of Health, 2004.
106 Cohen MH, Olszewski Y, Branson B *et al.* Using point-of-care testing to make rapid HIV-1 tests in labor really rapid. *AIDS* 2003; 17: 2,121–2,124.
107 Garcia PM, Kalish LA, Pitt J *et al.* Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *New Engl J Med* 1999; 341: 394–402.
108 Shaffer N, Chuachoowong R, Mock PA *et al.* Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet* 1999; 353: 773–780.
109 European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS* 1999; 13: 1,377–1,385.
110 Coll O, Hernandez M, Boucher C *et al.* Vertical HIV-1 transmission correlates with a high maternal viral load at delivery. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 14: 26–30.
111 Ioannidis JP, Abrams EJ, Ammann AJ *et al.* Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1,000 copies/ml. *J Inf Dis* 2001; 183: 539–545.
112 Sperling RS, Shapiro DE, Coombs RW *et al.* Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *New Engl J Med* 1996; 335: 1,621–1,629.
113 Goulston C, Mcfarland W, Katzenstein D. Human immunodeficiency virus type 1 RNA shedding in the female genital tract. *J Inf Dis* 1998; 177: 1,100–1,103.
114 Si-Mohamed A, Kazatchkine MD, Heard I *et al.* Selection of drug-resistant variants in the female genital tract of human immunodeficiency virus type 1-infected women receiving antiretroviral therapy. *J Inf Dis* 2000; 182: 112–122.
115 Shaheen F, Sison A, Mcintosh L, Mukhtar M, Pomerantz RJ. Analysis of HIV-1 in the cervicovaginal secretions and blood of pregnant and nonpregnant women. *J Hum Virol* 1999; 2: 156–166.
116 Mullen J, O'Shea S, Cormack I, Mears A, Magaya V. Antiretroviral drug resistance and genetic diversity of HIV-1 in the blood and female genital tract. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, USA), 2004 [Abstract 95b].
117 Highbarger H, Alvord W, Jiang M *et al.* Comparison of the Quantiplex, Version 3.0 assay and a sensitised Amplicor Monitor assay for measurement of human immunodeficiency virus type I RNA levels in plasma samples. *J Clin Micro* 1999; 37: 3,612–3,614.
118 Lew J, Reichelderfer P, Fowler M *et al.* Determinations of levels of human immunodeficiency virus type I RNA in plasma; reassessment of parameters affecting assay outcome. *J Clin Micro* 1998; 36: 1,471–1,479.
119 Parry J, Murphy G, Barlow K *et al.* National surveillance of HIV-1 subtypes for England and Wales: Design, methods and initial findings. *J Acquir Immun Defic Syndr* 2001; 26: 381–388.
120 Coste J, Montes B, Reynes J *et al.* Comparative evaluation of three assays for the quantitation of human immunodeficiency virus type I in plasma. *J Med Virol* 1996; 50: 293–302.
121 Damond F, Apetrei C, Descamps D *et al.* HIV-1 subtypes and plasma RNA quantification. *AIDS* 1999; 13: 286–287.
122 Parekh B, Phillips S, Granade T *et al.* Impact of HIV-1 subtype variation on viral RNA quantitation. *AIDS Res Hum Retroviruses* 1999; 15: 133–142.

123 Palmer S, Kearney M, Maldarelli F *et al.* Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in treatment-experienced patients are missed by standard genotype analysis. *J Clin Microbiol* 2005; 43: 406–413.

124 Adje C, Cheingsong Popov R, Roels W *et al.* High prevalence of genotypic and phenotypic antiretroviral (ARV) drug resistant HIV-1 strains among patients receiving ARV in Abidjan, Cote d'Ivoire. *XIII International AIDS Conference*, Durban, RSA, July 9-14, 2000. [Abstract TuOrB298].

125 Mandelbrot L, Landreau-Mascaro A, Rekacewicz C *et al.* Lamivudine-Zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; 285: 2083–2093.

126 Palmer S, Alaeus A, Albert J, Cox S. Drug susceptibility of subtypes A,B,C,D, and E human immunodeficiency virus type 1 primary isolates. *AIDS Res Hum Retroviruses* 1998; 14: 157–162.

127 Weidle P, Kityo C, Mugyenyi P *et al.* Resistance to antiretroviral therapy among patients in Uganda. *J Acquir Immun Defic Syndr* 2001; 26: 495–500.

128 Pieniazek D, Rayfield M, Hu D *et al.* Protease sequences from HIV-1 group M subtypes A-H reveal distinct amino acid mutation patterns associated with protease resistance in protease inhibitor-naïve individuals worldwide. *AIDS* 2000; 14: 1,489–1,495.

129 Shafer RW, Hsu P, Patick AK, Craig C, Brendel V. Identification of biased amino acid substitution patterns in human immunodeficiency virus type–1 isolates from patients treated with protease inhibitors. *J Virol* 1999; 73: 6,197–9,202.

130 Boden D, Hurley A, Zhang L *et al.* HIV-1 drug resistance in newly infected individuals. *JAMA* 1999; 282: 1135–1141.

131 Little S, Daar E, D'Aquila R *et al.* Reduced antiretroviral drug susceptibility among patients with primary HIV infection. *JAMA* 1999; 282: 1,142–1,149.

132 Yerly S, Kaiser L, Race E *et al.* Transmission of antiretroviral-resistant HIV-1 variants. *Lancet* 1999; 354: 729–733.

133 Nolan M, Glenn Fowler M, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J Acquir Immun Defic Syndr* 2002; 30: 216–229.

134 Eastman PS, Shapiro DE, Coombs RW *et al.* Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol 076. *J Inf Dis* 1998; 177: 557–564.

135 Ekpini R, Nkengasong J, Sibailly TS *et al.* Changes in plasma HIV-1-RNA viral load and CD4 cell counts, and lack of zidovudine resistance among pregnant women receiving short-course zidovudine. AIDS 2002; 16: 635–630.

136 Frenkel L, Wagner L, Demeter L *et al.* Effects of zidovudine use during pregnancy on resistance and vertical transmission of human immunodeficiency virus type 1. *Clin Inf Dis* 1995; 20: 1321–1326.

137 Kully C, Yerly S, Erb P *et al.* Codon 215 mutations in human immunodeficiency virus-infected pregnant women. Swiss Collaborative 'HIV and Pregnancy' Study. *J Inf Dis* 1999; 179: 705–708.

138 Palumbo P, Dobbs T, Holland B *et al.* Antiretroviral resistance mutations among pregnant HIV-infected women and their newborns in the US. Vertical transmission and clades. *XIII International AIDS Conference*, Durban, RSA, July 9-14, 2000. (TuPpB1230).

139 Welles SL, Pitt J, Colgrove RC *et al.* HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant transmission in the Women and Infants Transmission Study. *AIDS* 2000; 14: 263–271.

140 Clarke JR, Braganza R, Mirza A *et al.* Rapid development of genotypic resistance to lamivudine when combined with zidovudine in pregnancy. *J Med Virol* 1999; 59: 364–368.

141 Cunningham CK, Chaix ML, Rekacewicz C *et al.* Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Inf Dis* 2002; 186: 181–188.

142 Guay LA, Musoke P, Fleming T *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; 354: 795–802.

143 Eshleman SH, Mracna M, Guay L *et al.* Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 2001; 15: 1,951–1,957.

144 Martinson N, Morris L, Gray G *et al.* HIV resistance and transmission following single dose nevirapine in a PMCT cohort. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, USA). [Abstract 38].

145 Eshleman SH, Hoover D, Chen S *et al.* Comparison of Nevirapine resistance in women with subtype C compared with subtypes A and D following single-dose NVP. *12th Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA, February 22-25, 2005; 799: 2005.

146 Chaix M, Rekacewicz C, Bazin B *et al.* Genotypic resistance analysis in French women participating in PACTG 316/ANRS083. *8th Conference on Retroviruses and Opportunistic Infections* (February 4–8, 2001, Chicago, USA). [Abstract 470].

147 Palumbo P, Holland B, Dobbs T *et al.* Antiretroviral resistance mutations among pregnant human immunodeficiency virus type 1-infected women and their newborns in the United States: vertical transmission and clades. *J Inf Dis* 2001; 184: 1,120–1,126.
148 Mofenson L, Lambert JS, Stiehm A *et al.* Association of ZDV genotypic resistance with perinatal transmission in women receiving ZDV in pediatric ACTG protocol 185. *XIII International AIDS Conference,* Durban, RSA, July 9-14, 2000. [Abstract TuPpB1229].
149 Euroguidelines Group for HIV Resistance. Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: Recommendations for the European setting. *AIDS* 2001; 15: 309–320.
150 Coll O, Fiore S, Floridia M *et al.* Pregnancy and HIV infection: a European consensus on management. *AIDS* 2002; 16: S1–S18.
151 Tookey PA, Townsend CL, Cortina-Borja M, Masters JE, Peckham CS. Antiretroviral therapy and pregnancy outcome: UK/Ireland surveillance data 1990–2004. *7th International Congress on Drug Therapy in HIV Infection* (November 14-18, 2004, Glasgow, UK). [Abstract 11.3].
152 Brocklehurst P. Interventions for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* 2002, CD000102.
153 Lallemant M, Jourdain G, Le Coeur S *et al.* A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type I. *New Engl J Med* 2000; 343: 982–991.
154 Wade NA, Birkhead GS, Warren BL *et al.* Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New Engl J Med* 1998; 339: 1,409–1,414.
155 Wiktor SV, Ekpini E, Karon JM *et al.* Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet* 1999; 353: 781–785.
156 Ditrame ANRS 049 Study Group. 15-month efficacy of maternal oral zidovudine to decrease vertical transmission of HIV-1 in breast-fed African children. *Lancet* 1999; 354: 2,050–2,051.
157 Lallemant M, Jourdain G, Le Coeur S *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; 351: 217–228.
158 Gray G, Mcintyre J, Jivkov B *et al.* Preliminary efficacy, safety, tolerability, and pharmacokinetics of short course regimens of nucleoside analogs for the prevention of mother-to-child transmission of HIV. *XIII International AIDS Conference*, Durban, RSA, July 9-14, 2000. [Abstract TuOrB355].
159 Wade NA, Unadkat JD, Huang S *et al.* Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group Protocol 332. *J Inf Dis* 2004; 190: 2,167–2,174.
160 Pereira CM, Nosbich C, Baughman WL, Unadkat J. Effect of zidovudine on transplacental pharmacokinetics of ddI in the pigtailed macaque (*Macaca nemestrina*). *Antimicrob Agents Chemother* 1995; 39: 343–345.
161 Limpongsanurak S, van Leeuwen R, Macleod C. for the Ritonavir Vertical Transmission Study Group. Safety, tolerability and efficacy of ritonavir in the prevention of vertical transmission. *6th Conference on Retroviruses and Opportunistic Infections*, Chicago, IL, January 31-February 4, 1999. [Abstract 241].
162 Jackson J, Musoke P, Fleming T *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003; 362: 859–868.
163 Moodley D, Moodley J, Coovadia H *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Inf Dis* 2003; 187: 725–735.
164 Roongpisuthipong A, Siriwasin W, Asavapiriyanont S *et al.* Predictors of mortality in 18-month postpartum period among HIV infected women enrolled in a trial of short-course antenatal zidovudine, Bangkok, Thailand. *XIII International AIDS Conference,* Durban, RSA, July 9-14, 2000. [Abstract TuPeB3253].
165 Sibailly TS, Ekpini E., Boni-Ouattara E *et al.* Clinical course of HIV infection and surveillance for zidovudine resistance among HIV-infected women receiving short-course zidovudine therapy in Abidjan, Cote d'Ivoire. *XIII International AIDS Conference*, Durban, RSA, July 9–14, 2000. [Abstract TuPeC3354].
166 Silverman NS, Watts DH, Hitti J *et al.* Initial multicenter experience with double nucleoside therapy for human immunodeficiency virus infection during pregnancy. *Infect Dis Obstet Gynecol* 1998; 6: 237–243.
167 PETRA Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; 359: 1178–1186.
168 WHO http://www.who.int/3by5/arv_pMCT/en/.
169 Jourdain G, Ngo-Giang-Huong N, Le Coeur S *et al.* Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med* 2004; 351: 229–240.

170 Martin F, Navaratne L, Khan W *et al.* 97% Progression-free survival of HIV 1 pregnant women 33 months post-delivery. *12th Conference on Retroviruses and Opportunistic Infections*. Boston, MA, USA, February 22-25, 2005 [Abstract 807].

171 Mackie NE, Fidler S, Tamm N *et al.* Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med* 2004; 5: 180–184.

172 Taylor S, Allen S, Fidler S *et al.* Stop Study. After discontinuation of Efavirenz, plasma concentrations may persist for 2 weeks or longer. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004. [Abstract 131].

173 Haas D, Ribaudo H, Kim R *et al.* A common CYP2B6 variant is associated with Efavirenz pharmacokinetics and Central Nervous System Side Effects: AACTG Study NWCS214. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004 [Abstract 133].

174 Lyons F, Coughlan S, Byrne C, Hopkins S, Hall WW, Mulcahy F. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS* 2005; 19: 63–67.

175 Lorenzi P, Spicher VM, Laubereau B *et al.* Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. *AIDS* 1998; 12: F241–F247.

176 Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral therapy related lipodystrophy. *Lancet* 1999; 354: 1,112–1,115.

177 Martin JL, Brown DE, Matthews-Davis N, Reardon JE. Effects of antiviral nucleoside analogues on human DNA poymerases and mitochondrial DNA synthesis. *Antimicrob Agents Chemother* 1994; 38: 2,743–2,749.

178 Food and Drug Administration. *Important Drug Warning – Zerit and Videx*, 2–7-2001. 2001.

179 Eastone JA, Decker CF. New-onset diabetes mellitus associated with use of protease inhibitor. *Ann Intern Med* 1997; 127: 948.

180 Visnegarwala F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy. *Ann Intern Med* 1997; 127: 948.

181 Justman JE, Benning L, Danoff A *et al.* Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *AIDS* 2003; 32: 298–302.

182 Vithayasai V, Moyle GJ, Supajatura V *et al.* Safety and efficacy of saquinavir soft-gelatin capsules plus zidovudine plus optional lamivudine in pregnancy and prevention of vertical HIV transmission. *J Acquir Immun Defic Syndr* 2002; 30: 410–412.

183 Khan W, Hawkins DA, Moyle GJ *et al.* Pharmacokinetics, safety, tolerability and efficacy of saquinavir hard-gel capsules/ritonavir (SQV/r) plus 2 nucleosides in HIV-infected pregnant women. *XV International Conference on AIDS*, July, Bangkok, Thailand, 2004. [Abstract ThPeB064].

184 Acosta EP, Bardeguez A, Zorrilla CD *et al.* Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; 48: 430–436.

185 Morris AB, Cu-Uvin S, Harwell JI *et al.* Multicenter review of protease inhibitors in 89 pregnancies. *J AIDS* 2000; 25: 306–311.

186 Stek A, Khoury M, Kramer F *et al.* Maternal and infant outcomes with highly active antiretroviral therapy during pregnancy. *6th Conference on Retroviruses and Opportunistic Infections*. January 31-February 4, 1999, Chicago, IL, 1999. [Abstract 687].

187 Edwards S, Larbalestier N, Hay P *et al.* Experience of Nevirapine use in a London cohort of HIV infected pregnant women. *HIV Med* 2001; 2: 89–91.

188 Baylor M, Truffa M, Gibbs N. Hepatic toxicity of antiretrovirals in HIV-infected pregnant women: A review of the FDA's adverse event reporting system. *11th Conference on Retroviruses and Opportunistic Infections*, San Francisco, 2004. [Abstract 944].

189 Bershoff-Matcha SJ, Mundy LM, Henry JV. Adverse events to nevirapine therapy during Pregnancy. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004 [Abstract 939].

190 Hitti J, Frenkel L, Huang S *et al.* Toxicity with continuous Nevirapine in Pregnancy: Results from PACTG1022. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004. [Abstract 938].

191 Money D, Khoo D, Macdonald G *et al.* A comparison of toxicity in nevirapine vs protease inhibitor containing HAART regimens in pregnant women. *12th Conference on Retroviruses and Opportunistic Infections*, February 22-25, 2005, Boston, MA, USA, 2005. [Abstract 784].

192 Natarajan U, Pym A, Anderson J *et al.* The side effect profile associated with use of Nevirapine in a cohort of pregnant women in London. *7th Conference on HIV Drug Therapy* (Glasgow, Scotland, November 14–18), 2004. [Abstract P190].

193 Phanuphak N, Teeratakulpisarn S, Apornpong T, Phanuphak P. Comparison of hepatic and cutaneous toxicities in pregnant women with baseline CD4 o250 cells/mm3 versus those with CD4 4250 cells/mm3 receiving nevirapine (NVP) -containing highly active anti-retroviral therapy (HAART) for the prevention of mother-to-child transmission (PMCT) in Thailand. *7th International Congress on Drug Therapy in HIV Infection*, Glasgow, UK, 2004. [Abstract P322].

194 Phanuphak N, Apornpong T, Intarasuk S, Teeratakulpisarn S, Phanuphak P. Toxicities from Nevirapine in HIV-infected males and females, including pregnant females with various CD4 cell counts. *12th Conference on Retroviruses and Opportunistic Infections*, February 22-25, 2005, Boston, MA, USA, 2005 [Abstract 22].

195 Thomas T, Amornkul P, Mwidau J *et al.* Preliminary findings. Incidence of Serious Adverse Events attributed to Nevirapine among women enrolled in an ongoing trial using HAART to prevent mother-to-child HIV transmission. *12th Conference on Retroviruses and Opportunistic Infections*. Boston, MA, USA, February 22-25, 2005. [Abstract 809].

196 Morris A, Zorilla C, Vajaranant M *et al.* A review of protease inhibitor use in 89 pregnancies. *6th Conference on Retroviruses and Opportunistic Infections*, Chicago, IL, January 31–February 4, 1999. [Abstract 686].

197 Shapiro DE, Tuomala R, Samelson R *et al.* Antepartum antiretroviral therapy and pregnancy outcomes in 462 HIV-1 infected women in. [PACTG 367]. *7th Conference on Retroviruses and Opportunistic Infections*, San Francisco, CA, USA, January 30–February 2, 2000. [Abstract 664].

198 European Collaborative Study and the Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000; 14: 2,913–2,920.

199 European Collaborative Study. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS* 2004; 18: 2,337–2,339.

200 Tuomala RE, Shapiro DE, Mofenson LM *et al.* Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med* 2002; 346: 1,863–1,870.

201 Beckerman K, Covington D, Garcia P *et al.* Association between Antiretroviral therapy during pregnancy and prematurity/low birth weight. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004. [Abstract 97].

202 Jungmann EM, Mercey D, de Ruiter A *et al.* Is first trimester exposure to antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities. *Sex Trans Infect* 2001; 77: 441–443.

203 Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *New Engl J Med* 2000; 343: 1,608–1,614.

204 Gonzalez-Tome MI, Ramos J, Solis I *et al.* Gestational Diabetes and ART in Pregnant HIV-1-infected women. *12th Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA, February 22-*25,* 2005. [Abstract 68].

205 International Perinatal HIV Group. Mode of delivery and vertical transmission of HIV-1: a meta-analysis from fifteen prospective cohort studies. *New Engl J Med* 1999; 340: 977–987.

206 International Perinatal HIV Group. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS* 2001; 15: 357–368.

207 Lambert JS, Watts DH, Mofenson LM *et al.* Risk factors for pre-term birth, low birth weight and intrauterine growth retardation in infants born to HIV-infected pregnant women receiving zidovudine. *AIDS* 2000; 14: 1,389–1,399.

208 Burns DN, Landesman S, Wright DJ *et al.* Influence of other maternal variables on the relationship between maternal virus load and mother-to-infant transmission of human immunodeficiency virus type 1. *J Inf Dis* 1997; 175: 1,206– 1,210.

209 Grubert TA, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky BH, Dathe O. Complications after Caesarean section in HIV-1 infected women not taking antiretroviral therapy. *Lancet* 1999; 354: 1,612–1,613.

210 Semprini E, Castagna C, Ravizza M *et al.* The incidence of complications after Caesarean section in 156 HIV-1 positive women. *AIDS* 1995; 9: 913–917.

211 Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J *et al.* Post Caesarean morbidity in HIV-positive women. *Acta Obstet Gynecol Scand* 1999; 78: 789–792.

212 Smaill F, Hofmyer GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database Syst Rev* 2002: CD000933.

213 Avidan MS, Groves P, Blott M *et al.* Low complication rate associated with cesarean section under spinal anesthesia for HIV-1-infected women on antiretroviral therapy. *Anaesthesiology* 2002; 97: 320–324.

214 Duarte G, Read J, Gonin R *et al.* Mode of delivery and postpartum morbidity among HIV-1-infected women in Latin America and the Caribbean: The NICHD International Site Development Initiative Perinatal Study. *12th Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA, February 22-*25,* 2005. [Abstract 69].

215 Morrison JJ, Rennie JM, Milton P. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesaren section. *Br J Obstet Gynaecol* 1995; 102: 101–106.

216 Warszawaski J, Tubiana R, Le Chenadec J *et al.* Is intrapartum intravenous zidovudine sill beneficial to prevent mother-to-child HIV-1 transmission? *12th Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA, February 22-25, 2005. [Abstract 781].

217 Wimalasundera RC, Smith JH, Thom S *et al.* Is pre-eclampsia in HIV-positive women treated with antiretroviral therapy a manifestation of immune reconstitution. *Lancet* 2002; 360: 1,152–1,154.

218 Coll O, Suy A, Martinez E *et al.* Increased risk of Pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *11th Conference on Retroviruses and Opportunistic Infections* (February 8–11, 2004, San Francisco, CA, USA) 2004. [Abstract 921].

219 Mattar R, Amed AM, Lindsey PC, Sass N, Daher S. Preeclampsia and HIV infection. *Eur J Obstet Gynecol Reprod Biol* online.
220 Frank KA, Buchmann EJ, Schackis RC. Does human immunodeficiency virus infection protect against preeclampsia-eclampsia? *Obstetrics Gynecol* 2004; 104: 238–242.
221 Lee A. *Common problems in pregnancy. Therapeutics Pregnancy Lactation.* Oxford, Radcliffe Medical Press, 2000: 23–36.
222 *Anti-emetics use in pregnancy: overview by the national teratology information service in Leeds.* NK 2005.
223 Centre for Disease Suveillance and Control. HIV and AIDS in the United Kingdom. *Comm Dis Rep* 2002: 13.
224 Whittle H, Morris J, Todd J. HIV-2 infected patients survive longer than HIV-1 infected patients. *AIDS* 1994; 8: 1,620.
225 Berry N, Ariyoshi K, Jaffer S *et al.* Low peripheral blood viral HIV-1 RNA in individuals with high CD4 percentage differentiates HIV-2 from HIV-1 infection. *J Hum Virol* 1998;
1: 457–468.
226 Andreasson P, Dias F, Naucler A *et al.* A prospective study of vertical transmission of HIV-2 in Bissau, Guinea-Bissau. *AIDS* 1993; 7: 989–993.
227 Poulson A, Kvinesdal B, Abel L *et al.* Lack of evidence of vertical transmission of HIV-2 in a sample of the general population in Bissau. *J Acquir Immun Defic Syndr* 1992; 5: 25–30.
228 Smith N, Kennedy J, Bewley S *et al.* HIV-2 in pregnancy: to treat or not to treat? *Int J STD AIDS* 2001; 9: 246.
229 Smith N, Shaw T, Berry N *et al.* Antiretroviral therapy for HIV-2 infected patients. *J Infection* 2001; 42: 126–133.
230 Witvrouw M, Pannecouque C, Switzer WM, Folks TM, De Clecq E, Heneine W Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antiviral Ther* 2004; 9: 57–65.
231 Pieniazek D, Rayfield M, Hu D *et al.* HIV-2 protease sequences of subtypes A and B harbor multiple mutations associated with protease inhibitor resistance in HIV-1. *AIDS* 2004; 18: 495–502.
232 Schim van der Loeff M, Hansmann A, Awasana A *et al.* Survival of HIV-1 and HIV-2 perinatally infected children in The Gambia. *AIDS* 2003; 17: 2,389–2,394.
233 Sharland M, Blanche S, Castelli G, Ramos J, Gibb DM, PENTA Steering Committee. PENTA guidelines for the use of antiretroviral therapy. *HIV Med* 2004; 5: 61–86.
234 Gibb DM, Goodall RL, Dunn DT *et al.* Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000; 356: 904–907.
235 Resti M, Azzari C, Galli L *et al.* Maternal drug use is a preeminent risk factor for mother-to-child hepatitis C virus transmission: results from a multicenter study of 1372 mother-infant pairs. *J Inf Dis* 2002; 185: 567–572.
236 Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000; 31: 751–755.
237 Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viremia or human immunodeficiency virus infection. *Int J Epidemiol* 1998; 27: 108–117.
238 Spencer JD, Latt N, Beeby PJ *et al.* Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Viral Hepat* 1997; 4: 395–409.
239 Zanetti AR, Tanzi E, Paccagnini S *et al.* Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. *Lancet* 1995; 345: 289–291.
240 Ruiz-Extremera A, Salmeron J, Torres C *et al.* Follow-up of transmission of hepatitis C to babies of human immunodeficiency virus-negative women: the role of breast-feeding in transmission. *Pediatr Infect Dis J* 2000; 19: 511–516.
241 Tovo PA, Palomba E, Ferraris G *et al.* Increased risk of maternal-infant hepatitis C virus transmission for women coinfected with human immunodeficiency virus type 1. Italian Study Group for HCV Infection in Children. *Clin Inf Dis* 1997; 25: 1,121–1,124.
242 Pappalardo BL. Influence of maternal human immunodeficiency virus (HIV) co-infection on vertical transmission of hepatitis C virus (HCV): a meta-analysis. *Int J Epidemiol* 2003; 32: 727–734.
243 Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. *BJOG* 2004; 111: 579–584.
244 Magnani G, Degli Antoni AM, Cocca G *et al.* Risk of materno-fetal transmission of HIV infection with antiretroviral theapy and caesarian section: Experience fo the Parma Group. *Acta Biomed Ateneo Parmense* 2000; 71: 563–566.
245 Zuckerman J, Harrison TJ, Zuckerman AJ Prevention, *In:* Thomas HC, Zuckerman AJ, eds. *Viral Hepatitis.* London: Churchill Livingstone, 2004.
246 Tovo PA, Pembrey LJ, Newell ML. Persistence rate and progression of vertically acquired hepatitis C infection. European Paediatric Hepatitis C Virus Infection. *J Inf Dis* 2000; 181: 419–424.
247 Beasley RP, Hwang LY, Szmuness W *et al.* HBIG prophylaxis for perinatal HBV infections–final report of the Taiwan trial. *Dev Biol Stand* 1983; 54: 363–375.
248 Li XM, Yang YB, Hou HY *et al.* Interruption of HBV intrauterine transmission: a clinical study. *World J Gastroenterol* 2003; 9: 1,501–1,503.
249 Menendez C, Sanchez-Tapias J, Kahigwa E *et al.* Prevalence and mother-to-infant transmission of hepatitis viruses B, C, and E in Southern Tanzania. *J Med Virol* 1999; 58: 215–220.

250 Mirochnick M. Antiretroviral pharmacology in pregnant women and their newborns. *Ann NY Acad Sci* 2000; 918: 287–297.
251 Rongkavilit C, Van Heewsijk R, Limpongsanurak S *et al.* Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immun Defic Syndr* 2002; 29: 455–463.
252 Bryson YJ, Stek A, Mirochnick M *et al.* PACTG 353. A Phase I study of safety, pharmacokinetics and antiviral activity of combination nelfinavir (NFV), ZDV and 3TC in HIV-infected pregnant women and their infants. *7th Conf Retroviruses Opportunistic Infections*, San Francisco, January 30–February 2, 2000. [Abstract 715].
253 Faye A, Bertone C, Teglas JP *et al.* Early multitherapy including a protease inhibitor for human immunodeficiency virus type 1-infected infants. *Pediatr Infect Dis J* 2002; 21: 518–525.
254 Boucher FD, Modlin JF, Weller S *et al.* Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr* 1993; 122: 137–144.
255 Capparelli EV, Mirochnick M, Dankner WM *et al.* Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr* 2003; 142: 47–52.
256 Shetty AK, Coovadia HM, Mirochnick M *et al.* Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *J Acquir Immun Defic Syndr* 2004; 34: 482–490.
257 Vankandondera J, Luchters S, Hassink E, Pakker N, Mmiro F, Okong P. Reducing risk of HIV-1 transmission from mother to infant through breast-feeding using antiretroviral prophylaxis in infants (SIMBA-study). *2nd IAS Conference on HIV Pathogenesis and Treatment* (Paris, France) 2003. [Abstract LB07].
258 Taylor GP, Lyall E, Back D, Ward C, Tudor-Williams G. Pharmacological implications of prolonged in utero exposure to nevirapine. *Lancet* 2000; 355: 2,134–2,135.
259 Mirochnick M, Siminski S, Fenton T, Lugo M, Sullivan JL. Nevirapine pharmacokinetics in pregnant women and in their infacts after in utero exposure. *Pediatr Infect Dis J* 2001; 20: 803–805.
260 Rongkavilit C, Thaithumyanon P, Chuenyam T *et al.* Pharmacokinetics of stavudine and didanosine coadministered with nelfinavir in human immunodeficiency virus-exposed neonates. *Antimicrob Agents Chemother* 2001; 45: 3,585–3,590.
261 Giuliano M, Palmisano L, Galluzzo CM *et al.* Selection of resistance mutations in pregnant women receiving zidovudine and lamivudine to prevent HIV perinatal transmission. *AIDS* 2003; 17: 1,570–1,572.
262 Masquelier B, Chaix ML, Burgard M *et al.* Zidovudine genotypic resistance in HIV-1-infected newborns in the French perinatal cohort. *J Acquir Immun Defic Syndr* 2001; 27: 99–104.
263 Palumbo P, Holland B, Dobbs T *et al.* Antiretroviral resistance mutations among pregnant HIV-infected women and their newborns in the US. Vertical transmission and clades. *J Inf Dis* 2001; 184: 1,120–1,126.
264 Mcsherry GD, Shapiro DE, Coombs RW *et al.* The effects of zidovudine in the subset of infants infected with human immunodeficiency virus type-1 (Pediatric AIDS Clinical Trials Group Protocol 076). *J Pediatr* 1999; 134: 717–724.
265 Taha TE, Kumwenda N, Gibbons A *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission on HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; 362: 1,171–1,177.
266 Health Department. *HIV Post Exposure Prophylaxis.* Evidence from the UK Chief Medical Officer's Expert Advisory Group on AIDS 2001, UK. Health Department, July 2000.
267 Mofenson LM, Munderi P. Safety of antiretroviral prophylaxis of perinatal transmission for HIV-infected pregnant women and their infants. *J Acquir Immun Defic Syndr* 2002; 30: 200–215.
268 Hanson IC, Antonelli TA, Sperling RS *et al.* Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J Acquir Immun Defic Syndr* Hum Retrovir 1999; 15: 463–467.
269 The European CS. Height, weight, and growth in children born to mothers with HIV-1 infection in Europe. *Pediatrics* 2003; 111: e52–e60.
270 Culnane M, Fowler M, Lee SS *et al.* Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. *JAMA* 1999; 281: 151–157.
271 Barret B, Tardieu M, Rustin P *et al.* Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS* 2003; 17: 1,769–1,785.
272 European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr* 2003; 32: 380–387.
273 Dominguez K, Bertolli J, Fowler M *et al.* Lack of definitive severe mitochondrial signs and symptoms among deceased HIV-uninfected and HIV-indeterminate children <5 years of age, Pediatric Spectrum of HIV Disease Project (PSD), USA. *Ann NY Acad Sci* 2000; 198: 236–246.
274 Lindegren MI, Rhodes Phil, Gordon L, Fleming P. Drug safety during pregnancy and in Infants: Lack of mortality related to mitochondrial dysfunction among perinatally HIV-exposed children in pediatric HIV surveillance. *Ann NY Acad Sci* 2000; 918: 222–235.

275 Bulterys M, Nesheim S, Abrams E *et al.* Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women: retrospective review of perinatal exposure to antiretroviral drugs in the perinatal AIDS collaborative transmission study. *Ann NY Acad Sci* 2000; 918: 212–221.

276 Poirier MC, Divi RL, Al-Harthi L *et al.* Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immun Defic Syndr* 2003; 33: 175–183.

277 Hankins CD, Tookey PA, Lyall EGH, Peckham CS Follow-up of children exposed to antiretroviral therapy in pregnancy (CHART): a role for HIV physicians. *HIV Med* 2004; 5 (Suppl. 2): 35–36.

278 Scalfaro P, Chesaux JJ, Buchwalder PA, Biollaz J, Micheli JL. Severe transient neonatal lactic acidosis during prophylactic zidovudine treatment. *Intensive Care Med* 1998; 24: 247–250.

279 Giaquinto C, De Romeo A, Giacomet V *et al.* Lactic acid levels in children perinatally treated with antiretroviral agents to prevent HIV transmission. *AIDS* 2001; 15: 1,074–1,075.

280 Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S Enquete Perinatale Francaise Study Group. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS* 2003; 17: 2,053–2,061.

281 Landreau-Mascaro A, Barret B, Mayaux MJ, Tardieu M, Blanche S. Risk of early febrile seizure with perinatal exposure to nucleoside analogues. *Lancet* 2002; 359: 583–584.

282 Owens DK, Holodniy M, Mcdonald TW, Scott J, Sonnad S. A meta-analytic evaluation of the polymerase chain reaction for the diagnosis of HIV infection in infants. *JAMA* 1996; 275: 1,342–1,348.

283 Lambert JS, Harris DR, Stiehm ER *et al.* Performance characteristics of HIV-1 culture and HIV-1 DNA and RNA amplification assays for early diagnosis of perinatal HIV-1 infection. *J Acquir Immun Defic Syndr* 2003; 34: 512–519.

284 Bryson YJ, Luzuriaga K, Sullivan JL, Wara DW. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *New Engl J Med* 1992; 327: 1,246–1,247.

285 Simonds RJ, Brown T, Thea DM *et al.* Sensitivity and specificity of a qualitative RNA detection assay to diagnose HIV infection in young infants. Perinatal AIDS Collaborative Transmission Study. *AIDS* 1998; 12: 1,545–1,549.

286 Reisler RB, Thea DM, Pliner V *et al.* Early detection of reverse transcriptase activity in plasma of neonates infected with HIV-1: a comparative analysis with RNA-based and DNA-based testing using polymerase chain reaction. *J Acquir Immune Defic Syndr* 2001; 26: 93–102.

287 Burgard M, Blanche S, Mayaux MJ *et al.* Impact of Neonatal Prophylaxis on Early Diagnosis in Newborns. *10th Conference on Retroviruses and Opportunistic Infections* (San Francisco, CA, USA) 2003. [Abstract 868].

288 London HIV Consortium, Paediatric Sub-Group. *Developing Clinical Networks for Paediatric HIV Treatment and Care in London*. Cardiff: BHIVA, 2004.

289 Gibb DM, Duong T, Tookey PA *et al.* Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ* 2003; 327: 1,019.

290 Gaillard P, Fowler MG, Dabis F *et al.* Use of antiretroviral drugs to prevent HIV-1 transmission through breastfeeding: from animal studies to randomised clinical trials. *J Acquir Immune Defic Syndr* 2004; 35: 178–187.

291 Willumsen JF, Newell ML, Filteau S *et al.* Variation in breastmilk HIV-1 viral load in left and right breasts during the first 3 months of lactation. *AIDS* 2001; 15: 1,896–1,897.

292 Willumsen JF, Filteau S, Coutsoudis A *et al.* Breastmilk RNA viral load in HIV-infected South African women: effects of subclinical mastitis and infant feeding. *AIDS* 2002; 17: 407–414.

293 John-Stewart G, Mbori-Ngacha D, Ekpini E *et al.* Breastfeeding and HIV-1 transmission. *J Acquir Immune Defic Syndr* 2004; 35: 196–202.

294 Rollins N, Meda N, Becquet R *et al.* Preventing postnatal transmission of HIV-1 through breast-feeding: modifying infant feeding practices. *J Acquir Immune Defic Syndr* 2004; 35: 188–195.

295 Nduati R, John G, Mbori-Ngacha D *et al.* Effect of Breastfeeding and formula feeding on transmission of HIV-1: a randomised clinical trial. *JAMA* 2000; 283: 1,167–1,174.

296 Leroy V, Karon JM, Alioum A *et al.* Twenty-four month eefficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS* 2004; 16: 631–641.

297 Alioum A, Cortina-Borja M, Dabis F *et al.* Estimating the efficacy of interventions to prevent mother-to-child transmission of human immunodeficiency virus in breast-feeding populations: comparing statistical methods. *Am J Epidemiol* 2003; 158: 596–605.

298 Breast-feeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Inf Dis* 2004; 189: 2,154–2,166.

299 Gray G, Mcintyre J, Jivkov B *et al.* Preliminary efficacy, safety, tolerability, and pharmacokinetics of short course regimens of nucleoside analogs for the prevention of mother-to-child transmission of HIV. *XIII International AIDS Conference,* Durban, RSA, July, 9-14, 2000. [Abstract Tuorb355].

300 Dabis F, Msellati P, Meda N *et al.* 6 month efficacy, tolerance and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breast-fed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicenter trial. DITRAME Study Group. Diminution de la Transmission Mere-Enfant. *Lancet* 1999; 353: 756–792.

301 The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, SouthAfrica and Uganda (Petra study). A randomised, double-blind, placebo-controlled trial. *Lancet* 2002; 359: 1,178–1,186.

302 Brooks Jackson J, Musoke P, Fleming T *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18 month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003; 362: 859–868.