Disclaimer

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

British HIV Association
9.7.01

Writing group: Hermione Lyall[1], Maggie Blott[2], Annemiek de Ruiter[3], David Hawkins[4], Danielle Mercy[5], Zuber Mitchla[6], Marie-Louise Newell[7], Siobhan O'Shea[8], Richard Smith[9], Judith Sunderland[10], Ruth Webb[11], Graham Taylor[12].

Affiliations: [1]Department of Paediatrics, St Mary's Hospital, Imperial College, London. [2]Department of Obstetrics, Kings College Hospital, London. [3]Department of Genito-Urinary Medicine, Guys and St Thomas' Hospital, London. [4]St Stephens Centre, Chelsea & Westminster Hospital, London. [5]Mortimer Market Centre, University College Hospital, London. [6]HIV Pharmacist, Royal Free Hospital, London. [7]Department of Epidemiology and Biostatistics, Institute of Child health, London. [8]Department of Virology, Guys and St Thomas' Hospital, London. [9]Department of Obsterics and Gynaecology, Chelsea & Westminster Hospital, London. [10]Department of Midwifery, Newham General Hospital, London. [11]UK Coalition. [12]Department of Genito-Urinary Medicine, St Mary's Hospital, Imperial College, London.

Communicating author: Hermione Lyall (h.lyall@ic.ac.uk)

Sections:

Tables

Aims of the guidelines

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

Recommendations for management are given in the section on clinical scenarios, and summarised in table 3. An expanded version of these guidelines with an appendix on safety and toxicity data is available on the BHIVA website **Error! Bookmark not defined.**. The authors are available to discuss individual cases.

1) Summary

The risk of transmission is related to maternal health, obstetric factors and infant prematurity. Overall there is a close linear correlation between maternal viral load and risk of transmission, but as yet the evidence for a threshold below which transmission never occurs is limited[4]. This may be due to discrepancies between plasma and genital tract viral loads. However, the major studies of viral load and transmission have used assays with a lower limit of detection of 500-1000 HIV RNA copies/ml, and a relative insensitivity for some non-B sub-types. CD4 lymphocyte 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 [5]. The only obstetric factors that consistently show an association with risk of transmission are mode of delivery and duration of membrane rupture but invasive procedures in labour are generally avoided as they pose a theoretical risk of iatrogenic transmission. Delivery before 34 weeks of gestation has been shown to be associated with an increased risk of transmission [6].

Formula feeding has been advocated for positive women since the association with breast feeding and increased transmission was noted in 1992 [7]. The protective role of caesarean section has been clarified with both a meta-analysis [8] and a RCT reported in 1999 [9].

The findings of the first RCT, published in 1994, showing that monotherapy with zidovudine (AZT) could reduce transmission from 25% to 8% in a non breast feeding population[10], have been supported by numerous observational studies confirming this reduction in clinical practice. Subsequent studies have shown equivalent benefit in

mothers with more advanced disease and in those who are more heavily pre-treated. As standard treatment for non-pregnant adults is now with at least three antiretrovirals more women are taking combination therapy in pregnancy [2]. There are still relatively few data, however, on the safety of 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.

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

There are three groups to consider: HIV positive men with negative female partners, HIV negative men with positive female partners and HIV infected couples. All three groups may have fertility problems but for the discordant couples there is also the risk of sexual transmission of HIV. The risk of transmission to the woman, of approximately 1:500 per sexual encounter [11; 12] can be reduced, but not eliminated, by limiting exposure to the most fertile period [13]. 'Sperm washing' is a process whereby spermatozoa are removed from the surrounding HIV infected seminal plasma by a sperm swim-up technique[14]. To date there have been no seroconversions in women inseminated with washed sperm [15]. HIV positive men with low sperm counts, may be offered intracytoplasmic sperm injection following the sperm washing process [16]. Sperm washing is available in London, at the Chelsea & Westminster Hospital and St Thomas's, and in Birmingham, but not currently on the NHS. To protect an uninfected male partner, couples are equipped with quills, syringes and Gallipots and instructed on how to perform artificial insemination by partner at the time of ovulation [17]. For positive couples, safer sex to reduce transmission of viral variants is usually recommended. Couples wishing to conceive are advised to limit unprotected intercourse to the fertile period, or to follow the advice for discordant couples. The latter being especially important when there is virological failure.
In the past, in vitro fertilisation (IVF) has been much disputed for HIV infected couples with infertility. IVF is now ethically acceptable since the vertical transmission rate has fallen to < 1% along with an increased life expectancy for parents on HAART [18].

3) Sexual Health of HIV positive pregnant women

There are few data regarding the prevalence of genital infections in HIV positive women in the UK [19]. The majority of UK pregnant HIV infected women come from Sub-Saharan Africa where the prevalence of genital infections is high [20]. However, apart from the recommendation that all pregnant women should be screened for HIV, hepatitis B and syphilis, asymptomatic pregnant women are not routinely screened for genital infections. Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [21; 22]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with mother-to-child transmission (MCT) of HIV and may be inter-linked [23-25]. Although both *Chlamydia trachomatis* and *Neisseria gonnorrhoea* have been associated with chorioamnionitis, the organisms usually implicated are those

associated with bacterial vaginosis (BV) and *Ureaplasma Urealyticum* [21; 22]. A strong association between bacterial vaginosis and premature delivery has been reported [22; 26]. Organisms associated with bacterial vaginosis have been shown to stimulate HIV expression in vitro [27; 28]. There are preliminary data suggesting that BV may be associated with an increased risk of maternal HIV infection in pregnancy as well as premature delivery and HIV MCT [29]. Genital infections, particularly ulcerative diseases, are associated with sexual transmission of HIV [30; 31]. 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 [32; 33]. A recent study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis [34]. Viral load in cervico-vaginal specimens has been shown to be correlated with MCT of HIV-1 [35]. Usually, the genital tract VL will mirror the plasma VL [36], but discordance may occur with genital infection. Increased genital tract viral load secondary to infection could conceivably increase the risk of MCT.

In the absence of RCT's, but for the reasons outlined above, HIV positive pregnant women should be screened for genital infections. This should be done as early as possible in pregnancy and repeated at around 28 weeks, any infection detected should be treated according to UK national guidelines [37].

4) Psycho-social support for pregnant women with HIV

To support women to take advantage of the interventions to reduce transmission of HIV to their infants, professionals should be aware of the psycho - social issues. Women who are pregnant are usually advised to avoid taking medication if possible, but women with HIV are encouraged to take therapy to help prevent MCT, and some women struggle with this conflict. Full discussions about this dilemma will increase the likelihood of adherence to ART. Advice to avoid breast-feeding and caesarean section is also contrary to the norm and questions from family and friends may be difficult to answer. Women may require help with the practicalities of formula feeding as well as financial support.

Living with an HIV diagnosis can lead to fear about a breach of confidentiality, especially if the woman has been diagnosed during the pregnancy or not yet told anyone of her status. There should be a clear local referral pathway for HIV positive pregnant women. This should include: an HIV physician; midwife/obstetrician; paediatrician and may include a social worker, health advocate and voluntary groups. It is good practice for the woman to have met the paediatric team prior to delivery.

5) Assessment of HIV viral load in pregnancy

HIV RNA copy number varies depending on: the assay employed; biological variation of RNA; and specimen handling [38]. The contribution of these variables to HIV RNA concentrations appears to be of the order of 0.3 to 0.6 $\log_{10}$ copies/ml, although in some instances it may be as high as 1.0 $\log_{10.}$ The Bayer bDNA assay (version 3.0) generally

gives lower HIV RNA copy numbers than the Roche RT PCR (version 1.5) but the two assays have been shown to be highly correlated [39]. In order to ensure reliable and accurate quantification of HIV-1 RNA the same assay should be used to monitor viral load. In cases where there are discrepancies between viral load, CD4 cell number and clinical status it is advisable to re-test with another assay in which different nucleotide sequences are used to bind or amplify target RNA.

Accurate quantification of non-B subtypes of HIV-1 is an important requirement for monitoring pregnant women. Mismatches between the probes used in commercial assays and RNA target sequences may result in falsely low or undetectable viral loads among women infected with divergent subtypes. In the United Kingdom, 78% of infections among women attending antenatal clinics are non-B with 61% being subtype A and 29% subtype C [40]. Commercial assays were developed primarily using the B subtype of HIV-1 and their ability to quantify non B subtypes of the virus is variable [41; 42 43]

Detection of antiretroviral drug resistance

In general, sequence based genotyping assays of resistance require approximately 1000 HIV RNA copies/ml and samples with low viral loads may not be sequenced successfully. Current assays may also fail to detect minority species. Drug resistant virus quickly reverts to wild type in the absence of drug pressure consequently use of resistance testing to monitor treatment during pregnancy should ideally be conducted while the woman is still on therapy or within a few weeks of stopping [44]. Sexual transmission of drug resistant HIV is now well documented with prevalence rates, following recent infection, of approximately 10-20% in Europe and North America [45-47]. A recent UK study demonstrated a prevalence of 5% following primary HIV infection [48]. As with viral load assays, commercial resistance assays have been developed using the B subtype of HIV. Non-B subtypes may therefore be amplified and sequenced less efficiently than subtype B. However, non B subtypes generally have a drug resistance profile similar to subtype B [49].

Any women presenting in pregnancy on a non-suppressive ART regimen should have resistance testing undertaken [50]. Testing should also be considered for ART naïve women, especially if there is an epidemiological risk of primary resistance (e.g. an ART exposed partner).

5) Prescribing Antiretroviral therapy in Pregnancy

In the UK 15 compounds are currently available for treatment of HIV-1 infection, either licensed or through named patient access. Only zidovudine is specifically indicated for use in pregnancy (excluding the first trimester) to prevent HIV MCT. For most ART, prescription in pregnancy is cautioned.

Recommending antenatal HIV testing has significantly increased the number of HIV infected women identified in pregnancy, in addition an increasing number of women already known to have HIV are conceiving on ART. At preconception consultation or

some weeks into the first trimester of pregnancy they will wish to know whether they should interrupt, continue or change therapy. Few studies have addressed current practice. In this section we will summarise the efficacy data from observational and controlled studies (Table 1) and make weighted recommendations on the use of ART in pregnancy which balance the needs of the mother and infant with the limitations of the available data.

Monotherapy for reduction of mother to child transmission of HIV

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

Nucleoside Analogue Reverse Transcription Inhibitors (NRTIs) - monotherapy

The efficacy of zidovudine to reduce mother-to-child transmission of HIV-1 has been demonstrated in several large randomised controlled studies [10; 51; 52]and supported by epidemiological surveys [53 54 55; 56]. The efficacy of zidovudine ranges from: 67%, when started before the third trimester, and given to the mother by iv infusion during labour, and to the neonate; 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[57 58]. In a non-breast feeding population the transmission rate with AZT has been reduced to 6-8%[10; 54]. When Zidovudine and pre-labour caesarean section (PLCS) were combined in a cohort of women irrespective of viral load, transmission was reduced to <2 % [9].

Zidovudine will transiently decrease the plasma viral load. In ACTG 076 when zidovudine was commenced between weeks 14 and 28 of gestation, therapy was associated with a 0.24 $\log_{10}$ reduction in plasma viraemia at delivery [59]. In the Bangkok study zidovudine was commenced at week 36 resulting in a 0.57 $\log_{10}$ reduction in plasma viraemia at delivery[52]. This was considered to account for 80% of the efficacy of zidovudine to reduce transmission.

Viral load is an important predictor of transmission and zidovudine reduces transmission at all levels of maternal viraemia. However, in mothers with very high viral load (>100,000 RNA copies/ml) the transmission rate may be >60% and even with a 2/3 reduction in transmission the risk to the infant would still be around 20%. Additional measures are therefore required for these babies and probably for any mother with a viral load >10 – 20,000 copies/ml.

Resistance to AZT in pregnancy

Sequence changes in the HIV-1 RT associated with decreased viral sensitivity to zidovudine have been found, at the time of delivery, in only small numbers of women [60 61]. Higher plasma viral load and longer duration of therapy have been associated with the presence of resistance mutations at delivery[62 63] . In comparison with some other antiretroviral compounds zidovudine related mutations develop slowly, therefore shorter courses and restricting the use of zidovudine monotherapy to mothers with low viral load and high CD4 counts may limit the emergence of resistant strains. With increasing use of antiretroviral therapy primary (at the time of infection) or secondary (following therapy) acquisition of viral strains with reduced sensitivity to zidovudine may become increasingly

important [64] [65]. Whether resistant mutants are more or less transmissible remains controversial.

The safety and efficacy of didanosine and stavudine separately and combined is part of an on-going investigation [66].

Protease inhibitors (PIs) - monotherapy

PIs are highly protein bound and the data indicate that placental transfer in humans is limited. In a study of 86 pregnant women ritonavir monotherapy was initiated at gestation week 36 for a mean of 20 days. Median viral load reduction was 2.8 $\log_{10}$ and the transmission rate was 9.5% but twelve women discontinued treatment, ten because of elevated liver enzymes [67].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) - monotherapy

The rapid placental transfer and long half life of nevirapine have led to studies of the efficacy of nevirapine to reduce the risk of HIV MCT. In HIVNET 012 two doses of nevirapine, the first given to the mother in labour and the second to the neonate age 48-72 hours, were compared with zidovudine initiated in labour and prescribed to the neonate for one week. Transmission was reduced by 50% with nevirapine[68]. As with short-course zidovudine the transmission rates at one year are less than expected (15.7% with nevirapine and 24.1% with zidovudine) and the increased protection of nevirapine persisted even though the infants were breast-fed [69].

Mutations associated with decreased susceptibility to nevirapine occur rapidly and frequently on monotherapy [70]. In HIVNET 012, 19% (21/111) of mothers and 11/24 infected infants had genotypic evidence of nevirapine resistant virus [71].

In the SAINT study transmission rates at eight weeks were not significantly different from the HIVNET 012 study regimen (14%) with zidovudine 300mg plus lamivudine 150mg in labour and twice daily to mother and infant for one week post-partum (10.8%) [72]

Combination therapy for reduction of mother to child transmission

There are no large RCT's of combination therapy use in pregnancy, most studies reported are observational and some with very small numbers.

Dual nucleoside analogue therapy

In a French prospective non-randomised study of 440 women treated with zidovudine plus lamivudine from week 32, maternal plasma HIV viraemia was reduced by 0.95 $\log_{10}$ and transmission rate was 2.6% (compared historically with 6.5% on zidovudine monotherapy). Treatment was well tolerated by mothers and infants but at 6 weeks post-partum the M184V lamivudine mutation was detected in 52/132 women but not in any women treated for less than four weeks [73]. Similar findings were demonstrated in a smaller cohort [61]. In an international RCT 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[74].

Triple therapy with a PI

The most recent analysis of the US WITS cohort (Women and Infants Transmission Study) demonstrated a reduction in transmission with PI's, from 7.8% in mother-infant pairs receiving zidovudine monotherapy to 1.1% with ART including a PI [75]. In a study of 76 women taking a PI as part of combination therapy during pregnancy there were 15 pre-term deliveries (PTD) (<37 weeks) but 60% of the mother had identifiable risk factors for PTD such as a history of PTD, smoking and substance abuse [76]. A possible association between PI use in pregnancy and PTD has also been suggested by other studies [77; 78], but was not shown in 462 women participating in ACTG studies during 1998-9 [79].

Triple therapy with an NNRTI

In the ACTG 316 study nevirapine was added at labour to maternal and neonatal therapy whether it be none, mono, dual or triple. The 1.5% transmission rate among 1174 mother-infant pairs, was less than anticipated at study design (5%), and confirms the potency of current management strategies. Forty-nine percent of mothers had no detectable plasma viraemia at delivery. The study was closed when it became clear that it was not powered to demonstrate any benefit from Nevirapine used in this way [80]. Genotypic studies demonstrated resistance mutations to nevirapine in 11% (5/46) of mothers with detectable (>400 copies/ml) plasma viraemia at delivery [81].

7) Maternal drug toxicities in pregnancy

Pre-clinical and clinical safety data has been reviewed elsewhere [82] and can be found on the web site. Physiological changes in pregnancy may alter the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing and side effects.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside analogue drugs are generally well tolerated in pregnancy; reported incidences of adverse effects are similar to those reported in non-pregnant HIV-infected individuals [77]. Nucleoside analogues can cause mitochondrial dysfunction as they have varying

affinity for mitochondrial DNA γpolymerase, which may, result in mitochondrial DNA depletion [83]. Toxicity related to mitochondrial dysfunction has been reported in patients receiving long-term treatment with nucleoside analogues and although this generally resolves with discontinuation of the drug or drugs fatalities have been reported.
Early in 2001 the US Food and Drugs Administration [84]and the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP/228/01) and Bristol Myers Squibb advised that three pregnant women had died of lactic acidosis following treatment with stavudine and didanosine (as part of triple therapy) and that a further 4 cases of lactic acidosis in pregnancy had been reported with this combination. It is not clear whether the frequency of this complication is higher in pregnant than with non-pregnant women. The use of ddI/d4T in pregnancy should for the time-being be restricted to woman with resistance to or intolerance of other nucleoside analogues. Monitoring liver function and blood lactate in pregnant women on this combination is recommended.

Protease Inhibitors

Hyperglycaemia, new onset diabetes, exacerbation of existing diabetes mellitis and diabetic ketoacidosis have been reported with administration of protease inhibitors [85-87].
Women taking ART which includes a PI have been reported to 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%)[88].
In a study of 86 HIV-positive, treatment naïve women, side effects of ritonavir montherapy commenced in the 36th week of pregnancy were prominent [67]. Other observation studies have demonstrated similar side effects to those seen in the non-pregnant population [76; 89; 90;91].

Nevirapine

The use of nevirapine as part of combination antiretroviral therapy was retrospectively reviewed in a cohort of 46 HIV-infected pregnant women. Although, initiated in 30 during pregnancy, nevirapine was well tolerated and the only adverse effects probably related to nevirapine were rash (2) and biochemical hepatitis (2) [92].

Other Drug Treatments

Women on antiretroviral therapy are commonly on other therapies. In a multi-centre 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 carinii pneumonia prophylaxis combined with ART [93]. The need for prophylactic therapies in women of child-bearing potential should be regularly reviewed as immune function recovers on ART.

8) Obstetric management of pregnancy and delivery

Since the majority of vertical transmission occurs during the intrapartum period, it was proposed that pre-labour caesarean section with avoidance of labour and the birth canal might reduce the risk of transmission [94-96]. Definitive support for the protective effect of PLCS came from a trans-Atlantic meta-analysis of 15 prospective cohort studies [8] and a randomised controlled study of mode of delivery in Europe [9;9].
The meta-analysis of 8533 mother-child pairs confirmed that the vertical transmission rate was 50% lower in women who underwent caesarean section before the onset of labour or rupture of the membranes. This protective effect persisted when ART was used. In the RCT, there was an over all reduction in transmission of 70%, in a cohort of women with all levels of CD4 and disease status. The maternal complication rate of PLCS was very low.
In a further meta-analysis of the same cohorts, the risk of transmission increased approximately 2% for every hour of ROM up to 24 hours[97]. In women with an AIDS diagnosis the risk of transmission increased from 8% after 2 hours of ROM to 31% after 24 hours of ROM.

Maternal viral load data were not available for the meta-analyses or the mode of delivery RCT. It has subsequently been suggested that mothers with very low / undetectable viral load might consider vaginal delivery. In a recent meta-analysis of seven prospective studies from the US and Europe there were 44 transmissions in 1020 deliveries where maternal plasma viral load was < 1000 HIV RNA copies / ml at or around delivery [4]. The transmission rate for mothers on ART was 1% compared to 9.8% for no treatment. In multivariate analysis transmission was lower: with ART; caesarean section; greater birth weight; and higher CD4 count. These data were collected at a time when HIV-RNA PCR assays were less sensitive than currently, and suggest a protective effect of both ART and caesarean section even at very low viral loads. However, whether caesarean section has an additive effect at a delivery viral load of < 50 HIV RNA copies / ml is not known. Cost effectiveness analysis suggests that the vertical transmission rate would have to be less than 0.5% before caesarean section would be no longer cost effective[98].
The benefit of elective caesarean section in reducing the risk of vertical transmission is now clear, especially for women with detectable viral load. However possible surgical complications must be included in any discussion regarding mode of delivery. Some studies have suggested that post operative complications are increased in HIV infected women compared to the background population [99-101] others [9] found no difference. Reported complication rates are related to the level of maternal immunocompromise.

Management of Delivery

A plan for delivery management should be made in good time. Delivery by PLCS should be undertaken at 38 weeks[102] but there is some evidence that women infected with HIV do labour early and if there are concerns that delivery may occur sooner the date for the caesarean section could be brought forward [24;103]. If labour starts prior to the planned delivery date, intravenous zidovudine should be commenced if this is part of the ART regime, but the caesarean section should not be delayed to complete the induction course

of Zidovudine. If there is premature rupture of membrane, with or without labour, the risk of HIV transmission must be balanced with the risk of premature delivery. There is no known contra-indication to the use of short term steroids to promote fetal lung maturity in women with HIV.

Although a PLCS is the recommended mode of delivery for women with HIV, some women may still wish for a vaginal delivery. This may be an important consideration for women who are planning to return to a country where subsequent caesarean section deliveries may not be possible or safe. If a vaginal birth is planned the membranes should be left intact until delivery is imminent. Fetal electrodes and blood sampling must be avoided. If there are signs of fetal distress consideration should be given to performing an emergency caesarean section as the risk of vertical transmission of HIV is increased after emergency vaginal obstetric intervention.

Other Pregnancy issues

Prenatal diagnosis

HIV infected women contemplating invasive prenatal diagnosis should be counselled in a specialist fetal medicine unit and the best non-invasive screening tests available should be employed in the first instance. Data on the risks of transmission with chorionic villis sampling or second trimester amniocentesis are sparse. Administration of ART to cover the procedure should be considered.

Women who become unwell in the third trimester of pregnancy

Presentation in the third trimester with signs and symptoms of pre-eclampsia, cholestasis or other liver dysfunction may be due to these complications of pregnancy but may also be adverse effects of ART. Any woman presenting with vomiting, malaise or oedema should be investigated for acidosis, hepatitis, pancreatitis, and disseminated intravascular coagulation whether or not she has hypertension or proteinuria. If there is lactate acidaemia / acidosis discontinuation of ART even at this crucial time must be seriously considered.

9) Interventions to reduce mother to child transmission of HIV

Table 3 details 9 clinical scenarios where a different approach to therapy in pregnancy may need to be considered and the issues relating to each scenario are discussed in this section. Pre-labour caesarean section at 38 weeks is recommended as the mode of delivery in all scenarios. Consideration for vaginal delivery may be given for women on stable therapy with undetectable viral load, but there are as yet, insufficient data for this to be formally recommended.

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

Asymptomatic women with low plasma viral loads (less than 10 – 20,000 HIV RNA copies/ml) and good CD4 counts (> 200 – 350 cells/μl) do not require ART for their own health [3] AZT monotherapy with PLCS can be advocated for them to reduce vertical transmission as well as ART exposure in pregnancy. An alternative regimen for those wishing to deliver with no detectable viraemia would be Short Term Triple Antiretroviral Therapy "START" (see below).

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

US [104] and UK [3] guidelines currently recommend that women with advanced HIV who would normally be treated with ART should be managed as if they were not pregnant. For these women, for asymptomatic women with high viral load and for women with prior zidovudine exposure and zidovudine resistant virus combination therapies are recommended. Until recently it was thought that with the exception of the third group zidovudine should always be included as it was the only compound shown to have reduced transmission. However, there are now data for both ritonavir and nevirapine monotherapies which suggest equivalence with zidovudine (see above). Since triple combinations reduce plasma viraemia to less than 50 copies/ml, vertical transmission, unless occurring prior to the initiation of therapy or in mothers in whom the viral load is underestimated, is likely to be a rare event. Although biologically plausible this assumption still needs to be confirmed epidemiologically.

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

Scenario 4,5: Women who conceive on therapy

Women who conceive whilst on antiretroviral therapy may wish to discontinue therapy during the first trimester. There are no data to support or refute this. Consideration should be given to maternal health and immune status at the time of initiating therapy as well as

at the current time – viral rebound will occur within two to three weeks and 'strategic treatment interruptions' have been associated with significant CD4 lymphocyte decline. This may not only jeopardise maternal health but in theory result in reactivation of infections associated with congenital abnormalities e.g. CMV. Many women will not realise or report their pregnant state until well into the period of organogenesis. If the mother's treatment is failing then this should be changed in time to ensure the lowest possible viraemia at the time of delivery. Resistance testing can help to identify the best options. Only exceptionally should antiretroviral therapy be initiated in or changed during the first trimester. Reasonable exceptions include serious illness for which antiretrovirals are the only recognised therapy.

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

For women who present very late in gestation or in labour, for whom no transmission risk assessment has been possible it seems sensible to include compounds that rapidly cross the placenta and have reliable pharmacokinetics in the neonate. In this situation the most effective antiretroviral therapy is nevirapine. Given the high risk of resistance developing in the mother with even a single dose of nevirapine monotherapy[71; 81], two other compounds, usually nucleoside analogues such as zidovudine and lamivudine should be started. During labour zidovudine should preferably be infused IV and all treatment should be continued after delivery until the mother's clinical, immunological and virological status have been determined. Consideration should be given to continuing triple therapy until maternal plasma viraemia has become undetectable which would theoretically reduce the risk of development of resistance to current therapy (see above for details on stopping nevirapine in relation to other drugs).

Scenario 9: Presentation of the infant after delivery

Where it is only ascertained after delivery that an infant has been born to an HIV infected mother, post exposure prophylaxis (PEP) should be offered as soon as possible. There is observational data that AZT can reduce transmission in this situation if given within 48 hours of delivery [56]. Although there are no data, it would seem logical and consistent with other current PEP recommendations for high risk exposure to offer triple combination therapy for four weeks[105] (see below for ART choices).

10) Management of infants born to HIV infected mothers

Exposure to ART

Most neonates born in the UK to mothers known to have HIV will be exposed to ART *in utero*, during delivery and after birth for the first 4-6 weeks of life. Neonatal drug metabolism is generally slower than that of older infants or children, and premature neonates have even less efficient metabolism. Neonatal dosing regimens have been developed for most of the nucleoside analogues and for nevirapine (Table 4). Adequate

neonatal blood levels are difficult to achieve with nelfinavir and there is little experience of other PI's [106]. In Europe, the only ART available for intravenous (IV) use in sick and / or premature neonates, unable to take oral medication, is ZDV. Reduced oral and IV dosing schedules for premature infants have only been developed for ZDV. Neonatal metabolism of nevirapine is induced where there is antenatal exposure, so if this drug is subsequently given to the neonate a different regime is required [107;108].

When to Consider Combination ART in Neonates

There have been very few studies of combination therapy in neonates[90;106;109]. Whether combination ART to the neonate has any additional benefit over single drug treatment is not known. Where a mother on combination therapy delivers with no detectable viraemia, our current practice is to use mono-therapy for the neonate, as this is easier for the family and may reduce the incidence of adverse events in the neonate. The drug chosen from the maternal combination is usually the NRTI with the best-known infant pharmacokinetics (eg ZDV, 3TC etc). With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred. Zidovudine should not be given to an infant born to a mother who is receiving stavudine because of their theoretical competitive interaction.

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

1) where an unplanned delivery occurs, either prematurely prior to starting ART, or after a late presentation when details of maternal HIV parameters may not be available (scenario's 6,7,8).
2) where the mother is only found to be HIV infected after delivery (scenario 9).

There have been no trials of combination ART for infants in these situations, but as in other post-exposure prophylaxis cases it should also be considered for neonates. We have used ZDV, 3TC and NVP for infants born to ART naïve women, but for non-naïve mothers other combinations might be required if there is a possibility of resistance. Resistance testing should be carried out in the mother in such a situation and as early as possible in the infant as well, if infected.

Duration of Treatment for Neonates

In PACTG 076, ZDV was administered for 6 weeks after birth and this subsequently became standard of care[10]. However, in a recent Thai study, a three day course of neonatal zidovudine was equivalent to one months therapy provided the mother had received zidovudine from 28 weeks gestation [51]. In UK centres, neonates are currently treated for 4-6 weeks.

Side Effects of Treatment

Long term

Long term side effects of perinatal exposure to ART can be considered in four main categories: teratogenic; carcinogenic; developmental; and mitochondrial. Teratogenicity is

most likely to be a problem with first trimester exposure to ART +/- other drugs. To date, no increase in total number nor any specific fetal abnormality have been identified, but the voluntary reporting rate is disappointingly low [110]. Detailed fetal anomaly scanning at 18-20 weeks is advised after first trimester exposure. NRTI exposure could theoretically lead to a longterm risk of carcinogenicity, but no increased rate has been identified [111]. In the UK, the register of cancer and deaths is linked anonymously to the register of infants born to mothers with HIV to high light any relationship. So far, no adverse developmental effects of ART exposure have been demonstrated in children [112]. Mitochondrial toxicity, including fatal encephalopathy, after perinatal ART exposure was first reported from the prospectively followed French cohort[113], and in an updated analysis toxicity was suspected in 18/2547 (0.7%) of exposed uninfected children [114]. Deaths related to mitochondrial toxicity have not been identified in other large cohorts [115]. Long term follow up of infants from PACTG 076, found two ZDV exposed children with unexplained retinopathy and cardiomyopathy, both potential mitochondrial toxicities [112]. Another study did not demonstrate any evidence of cardiomyopathy [116].

Short term

Short term, acute mitochondrial toxicity may also be a problem in the new-born, exacerbating the metabolic stress of delivery. A small number of sick infants have been reported with severe lactic acidosis, multi-system failure and anaemia, not attributable to any other cause, all have recovered with supportive care [117;118]. Elevated lactic acid levels have also been found in asymptomatic ART exposed infants [119].

Symptomatic neonatal anaemia is increasingly reported in infants exposed to ART, and may be worse with combination ART [120]. Transfusion is rarely required and most children respond to discontinuation of marrow suppressive therapy. Abnormal liver function has been reported in infants exposed to zidovudine with lamivudine[120]. In a small study, infants exposed to PIs *in utero* had significantly higher γGT levels than therapy naïve or zidovudine monotherapy exposed infants [121]. In a study of the safety and tolerance of ritonavir in combination with lamivudine and zidovudine given to mothers, 3/6 infants were born prematurely, two with severe hypoglycaemia, whilst the third infant, delivered severely preterm, died. One infant had grade 3/4 hyperbilirubinaemia, one had neutropenia and two were significantly anaemia [90]. High triglyceride levels were documented transiently in 2/6 infants treated with nelfinavir (combined with stavudine plus didanosine), despite the fact that inadequate plasma levels of nelfinavir were achieved [109].

In view of the metabolic abnormalities increasingly reported with ART, exposed neonates should have base line investigations including: full blood count; pH; lactate; glucose; Urea & elecrolytes; liver function tests; trigylcerides and amylase; as well as diagnostic HIV PCR tests. These tests may be repeated with each set of HIV diagnostic samples.

Laboratory diagnosis of HIV infection in non-breast fed Infants

The gold standard test for HIV infection in infancy is HIV DNA PCR on peripheral blood lymphocytes [122]. As most infants are infected intrapartum and blood levels may still be very low, HIV DNA is not amplified from all infected infants at birth. Indeed a positive HIV PCR result within 72 hours of birth has been taken as evidence of intra-uterine transmission [96]. However, by 3 months of age > 95% of non-breast fed HIV infected infants will be PCR positive. In view of the genomic diversity of HIV a maternal sample should be amplified with the infant sample to confirm that the primers used can detect the maternal virus. If maternal virus cannot be detected by HIV DNA PCR, then different primer sets, or a different test e.g. HIV culture / HIV RNA PCR should be used [123]. Our current practice is to test infants at one day, one month, and three months of age. If all these tests are negative and the baby is not being breast fed, the parents are informed that the child is not infected. Loss of maternal antibodies is subsequently confirmed at 18 months of age. It is not necessary to carry out other surrogate or less sensitive tests (eg CD4, immunoglobulins, p24 antigen) unless there is a concern about the sensitivity of the HIV DNA PCR. Use of HIV RNA PCR ("viral load tests") for infant diagnosis has been increasingly reported, but these tests give false positive results of low copy number, causing unnecessary worry to families [124;125].

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

Prophylaxis, Immunisations and Clinical Monitoring

Primary pneumocystis carinii pneumonia (PCP) in infants with HIV remains a disease with a high mortality and morbidity [126]. However as the risk of neonatal HIV infection has fallen to <1% with antenatal interventions, the necessity for PCP prophylaxis has declined and in most European countries is no longer prescribed. PCP prophylaxis should be prescribed to infants born to mothers who received no interventions.

Infants born to HIV infected mothers should follow the routine immunisation schedule except that, BCG should not be given until the infant is confirmed un-infected. The risk of live oral polio vaccination (OPV) to HIV infected infants and their carers has not proved significant, so it is unnecessary to substitute killed injected polio vaccine. The hepatitis status of the HIV infected mother should be ascertained, so that Hepatitis B vaccination can be carried out if necessary. PCR amplification is required for early diagnosis of HCV infection in infants born to HCV infected mothers.

Reporting and long term follow up

Clinicians caring for women with HIV and their children have a responsibility to report them to the UK National study of HIV in pregnancy, via the RCOG antenatally and the BPSU after birth. All women who receive ART in pregnancy should be registered prospectively with the International Drug Registry. BPSU follow up of HIV exposed

uninfected infants will now extend beyond 18 months to at least 5 years of life to assess for longer term affects of ART exposure (personal communication, Pat Tookey).

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

11) Infant feeding

Breastfeeding is an important route of transmission. In the UK, where safe infant feeding alternatives are available, HIV-infected women are advised to refrain from breast feeding. Where a mother acquires primary HIV infection after delivery, whilst breastfeeding, the risk of transmission through breastfeeding is about 30% [7]. In established infection, the additional risk of transmission through breastfeeding, over and above the intra-uterine and intra-partum contribution, is estimated to be between 7 and 22% [7]. These estimates agree with those from prospective studies, and from a randomised trial [127].

If a woman chooses to breast feed despite the evidence, then she should be advised to breastfeed exclusively as this may reduce the risk of transmission, [128] and for a shorter rather than longer period. If she is taking antiretroviral medication it should be explained that there is no evidence that this will protect the infant. Although ART is likely to reduce free virus its effect on cell associated virus in the milk is not known.

12) Pregnancy in women with HIV-2 infection

HIV-2 is endemic in West Africa and other areas of high prevalence include parts of India and Portugal. Thirty-two cases of HIV-2 infection had been reported in the UK and 11 of these infections were in women [129]. 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. [130;131]. Vertical transmission rates of HIV-2 are also low, 0-4% in breast fed infants, in the absence of any interventions [132-134]. 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 / µl as this is usually associated with a detectable viraemia [135]. NNRTI's have little inhibitory activity against HIV-2 and are therefore not recommended but the virus is susceptible to nucleoside reverse transcriptase inhibitors and some protease inhibitors. 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. 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. There is one laboratory in the UK which can provide this service (contact Dr Judy Brewer, Royal London Hospital and St. Batholomew's). Infants born to infected women can be monitored for HIV-2 DNA PCR and loss of HIV-2 antibodies by 12-18 months of age.

Reference List

1. US Department of Health and Human Services. Agency for Health Care Policy and Research. Acute pain management: operative or medical procedures and trauma. Rockville (MD): Clinical Practice Guideline No.1.AHCPR Publication No.92-0023.p.107 . 1993.

2. BHIVA Guidelines Co-ordinating Committee. British HIV Association Guidelines for antiretroviral treatment of HIV seropositive individuals. *Lancet* 1997;**349**:1086-1092.

3. BHIVA Treatment Guidelines Writing Sub-Committee. British HIV association guidelines for the treatment of HIV disease with anti-retroviral therapy (2001). *HIV Medicine* 2001; **in press**:

4. Ioannidis JP, Abrams EJ, Ammann AJ, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis* 2001;**183**:539-545.

5. The European Collaborative Study. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS* 1999;**13**:1377-1385.

6. The European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. *Lancet* 1992;**339**:1007-1012.

7. Dunn DT, Newell M-L, Ades AE, Peckham C. Estimates of the risk of HIV-1 transmission through breastfeeding. *Lancet* 1992;**340**:585-588.

8. The 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.

9. The 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**:1035-1039.

10. 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**:1173-1180.

11. Saracco A, Musicco M, Nicolosi A, et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Sydnr* 1993;**6**:497-502.

12. Maestro TD, de Vincenzi I. Probabilities of sexual HIV transmission. *AIDS* 1996;**10**:575-582.

13. Mandelbrot L, Heard I, Henrion-Geant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. *Lancet* 1997;**349**:850-851.

14. Semprini AE, Levi-Setti P, Bozzo M, et al. Insemination of HIV-negative women with processed semen of HIV-positive partners. *Lancet* 1992;**340**:1317-1319.

15. Gilling-Smith C. HIV prevention. Assisted reproduction in HIV-discordant couples. *AIDS Reader* 2000; **10**:581-587.

16. Marina S, Marina F, Alcolea R, Nadel J, Exposito R, Huguet J. Pregnancy following intracytoplasmic sperm injection from an HIV-1-seropositive man. *Hum Reprod* 1998;**13**:3247-3249.

17. Smith JR, Forster GE, Kitchen VS, Hooi YS, Munday P, Paintin DB. Infertility management in HIV positive couples: a dilemma. *BMJ* 1991;**302**:1447-1450.

18. Gilling-Smith C, Smith RJ, Semprini AE. HIV and infertility: time to treat. *BMJ* 2001;**322** :566-567.

19. Madge S, Phillips AN, Giffioen 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. *Int J Epidemiol* 1998;**27**:1068-1071.

20. 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 Med* 1995;**71**:207-211.

21. 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.

22. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *New Engl.J.Med.* 2000;**342**:1500-1507.

23. 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** :1617-1623.

24. The European Collaborative Study. Vertical transmission of HIV-1: maternal immune status and obstetric factors. *AIDS* 1996;**10**:1675-1681.

25. 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 Infect Dis* 1999;**179**:319-328.

26. 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**:1737-1742.

27. Hashemi FB, Ghassemi M, Roebuck KA, Spear GT. Activation of Human Immunodeficiency virus Type 1 Expression by *Gardnerella vaginalis*. *J Infect Dis* 1999;**179**:924-930.

28. 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 Infect Dis* 2000;**181**:1574-1580.

29. Taha TE, Gray RH. Genital tract infections and perinatal transmission of HIV. *Ann N Y Acad Sci* 2000;**918**:84-98.

30. 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.

31. 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.

32. 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**:F85-F93

33. 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 Infect Dis* 2000;**181**:1950-1956.

34. 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.

35. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. Bangkok Collaborative Perinatal HIV Transmission Study Group. *J Infect Dis* 2000;**181**:99-106.

36. 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 Infect Dis* 2000;**179**:871-882.

37. Anonymous UK national guidelines on sexually transmitted infections and closely related conditions. *Sex.Transm.Inf.* 1999;**75**:

38. 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**:1471-1479.

39. 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**:3612-3614.

40. 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 Immune Defic Sydnr* 2001;**in press**:

41. Coste J, Montes B, Reynes J, Peeters M, 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.

42. Parekh B, Phillips S, Granade T, Baggs J, et al. Impact of HIV-1 subtype variation on viral RNA quantitation. *AIDS Res Hum Retroviruses* 1999;**15**:133-142.

43. Damond F, Apetrei C, Descamps D, et al. HIV-1 subtypes and plasma RNA quantification. *AIDS* 1999;**13**:286-287.

44. Devereux H, Youle M, Johnson M, et al. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS* 1999;**13**:123-127.

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

46. Little S, Daar E, D'Aquila R, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. *JAMA* 1999;**282**:1142-1149.

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

48. Pillay D, Cane P, Shirley J, et al. Detection of drug resistance associated mutations in HIV primary infection within the UK. *AIDS* 2000;**14**:906-907.

49. Adje, C., Cheingsong Popov, R., Roels, W., and 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 (TuOrB298). 2000. Durban, RSA.

50. The 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.

51. 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.

52. 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.

53. Cooper ER, Nugent R, Diaz C, et.al. After AIDS Clinical Trial 076: the changing pattern of zidovudine use during pregnancy, and subsequent reduction in the vertical transmission of human immunodeficiency virus in a cohort of infected women and their infants. *J Infect Dis* 1996;**174**:1207-1211.

54. 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.

55. AnonymousTherapeutic and other interventions to reduce the risk of mother-to-child transmission of HIV-1 in Europe. The European Collaborative Study. *Br J Obstet Gynaecol* 2000;**105**:704-709.

56. 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**:1409-1414.

57. 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.

58. Ditrame ANRS 049 Study Group. 15-month efficacy of maternal oral zidovudine to decrease vertical transmission of HIV-1 in breastfed African children. *Lancet* 1999;**354**:2050-2051.

59. 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**:1621-1629.

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

61. 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.

62. Palumbo, P., Dobbs, T., Holland, B., Luo, C., Pau, C., Respess, S., Buterys, M., and for the Perinatal AIDS Collabortive Transmission Study. Antiretroviral resistance mutations among pregnant HIV-infected women and their newborns in the US: Vertical transmission and clades. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA (TuPpB1230).

63. Sibailly, TS., Ekpini, E., Boni-Ouattara, E., Nkengasong, J., Maurice, C., Kouassi, MK., Roels, TH., Greenberg, AE., and Wiktor, SV. Clinical course of HIV infection and surveillance for zidovudine resistance among HIV-infected women receiving short-course zidovudine therapy in Abidjan, Cote d'Ivoire. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA TuPeC3354.

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

65. 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.

66. Gray, G., McIntyre, J., Jivkov, B., Schorn, M., Lala, S., Reynolds, L., Ledeine, J-M., Van Beek, A., and Schnittman, S. 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. 9-14 July, 2000, Durban, RSA (TuOrB355).

67. Limpongsanurak, S., van Leeuwen, R., Macleod, C., and 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 January 31- February 4, 1999, Chicago, USA (241).

68. 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.

69. Owor, M., Deseyve, M., Dueifeld, C., Musisi, M., Fleming, T., Musoke, P., Guay, L. A., Mmiro, F., and Jackson, B. The one year safety and efficacy data of the HIVNET 012 trial. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA (LbOr1). 2000.

70. Havlir D, Cheeseman SH, McLaughlin M, et al. High-Dose Nevirapine: Safety, Pharmacokinetics, and Antiviral Effect in Patients with Human Immunodeficiency Virus Infection. *J.Infect.Dis* 1995;**171**:537-545.

71. Eshleman, SH., Mracna, M., Guay, L. A., Deseyve, M., Cunningham, S., Musoke, P., Mmiro, F., and Jackson, JB. Selection of Nevirapine Resistance Mutations (NVP^R) in Ugandan women and infants receiving NVP prophylaxis to prevent vertical transmission (HIVNET-012). 8th Conference on Retroviruses and Opportunistic Infections Feb 4-8, 2001, Chicago, IL, USA (516).

72. Moodley, D. The SAINT Trial: Nevirapine (NVP) versus zidovudine (ZDV) + lamivudine (3TC) in prevention of peripartum HIV transmission. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA (LbOr2)

73. 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.

74. Gray, G. The PETRA study: early and late efficacy of three short ZDV/3TCcombination regimens to prevent mother-to-child transmission of HIV-1. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA (LbOr5).

75. Blattner, W., Cooper, E., Charurat, M., Thompson, B., Hanson, C., Mofenson, L. M., Pitt, J., Handlesman, E., Diaz, C., Hayani, K., Smeriglio, V., and Hoff, R. Effectiveness of potent antiretroviral therapy on reducing perinatal transmission of HIV. The XIII International AIDS Conference, 9 - 14 July 2000, Durban, RSA.

76. Morris AB, Cu-Uvin S, Harwell JI, et al. Multicentre review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Sydnr* 2000;**25**:306-311.

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

78. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000;**14**:2913-2920.

79. Shapiro, D. E., Tuomala, R., Samelson, R., Burchett, S. K., Ciupak, G., McNamara, J., Pollack, H., and Read, J. Antepartum antiretroviral therapy and pregnancy outcomes in 462 HIV-1 infected women in 1998-1999 [PACTG 367]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA 30 Jan - 2 Feb, 2000.

80. Dorenbaum, A. for the PACTG 316 Study Team. Report of results of PACTG 316: An international Phase III trial of Standard Antiretroviral (ARV) prophylaxis plus nevirapine (NVP) for prevention of perinatal HIV transmission. 8th Conference on Retroviruses and Opportunistic Infections, 4-8 Feb 2001, Chicago, IL, USA (LB7).

81. Cunningham, CK., Britto, P., Gelber, R., Dorenbaum, A., Mofenson, L. M., Culnane, M., Sullivan, J., and and the PACTG 316 Team. Genotypic Resistance analysis in women participating in PACTG 316 with HIV RNA > 400 copies/ml. 8th Conference on Retroviruses and Opportunistic Infections, 4-8 Feb 2001, Chicago, IL, USA (712).

82. Taylor GP, Low-Beer N. Antiretroviral therapy in Pregnancy: A focus on safety. *Drug Safety* 2001;**24**: in press

83. 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**:1112-1115.

84. Food and Drug Administration. Important Drug Warning - Zerit and Videx. 7-2-2001. **Error! Bookmark not defined.**

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

86. Lumpkin, MM. Reports of diabetes and hyperglycemia in patients receiving protease inhibitors for the treatment of human immunodeficiency virus (HIV). Food and Drug Administration,Rockville,MD . **Error! Bookmark not defined.**

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

88. Justman, J., Dancff, A., Benning, L., Robinson, E., Weber, K., Minkoff, H., Levine, A., Young, M., Greenblatt, R., and Anastos, K. Association of diabetes and protease inhibitor use in a large natural history cohort of HIV+ women. 6th Conference on Retroviruses and Opportunistic Infections. 31 Jan - 4 Feb, 1999, Chicago, IL, USA. (661).

89. Scott, G., Shapiro, D. E., Scott, W., Cunningham, B., Smith, E., Mofenson, L. M., Flynn, PM., and O'Sullivan, MJ. Safety and tolerance of ritonavir in combination with lamivudine and zidovudine in HIV-1 infected pregnant women and their infants. 6th Conference on Retroviruses and Opportunistic Infections, 31 Jan - 4 Feb, 1999, Chicago, IL, USA. (688).

90. 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, 31 Jan - 4 Feb, 1999, Chicago, IL, USA. (687).

91. Vithayasai V, Hawkins D, Subjatura V, et al. Safety and Efficacy of Saquinavir-Sft Gelatin Capsules + Zidovudine + Optional Lamivudine in Pegnancy and Prevention of Vertical HIV Transmission. 1st IAS Conference on HIV Pathogenesis July 2001, Buenos Aires, Argentina (759).

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

93. Jungmann, E., Edwards, S., Booth, T., Donoghy, S., Mercey, D., Lyall, H., Mohan, D., de Ruiter, A., and Taylor, GP. ART and PCP prophylaxis in early pregnancy: A highly teratogenic combination? 2nd Conference on Global Strategies for prevention of HIV transmission from Mother to Infants.Sept 1-6, Montreal, Canada. 1999.

94. Simonon A, Leparge P, Karita E, et al. An assessment of the timing of mother-to-child transmission of human immunodeficiency by polymerase chain reaction. *J Acquir Immune Defic Sydnr* 1994;**7**:952-957.

95. Newell M-L. Mechanisms and timing of mother to child transmission of HIV-1. *AIDS* 1998;**12** :831-837.

96. 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**:1246-1247.

97. The 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.

98. Mrus JM, Goldie SJ, Weinstein MC, Tsevat J. The cost-effectiveness of elective caesarean section delivery for HIV-infected women with detectable HIV RNA during pregnancy. *AIDS* 2000;**14**:2543-2552.

99. 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.

100. 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.

101. 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**:1612-1613.

102. Morrison JM, 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.

103. The European Collaborative Study. Is Zidovudine therapy in pregnant HIV infected women associated with gestational age and birth weight. *AIDS* 1999;**13**:119-124.

104. Department of Health and Human Resources. Guidelines for the use of antiretroviral agents in HIV infected adults and adolescents. 23-4-2001. **Error! Bookmark not defined.**

105. HIV Post Exposure Prophylaxis. Evidence from the UK Chief Medical Officer's Expert Advisory Group on AIDS. 2001. UK Health Department July 2000.

106. Bryson, Y. J., Stek, A., Mirochnick, M., Connor, J., Huang, S., Hughes, M., Mofenson, L. M., Culnane, M., Snidow, J., and Gersten, M. PACTG 353. A Phase I study of safety, pharmacokinetics and antiviral activity of combination nelfinavir (NFV), ZDV and 3TC in HIV-infected pregnant women and their infants. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, USA, 30 Jan - 2 Feb, 2000 (715).

107. Taylor GP, Lyall E, Back D, Ward C, Tudor-Williams G. Pharmacological implications of prolonged in utero exposure to nevirapine. *Lancet* 2000;**355**:2134-2135.

108. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet* 2000;**39**:281-293.

109. Rongkavilit, C., Prisuwanna, P., Van Heewsijk, RPG., Limpongsanurak, S., Srigritsanapol, A., Boonrod, C., Mahanontharit, A., Chuenyam, M., and Phanuphak, P. Safety and pharmacokinetics of nelfinavir when administered with stavudine and didanosine in HIV-1 exposed newborn infants. The XIII International AIDS Conference, Durban, RSA. 9 - 14 July 2000 (MoPeB2188).

110. The Antiretroviral Pregnancy Registry (Interim Report) 1 Jan 1989 - 31 Jul 2000. 2000. Wilmington, NC, USA, Registry Project Office.

111. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J.Acquir.Immune Defic.Sydnr.Hum.Retrovir.* 1999;**15**:463-467.

112. 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.

113. Blanche S, Mandelbrot L, Rustin P, et al. Persistant mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;**354**:1084-1089.

114. Delfraissy, J-F., Blanche, S., Tardieu, M., Barret, B., Rustin, P., Mayaux, MJ. Mitochondrial and mitochondrial-like symptoms in children born to HIV-infected mothers. Exhaustive evaluation in a large prospective cohort. 8th Conference on Retroviruses and Opportunistic Infections Feb 4-8, 2001, Chicago, IL, USA (625B).

115. Bulterys M, Nesheim SR, Abrams EJ, 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. *Annals of the New York Academy of Sciences* 2000;**918**:212-221.

116. Lipshultz SL, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. *New Engl.J.Med.* 2000;**343**:759-766.

117. 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.

118. Foster, C., Boix, H., Tudor-Williams, G., Acolet, D., and Lyall, EGH. Lacticacidiosis and hypoglycaemia in three neonates exposed to antiretrovirals in utero. 27-4-2001. 7th Annual Conference of the British HIV Association 27-29 April 2001, Brighton.

119. Giaquinto, C., De Romeo, A., Giacomet, V., Ruga, E., Burlina, AB., De Rossi, A., and D'Elia, R. Is Lactic acid a predictor of mitochondrial dysfunction in ARV-exposed noninfected infants. 7th Conference on Retroviruses and Opportunisits Infections, Jan 30 - Feb 2, 2000 San Francisco, USA (67).

120. 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.

121. Galli, L., Peruzzi, M., Ballotti, S., de Luca, M., Farina, S., and de Martino, M. Combined antiretroviral treatment, but not zidovudine monotherapy, in gestation may damage biliary epithelium in infants. The XIII International AIDS Conference, Durban, RSA. 9 - 14 July 2000 (TuPeB3258).

122. 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**:1342-1348.

123. Stainsby C, Lyall E, Taylor GP, et al. Early diagnosis of HIV-1 status in neonates. *HIV Medicine* 1999;**1**:50-51.

124. Stainsby, C., Lyall, EGH., Taylor, GP., Galpin, S., Clarke, JR., McClure, MO., and Weber, JN. A significant number of uninfected infants can be HIV RNA (False) Positive. 2000. 5th International Congress on Drug Therapy in HIV Infection 22-26 October 2000 Glasgow UK.

125. Rich JD, Merriman NA, Mylonakis E, et al. Misdiagnosis of HIV infection by HIV-1 Plasma Viral Load Testing: A case series. *Ann.Int.Med.* 1999;**130**:37-39.

126. Williams AJ, Duong T, McNally LM, et al. Pneumocystis carinii pneumonia and cytomegalovirus infection in children with vertically acquired HIV infection. *AIDS* 2001;**15**:335-339.

127. 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**:1167-1174.

128. Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS* 2001;**15**:379-387.

129. Centre for Disease Suveillance and Control. AIDS and HIV infection in the United Kingdom: monthly report. *Comm Dis Rep* 1998;**8**:351-352.

130. Whittle H, Morris J, Todd. HIV-2 infected patients survive longer than HIV-1 infected patients. *AIDS* 1994;**8**:1620

131. Berry N, Ariyoshi K, Jaffer S, et al. Low peripheral blood viral HIV-2 RNA in individuals with high CD4 percentage differentiates HIV-2 from HIV-1 infection. *J Hum Virol* 1998;**1**:457-468.

132. 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.

133. 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 Immune Defic Sydnr* 1992;**5**:25-30.

134. 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

135. Smith N, Shaw T, Berry N, et al. Antiretroviral therapy for HIV-2 infected patients. *J Infection* 2001;**in press**: