

British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008

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Introduction

The success of antenatal testing for HIV means that more clinicians than ever are involved in the care of women with HIV who are pregnant. Despite very few recent randomized controlled trials regarding the use of antiretroviral therapy in pregnancy or obstetric interventions practice is changing. This is informed largely by observational data and theoretical considerations and these guidelines reflect this. The Cochrane Systematic Review of randomized controlled trials in this area shows how limited the guidelines would be were they to be restricted to such high level evidence.

Changes from the 2005 guidelines include the following

- A greater range of clinical scenarios to include more consideration of adverse obstetric events especially prematurity. This reflects the nature and volume of calls to the Writing Committee from fellow clinicians.
- Clearer recommendations regarding documentation of antenatal HIV testing, consideration to be given to repeat testing of women noted to be at continuing higher risk of HIV acquisition and advice to recommend near patient HIV testing for untested women in labour
- A further reduction in detail on teratogenicity as this is better covered by reference to the Antiretroviral Pregnancy Registry.
- There are few substantive changes to the recommendations on the use of individual antiretroviral therapies. The option of zidovudine monotherapy plus pre-labour Caesarean section (PLCS) for selected women is supported by new data from the UK and Ireland cohort.
- There is more detail in the obstetric management section, reflecting the greater diversity of clinical situations being encountered, in part as a result of more women choosing to take short-term antiretroviral therapy (START) and try for an elective vaginal delivery. Data from two large European cohorts provide support for planning a vaginal delivery if HIV viral is undetectable on HAART.

- The recommendations for infant feeding in the UK remain unchanged.

1. Summary of recommendations

Section 4. Antenatal HIV testing (Recommendation Grade C / Level IV)

Maintaining and improving antenatal test uptake

- All pregnant women should be recommended HIV testing at an early stage in pregnancy, or as soon as possible if they present for antenatal care at a later stage.
- Simple, robust and uniform systems are needed in all units and areas to record the number of women booking for antenatal care, being offered an HIV test, declining or accepting the offer and being tested.

Identifying seroconversions in pregnancy

- The number of infected infants born to women who test negative in early pregnancy is low. Nevertheless, any indication that a woman is at continuing risk of acquiring infection in pregnancy should be recorded, and repeat testing offered.

Rapid testing

- Rapid or near patient testing should be considered for women who arrive in labour unbooked and a reactive result should be acted upon

Recording HIV test results

- Midwives and doctors reviewing women during antenatal care should ensure that the HIV test result is clearly documented.
- Staff undertaking invasive genetic screening tests must be aware of a woman's HIV status.
- Labour ward staff must be aware of a woman's HIV status. Test results should be available on labour wards, with clear protocols for checking the status of women arriving in labour.

Section 5. Preconception and fertility management in men and women infected with HIV

Recommendation Grade B / Level III

- 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 centres and patient-funded in over 50% of cases

Section 6. Sexual health of HIV-positive pregnant women Recommendation Grade C / IV

- Routinely screen for genito-urinary tract infections at presentation
- Consider re-screening in the third trimester
- Repeat treponemal serology in the third trimester

Section 7. Psycho-social issues Recommendation Grade C / IV

- The minimum composition of the antenatal multidisciplinary team is: HIV specialist, Obstetrician, Specialist Midwife, Paediatrician
- A thorough early assessment of the social circumstances of a newly diagnosed HIV-positive pregnant woman is essential
- HIV-positive pregnant women should be encouraged to disclose their HIV status to their partner
- Testing any other children for HIV is recommended

Section 8. Viral load and resistance Recommendation Grade C / IV

- Viral load is an important determinant of transmission
- Quantify HIV plasma load:
 - At least every 3 months and at week 36 in women on established therapy
 - 2 weeks after starting or changing therapy
 - At delivery
- Use a second assay where there are discrepancies between viral load, CD4 cell count and clinical status
- Determine HIV genotype (or phenotype):
 - Pre-therapy (at presentation)
 - If viraemic on established therapy
 - At delivery if on monotherapy
 - Within 6 weeks of stopping suppressive therapy

Section 9. Management of opportunistic infections in pregnancy Recommendation Grade C / IV

- Investigations and management should not be delayed due to pregnancy
- Management of opportunistic infections is rarely altered by pregnancy

**Section 10. Antiretroviral therapy in pregnancy: efficacy Recommendation Grades A- C
/Levels I- IV (see individual scenarios)**

- See individual scenarios
- Balance the risk of HIV transmission with the toxicities of therapy
- Zidovudine monotherapy remains a valid option for women:
 - With repeatedly <6–10,000 HIV RNA copies/ml plasma
 - Wild type virus
 - Not requiring HAART for maternal health
 - Not wishing to take HAART during pregnancy
 - Willing to deliver by PLCS
 - Commence by 28 weeks
- Do not prescribe dual NRTI therapy
- Prescribe effective (\geq three drug) combination therapy:
 - If indicated for maternal health as per adult guidelines starting after the first trimester
 - If baseline maternal viraemia >10,000 copies/ml and no maternal indication for HAART, commencing at 20-28 weeks
 - As an alternative to ZDV monotherapy plus pre-labour Caesarean section
 - If drug resistance detected on genotype/phenotype
- Short-term antiretroviral therapy (START) for prevention of mother-to-child transmission should:
 - Be discontinued after delivery ideally when viral load <50 copies/ml
 - Be discontinued with careful consideration of the half-life of each component to avoid unplanned monotherapy after stopping, especially for drugs with a low genetic barrier to resistance
- Avoid stavudine plus didanosine as NRTI backbone whenever possible (and monitor lactate if unavoidable)
- HAART commenced prior to conception should usually be continued throughout pregnancy

Section 11. Antiretroviral therapy in pregnancy: toxicity Recommendation Grade B / III

- The association between protease inhibitors and impaired glucose tolerance is inconclusive
- HAART is associated with pre-term delivery (PTD), especially delivery before 34 weeks

Section 12. Antiretroviral therapy in pregnancy: pharmacokinetics Recommendation Grade C / IV

- Use current adult doses for all antiretroviral therapy in pregnancy
- Use therapeutic drug monitoring of protease inhibitors and new agents where available

Section 13. Obstetric management of pregnancy and delivery Recommendation Grade A -C / Level Ib-IV See individual scenarios

- In addition to any obstetric considerations, PLCS is recommended for:
 - All women taking ZDV monotherapy
 - Women on combination therapy with detectable (>50 cpm) viraemia
- PLCS should be considered for women with HIV/HCV coinfection
- PLCS is an option for women with undetectable plasma HIV on HAART
- PLCS to prevent mother-to-child transmission should be planned for :
 - 38 weeks if detectable (>50 cpm) viraemia or ZDVm
 - 39 weeks if HAART and undetectable viraemia
- Elective vaginal delivery is an option for women with no detectable viraemia on HAART
- Avoid invasive monitoring of fetus and artificial rupture of membranes
- Prescribe appropriate peri-operative antibiotics for all CS and for pre-labour rupture of membranes
- Give corticosteroids for threatened pre-term delivery <34 weeks
- Consider maternal single dose NVP in threatened pre-term delivery to load the baby who may not be able to take oral medication
- Consider expedited delivery for PPRM
- Expedited delivery for term PROM
- Communication between team members is essential and each delivery (by whatever mode) should be planned
- Ensure provision of appropriate formulations of neonatal therapy on the delivery/post-natal ward
- Give the mother a written care plan with contact details for emergency admissions
- Advise antiretroviral therapy for invasive genetic diagnostic tests
- Intravenous zidovudine is indicated for mothers on ZDV monotherapy and for mothers with >50 HIV RNA copies/ml plasma on HAART

Section 14. Pregnancy and HIV-2 infection Recommendation Grade C / IV

- Ensure that HIV-2 infection is diagnosed
- If HIV-2 viral load is known to be <50 copies/ml antenatal/peripartum, neonatal intervention may be unnecessary
- If HIV-2 is detectable, appropriate (HIV-2 specific) HAART is recommended
- Do not prescribe NNRTIs or ZDVm
- Breastfeeding probably best avoided
- Vaginal delivery is an option if HIV-2 viral load undetectable

Section 15. HIV and hepatitis B and C co-infections Recommendation Grade C / IV

- All HIV-positive pregnant women should be tested for hepatitis B virus (HBV)
- Infants born to women who are HBsAg positive and HBeAg positive, as well as those with high levels of HBV viraemia should receive HBV vaccination with additional passive immunisation with HBIG
- ART for pregnant women with HIV/HBV co-infection should include drugs with activity against HBV
- All HIV-positive pregnant women should be tested for hepatitis C virus (HCV)
- HCV-positive HIV-positive women should be treated with combination ART
- PLCS should be considered for all mothers co-infected with HIV and HCV

Section 16. Management of infants born to HIV-infected mothers Recommendation Grade A-C /Levels Ib- IV

- Most infants should be given zidovudine monotherapy BD for 4 weeks
- Alternative suitable ART monotherapy may be given if maternal therapy does not include ZDV
- Triple therapy should be given as post-exposure prophylaxis for infants born to untreated mothers or mothers with detectable viraemia despite combination therapy

Safety

- No evidence of any increase in congenital malformations in humans with first trimester exposure to any antiretroviral therapy (including efavirenz) to date
- Inadequate data to exclude a teratogenic risk for most individual drugs and for all combinations

- Laboratory evidence of mitochondrial depletion in infants exposed to ART perinatally but clinical importance uncertain.
- Prolonged haematological (but not clinical) effects of ZDV in exposed uninfected infants

Laboratory diagnosis of HIV infection in non-breastfed infants

- To exclude HIV infection DNA PCR is required 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

Section 17. Infant feeding Recommendation Grade B /Level IIb

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

2. Scenarios: interventions to reduce mother-to child transmission of HIV: clinical scenarios

Appendix 1 summarizes nine 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.

See clinical scenarios and Section 16 on paediatric management for information regarding antiretroviral therapy for the neonates as well as Tables 3 and 4. As a general principle, when interventions go according to plan and there is no relevant resistance, a monotherapy component of the maternal regimen, usually zidovudine, is administered to the baby for 4 weeks. Where the baby is about to be delivered and the viral load is not fully suppressed, unless the plan was for the mother to have ZDV monotherapy and a PLCS, the baby is likely to need combination post-exposure prophylaxis (PEP), which, if there is no contraindication, will usually consist of zidovudine, lamivudine, and NVP.

Scenario 1: where mothers do not yet require treatment for their HIV infection

Asymptomatic women who do not require antiretroviral treatment for their own health, according to current BHIVA Guidelines may be treated with a short-term antiretroviral therapy (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. At present it is recommended that this should contain zidovudine and lamivudine unless there are any contraindications. It is also recommended that this regimen should contain a boosted protease inhibitor (PI). 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 carefully in a planned manner to cover the NNRTI 'tail' and avoid the development of maternal drug resistance. The optimal time to commence START is unclear but the aim should be to start by 28 weeks. Commencing prior to fetal viability (24 weeks) may be prudent. An earlier start between 20 and 24 weeks may be advisable for a woman with a high baseline viral load who is aiming to achieve an undetectable viral load by 36 weeks in order to proceed to a vaginal delivery. If the viral load is <50 copies/ml at 36 weeks, a trial of labour can be anticipated.

Intravenous zidovudine is not considered necessary in this situation and oral dosing of HAART should continue throughout delivery. Some mothers who achieve an undetectable viral load will still prefer a PLCS, which should be scheduled for 39 weeks (see Section 13)

An alternative approach, in women who do not require treatment for themselves, and who repeatedly have a viral load of less than 10,000 copies/ml, is to use ZDV monotherapy, combined with a pre-labour caesarean section at 38 weeks with a zidovudine infusion commencing 4 hours prior to the section. The risk of vertical transmission is low, and this reduces antiretroviral exposure to the fetus in pregnancy. The risk of pre-term delivery is significantly lower with this approach than with the use of HAART. In addition, 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.

The optimal time to commence ZDV monotherapy is unclear but ideally this should be commenced by 28 weeks and commencing prior to fetal viability (24 weeks) may be prudent.

Scenario 2: mother needs to start HAART for her own health

Women who are deemed to need HAART for their own health should commence this early although this can usually be deferred until after the first trimester. It is recommended that these women should be treated with antiretroviral regimens as per the BHIVA Guidelines for The Treatment of HIV Infected Adults with Antiretroviral therapy (2006).

<http://www.bhiva.org/cms1191541.asp>

Consideration should be given to safety and efficacy data available in pregnancy, tolerability and whether treatment is likely to be continued after delivery. There is most experience in pregnancy with zidovudine and lamivudine as the nucleoside backbone, which is therefore usually recommended in combination with either a protease inhibitor or a non-nucleoside drug (see Section 5). If an undetectable viral load is achieved by 36 weeks a trial of labour may be possible as in scenario 1. If viral load is >50copies/ml at 36 weeks, see Scenario 4.

Scenario 3: mother conceives on HAART

If a mother conceives on HAART, has an undetectable viral load, and is tolerating the combination well she should have the pros and cons of continuing this regimen discussed. As a general

principle however, in this situation she should be encouraged to continue this regimen, even if this contains efavirenz. The antiretroviral pregnancy register does not show an additional risk with this approach (www.apregistry.com) (see Section 11). Obstetric management should be as per Scenario 2 with the option of a trial of labour or a PLCS at 39 weeks depending on maternal wishes or obstetric history.

If the mother conceives on HAART, which 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. If the viral load is <50 at 36 weeks then she can proceed as above, if not see Scenario 4.

Scenario 4: On START or HAART with viral load >50 copies/ml at 36 weeks

A genotype test should be performed and treatment changed to the best option. A PLCS should be planned for 38 weeks with 4 hours of IV ZDV if the genotype does not show resistance to ZDV. Combination PEP should be prescribed to the neonate based on the genotype. Consider the use of single-dose NVP to the mother, to load up the baby.

Scenario 5: Late presentation >32 weeks, before onset of labour

With improved turnaround times for viral load testing, a woman presenting beyond 32 weeks may still be managed with a view to a possible vaginal delivery if she commences HAART and achieves a viral load of <50 by 36 weeks as in scenario 2. If the viral load is >50 at 36 weeks she should have a PLCS at 38 weeks with IV ZDV, and the baby should receive combination PEP.

Scenario 6: threatened pre-term delivery +/- ROM

A vaginal swab should be taken for bacteriology, and if gestation $<34/40$, intramuscular steroids should be started aiming for two doses 24 hours apart for fetal lung maturation. If the mother is drug naïve, take baseline bloods for CD4 and viral load if not known, and commence HAART. NVP should be included in the regimen as it crosses the placenta rapidly. This can be in the form of single-dose NVP commenced at the same time as PI-based HAART if the CD4 is high or unknown, or an ongoing NVP-containing regimen if the CD4 is low. If ongoing NVP is commenced without

knowledge of the CD4, ensure that the baseline CD4 result is checked with a plan to substitute the NVP if the CD4 is high.

If the mother is already on HAART but the viral load is >50 copies/ml, review and optimize HAART and add sd NVP for the reasons above. For the mother on HAART with a viral load <50 copies/ml, continue HAART, but consider sd NVP, especially if <32 weeks, if she is not on NNRTI.

Once two doses of steroids have been administered, the decision whether to perform an emergency Caesarean section at <34 weeks can be taken. The timing of this procedure will involve balancing the risk of mother-to-child transmission of HIV-1 with the risks of severe prematurity (<30/40). This should involve multidisciplinary discussion with the obstetricians, neonatologists and HIV physicians. The decision to deliver will balance HIV transmission risk with fetal age, size and neonatal facilities. At >30 weeks this balance may favour proceeding to an emergency Caesarean section once two doses of steroids have been administered, and ≥ 34 weeks, an emergency Caesarean section should be performed as soon as possible. There have been no randomized controlled trials to inform these decisions.

In the scenario of threatened pre-term labour, or PPRM in a patient either not yet on HAART or with a known viral load >50copies/ml as well as the measures above, it may be worth commencing intravenous zidovudine. This can be reviewed taking into consideration which drugs have been commenced, what the viral load is, and the likely timescale of delivery.

Scenario 7: term pre-labour ROM

The antiretroviral management in this situation is as for Scenario 6. Commence HAART including a single dose of NVP, intravenous zidovudine, and proceed to Caesarean section after 2–4 hours. If the mother is on HAART with a fully suppressed viral load, a decision should be made as to whether induction of labour, as opposed to an emergency Caesarean section, is possible.

Scenario 8: mother diagnosed after delivery

Where it is only ascertained after delivery that an infant has been born to an HIV-infected mother, where maternal interventions have been declined or when interventions were introduced after

labour had started, post-exposure prophylaxis (PEP) should be offered as soon as possible. There is observational data that ZDV 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 regimen recommendations for high-risk exposure to offer triple-combination therapy for 4 weeks.

Scenario 9: mother presents in labour

If the mother's HIV status is unknown, a point of care test should be performed where possible and a reactive result must be acted on immediately. If the result is reactive or she is known to be HIV-positive, baseline samples should be taken and NVP-containing HAART commenced (either as sd NVP with a PI-containing regimen, or as an ongoing NVP regimen) see Scenario 6. Intravenous ZDV should also be commenced. If the mother is not about to deliver, an emergency Caesarean section should be performed at least 2 hours post NVP.

NB: In any of the above scenarios when NNRTI-containing HAART is administered to the mother, with a view to discontinuing HAART following delivery, therapy should be discontinued in a manner designed to avoid inadvertent NNRTI monotherapy.

3. Background: UK prevalence of HIV in pregnancy and risk of transmission

The prevalence of HIV infection amongst women giving birth in England and Wales has increased every year since 1990. The unlinked anonymous survey on residual neonatal dried blood spots shows that in 2005 overall UK prevalence was one in 450 (0.22%), one in 227 (0.44%) in London and one in 769 (0.13%) in the rest of England(1). The majority of these women are from sub-Saharan Africa. In 2005, 1100 children were born to women diagnosed with HIV infection(2).

The prevalence of HIV infection amongst women giving birth in the UK has increased every year since 1990. Results from the unlinked anonymous survey based on residual neonatal dried blood spots shows that in 2006 the prevalence of HIV infection in women giving birth reached one in 238 (0.42%) in London, one in 705 (0.14%) in the rest of England, and 1 in 440 (0.23%) in England and Scotland overall^[1]. The majority of these women are from sub-Saharan Africa. In 2006, 1100 children were born in the UK to women diagnosed with HIV infection(2).

In the UK, the rate of mother-to-child transmission from diagnosed women was 25.6% in 1993 at which time interventions were virtually non-existent (3) whereas between 2000 - 2006, with high uptake of interventions, the transmission rate was 1.2% 95% CI: 0.9-1.5%, Transmission rates were not significantly different according to whether mothers were on HAART regardless of mode of delivery (PLCS v Planned vaginal delivery) or taking ZDV monotherapy and delivering by pre-labour Caesarean section(4).

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 when plasma viraemia was less than 400 HIV RNA copies/ml(5). The only obstetric factors that consistently show an association with risk of transmission are mode of delivery, duration of membrane rupture and delivery before 32 weeks of gestation.

4. Antenatal HIV testing

Prior to the widespread implementation of the routine offer and recommendation of antenatal HIV testing in the UK detection rates prior to delivery were poor. In the mid-1990s only about a third of infected pregnant women was diagnosed, and most of those were aware of their infection status before they became pregnant(6). In England, the routine offer policy was laid out in a Health Service Circular issued in 1999; this proposed a 90% uptake target by the end of 2002, with the aim of diagnosing 80% of infected women before delivery in time to offer appropriate interventions(7). Similar policies were subsequently adopted elsewhere in the UK and had already been put in place in the Republic of Ireland.

By the end of 2003 virtually all UK maternity units had implemented the routine offer policy(8). While over two-thirds achieved >80% uptake in 2003 only about one-third reached the 90% target. More recent national data are not available, but standards for monitoring antenatal HIV screening were published in 2003(9), and routine national and regional audit systems are currently being developed.

Despite the improved uptake, as the prevalence of HIV in pregnancy continues to rise, a substantial number of women remain undiagnosed by the time of delivery, leading to potentially avoidable cases of mother-to-child transmission.

Between 2000 and 2004 the majority of HIV-infected women diagnosed before delivery were identified through antenatal testing. However, since 2005 the situation has reversed and a greater proportion of infected women are already diagnosed before they conceive(2). An audit of the circumstances surrounding nearly 90 perinatal transmissions in England in 2002–2005 demonstrated that over two-thirds of these infants were born to women who had not been diagnosed prior to delivery. About half of those undiagnosed women had declined antenatal testing. A smaller proportion had tested negative and were likely seroconversions in pregnancy. At present, although desirable, there is no suggestion that universal retesting in the third trimester will become national policy and therefore case by case assessment to determine whether a woman is at continuing risk of acquiring HIV infection in pregnancy is the only option with repeat testing offered. Many of the recommendations of this audit are incorporated in the relevant sections of these guidelines

(<http://nww.esussexiaiu.nhs.uk/docs/specialised/VerticaltransmissionFullreportOctober2007.pdf>).

Rapid or near patient testing should be recommended to women who arrive in labour unbooked and a reactive result should be acted on immediately– see Scenario 9.

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

Preconceptual advice.

1. Aim to delay conception until opportunistic infections have been treated and PCP prophylaxis no longer required. (Section 9)
2. Commence folic acid.
3. Discuss switching away from didanosine and efavirenz if reasonable alternatives are available and viral suppression is not likely to be jeopardized. (Section 11)
4. Avoid transmission to partner especially if uninfected.

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 0.001%^(10;11). The risk is significantly reduced if the male has undetectable viral load through use of HAART but is not eliminated as significant virus can still be shed in semen under these conditions as serum and semen viral load are not always correlated^(12;13). The risk can be further reduced by limiting exposure to the fertile period of the female cycle and ensuring that all genital tract infections have been treated. The only prospective study of couples trying to conceive through timed intercourse was conducted before the routine use of HAART and 4% of the female partners seroconverted^(14;14). A more recent retrospective study in Spain of 40 discordant couples conceiving in which the male partner had fully suppressed HIV replication on therapy for at least 6 months, reported no transmissions⁽¹⁵⁾. However, numbers are too small to draw any valid conclusions about the safety of natural conception in such cases but the study reflects common practice. Further prospective studies are warranted. Alternative options for serodiscordant couples, well established to reduce risk, include donor insemination, which removes the possibility of genetic parenthood from the infected male but eliminates any risk of HIV transmission during conception and sperm washing. Sperm washing 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⁽¹⁶⁾. The efficacy of the wash is then verified with a post wash HIV RNA assay before being used in treatment⁽¹⁷⁾. The treatment is relatively simple and significantly safer than timed unprotected intercourse, with no reported cases of seroconversion in either female partner or child born in over 3000 cycles of sperm washing combined with intrauterine insemination, IVF or intra-cytoplasmic sperm injection reported in the literature to date^(18;19). To minimize the risks of multiple pregnancy and ovarian hyperstimulation, couples should have natural cycle insemination unless fertility factors are identified when fertility drugs for superovulation or IVF/ICSI should be considered. The disadvantage of sperm washing is that the treatment is at present only provided by a limited number of fertility centres in the UK, Europe and Northern America. National Institute of Clinical Excellence guidelines published February 2004 on fertility have recommended sperm washing in serodiscordant couples as a risk-reduction process⁽²⁰⁾. 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 (C. 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.

The risk of viral transmission for discordant couples in which the female partner is infected with HIV is reduced but not eliminated when the viral load is undetectable through HAART. Current recommendation is that these couples should avoid unprotected intercourse and be advised on the technique of self-insemination during the fertile time of the cycle using quills, syringes and sterile containers⁽¹⁸⁾. 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^(18;21). Whilst the issue of superinfection in concordant couples continues to be debated^(22;23) current recommendations for these couples are to avoid unprotected intercourse and to consider sperm washing to minimize the risk of transmitting a viral variant to the female partner and future child. If the couple are not able to access or afford such services then they should be fully counselled on the risks of superinfection.

It is now well accepted that HIV-infected men and women should not be denied access to fertility treatment, provided the welfare of the child has been addressed⁽²⁴⁻²⁷⁾ The HFEA Act (1990) requires treatment centres to take into account the state of health of both prospective parents and social circumstances in respect of the welfare of any child arising as a result of treatment. Consideration should be given to maternal prognosis (treatment options and adherence) and commitment to comply with interventions during pregnancy and post-natally to minimize vertical transmission risk.

Assisted reproductive techniques for infertility such as IVF should continue to be monitored, 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⁽²¹⁾. Centres electing to treat HIV-infected patients should have separate laboratory facilities to eliminate the risk of cross-contamination to uninfected samples⁽²¹⁾.

In the UK, sperm-washing is currently available at the Chelsea and Westminster Hospital
www.londonfertility.co.uk

6. Sexual health of HIV-positive pregnant women

There are few data regarding the prevalence of genital infections in HIV-positive women in the United Kingdom(28). At present, the majority of pregnant HIV-infected women in the United Kingdom come from, and mostly acquired HIV in, sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV-infected population, can be high(29). Recent figures from the Health Protection Agency show that while prevalence of HIV infection among pregnant women born in sub-Saharan Africa has remained relatively stable in recent years (2.2% in 2000, 2.4% in 2006) there has been a three fold increase in prevalence among women born in Central America and the Caribbean over the same period, rising from 0.21% in 2000 to 0.61% in 2006^[1]. A high prevalence of genital infections in women of Afro-Caribbean origin has been reported(30). 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(31;32). Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with mother-to-child transmission of HIV and may be interlinked(33-35). However a Phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission showed no benefit in reducing mother-to-child transmission in the context of single-dose NVP prophylaxis. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoea* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma urealyticum*(31;32). A strong association between BV and premature delivery has been reported (32;36). 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 mother-to-child transmission of HIV(37). 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^{(38),(39)}. 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 mother-to-child transmission 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(40;41). 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 (42;43). A study from Zimbabwe has shown a correlation between HSV-2 antibody status and HIV-1 MTCT(44). A study from Thailand showed that perinatal CVL HSV 2 shedding is associated with increased risk of intrapartum HIV transmission and that the effect was independent of CVL and plasma HIV viral load. This study was, however, in the context of either zidovudine monotherapy from 36 weeks or placebo(45). That there may still be an increased risk associated with HSV shedding with patients on HAART is suggested by a randomized, double-blind, placebo-controlled trial of herpes-suppressive therapy in HIV-1/HSV-2-infected women taking HAART in Burkina Faso, which demonstrated that valacyclovir 500 mg twice a day further reduced genital HIV replication in those women with residual HIV shedding despite antiretroviral therapy(46). Genital HSV should be treated as per non-pregnant women. Continuous suppressive therapy with acyclovir may be required, is effective and safe(47).

Organisms associated with BV have been shown to stimulate HIV expression *in vitro* (48;49). A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis(50). Viral load in cervico-vaginal specimens has been shown to correlate with mother-to-child transmission of HIV-1(51). Genital tract viral load will usually mirror the plasma viral load(52), but there is increasing evidence of compartmentalisation of HIV-1 between the plasma and genital tract. Genital tract HIV-1 has been detected in women with an undetectable plasma viral load(53;54) and genetic diversity of virus from the two compartments has been reported(55). A number of factors may be responsible for this, including, differential drug penetration into body compartments and the presence of genital tract

infections. At present the majority of HIV-infected pregnant women in the United Kingdom deliver by pre-labour Caesarean section but, increasingly, those women with an undetectable plasma viral load are undergoing a trial of labour. In addition, women planning a pre-labour Caesarean section may rupture their membranes prematurely which may result in a vaginal delivery. Thus, an increasing number of fetuses will be exposed to the cervico-vaginal secretions of HIV-positive women.

In the absence of 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 consideration should be given to repeating this 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. Partner notification should take place where indicated, to avoid re-infection.

In pregnancy, warts are often more severe and less responsive to therapy, which may need to be deferred to the postpartum period. 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 post-natal, unless invasive cervical cancer is suspected when biopsies will be required. Irrespective of HIV status, it is prudent to do these in the operating theatre, since bleeding may be brisk.

7. Psychosocial issues

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.

The prevention of mother-to-child transmission can only be achieved if the pregnant woman embraces the medical interventions appropriately. In a number of cases the psychosocial issues may threaten to impede or obstruct the process of reducing mother-to-child transmission.

The antenatal HIV team

Antenatal HIV care should be delivered by a multidisciplinary team (MDT) the precise composition of which will vary. The minimum team would comprise: HIV specialist, Obstetrician, Specialist Midwife, Paediatrician and the recommendation of peer and voluntary sector support. All efforts should be made to involve the woman's GP and health visitor. It may be necessary to involve some of the following: patient advocates; social workers; legal advocacy; clinical psychologists; psychiatrists; counsellors; health advisors; CAB (Citizens Advice Bureau) workers; interpreters; community midwives; clinical nurse specialists and health visitors(56). 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. An early assessment of the social circumstances of a newly diagnosed HIV-positive woman is important. Patients who initially refuse interventions or default from outpatient follow-up need to be identified and actively followed up with particular care.

Peer support

Support by trained peer support workers is a valuable component of the management of HIV-positive pregnant women. Many newly diagnosed HIV-positive pregnant women are initially reluctant to engage with peer support, however, the great majority of women who do engage with it find that it becomes one of the most highly valued of all the interventions that they undertake(57).

Disclosure of HIV

The importance of informing appropriate health care workers should be emphasized. This includes midwives, GPs, health visitors and paediatricians. The process of in-patient care should be explained clearly so that the women can be helped to inform ward staff explicitly about levels of disclosure to visitors.

Levels of disclosure of newly diagnosed pregnant women about their HIV status to their partners varies from 30% to 75% depending on the setting(56;58;59). Disclosure should be encouraged in all cases but may be viewed as a process that may take some time(60;61). 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(62-64). 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. Difficult disclosure cases should be managed by the MDT. It is important to accurately record discussions and disclosure strategy in difficult cases.

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.

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 breastfeeding. 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 enquirers(65).

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(56;58;66). Such couples require advice regarding condom use and PEPSE (www.bashh.org/guidelines/ceguidelines.htm).

Welfare and immigration

Many HIV-positive women will have issues relating to social support needs and/or immigration issues. In both cases it is important to identify the issues as early as possible so that women can be referred for appropriate specialist advice and support. Dispersal is an issue that arises and is generally felt to be inappropriate in pregnant women, especially if they are late in pregnancy or are recently delivered(67) (68).

Formula-feeding support

Women with very limited funds should have access to supplementary formula feed(69).

HIV testing of existing children

This issue should be raised with all newly diagnosed pregnant women who have other children. Absence of symptoms does not imply HIV negative even in children reaching teenage. In practice the testing of these children is often most easily done when the newborn is attending paediatric follow-up for HIV diagnostic tests.

Adherence to antiretroviral therapy

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.

Resistance to intervention

Rarely, women may choose to refuse any intervention during pregnancy or declare their intention to breastfeed the baby against advice. Common reasons may include fear of accepting their HIV status, religious reasons, fear of disclosure to partners, and other family members forbidding the woman from taking up interventions. In cases where the woman threatens to breastfeed against advice it may become a child protection issue, once the child is born. These cases are very rare but should be discussed with Social Services pre-delivery so that a strategy can be developed.

Eligibility for treatment

Legislation concerning eligibility to free NHS healthcare in the UK changed in 2004. Patients who have been resident in the UK for 12 months no longer have an automatic entitlement to free care in the NHS. There is an exclusion for 'immediately necessary care' and it could be argued that treatment of an HIV-positive pregnant woman falls within this category. Unfortunately this has been interpreted differently within different Trusts, in some cases denying free treatment and thereby putting the health of mothers and their unborn babies at risk. No hospital should refuse treatment for HIV positive pregnant women to prevent transmission of HIV to the baby. However it is possible that women who are otherwise ineligible for free NHS care may be liable for charges subsequently.

It is advisable to get advice from colleagues, the GMC, BMA and Medical Defence Organizations in difficult cases. Legal advice can also be sought from organizations such as the THT (www.tht.org.uk).

<http://www.tht.org.uk/informationresources/publications/policybriefingpapers/accesstohivservices.pdf>

<http://www.nat.org.uk/download?rootDocumentId=109&eid=U57GRTWCNZKHM>

<http://www.nat.org.uk/document/253>

Postnatal issues

Postnatal depression is relatively common in the general population, tends to be under-diagnosed and is a risk in HIV-positive women. Women with, or at risk of, antenatal depression should be assessed early and referred onward appropriately.

8. Viral load and resistance

HIV viral load

The risk of mother-to-child transmission correlates with maternal viral load even among women receiving antiretroviral therapy(70-72). 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(73-75). 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. A transmission rate of 0.1% (3/2117) has been observed in the UK and Ireland cohort if the HIV viral load is less than 50 copies/ml plasma on HAART(4). Studies have generally demonstrated correlation between viral load in plasma and cervicovaginal secretions(52;76), 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(54). Responses to antiretroviral therapy and selection of drug-resistant variants may differ between plasma and CVS(77) and there is evidence of genetic diversity between viral populations in the blood and female genital tract which could account for this(78-80). Consequently, plasma viral load may not always reflect activity of HIV in the genital tract and this could account for those rare cases of perinatal transmission in women with low or undetectable plasma viral load(74).

A number of commercial assays are available for quantification of HIV-1 RNA, the most widely used in the United Kingdom being the Bayer Versant HIV-1 RNA 3.0 branched chain DNA (bDNA) assay, Roche Cobas Ampliprep/Cobas Taqman system and the Abbott Real Time HIV-1 assay. Although these assays have been shown to correlate, HIV RNA copy number may vary by approximately 0.5–1.0 log₁₀ (81;82). In order to ensure reliable and accurate quantification of HIV-1 RNA the same assay should be used to monitor viral load unless a lack of sensitivity is suspected. Real-time PCR can qualitatively detect HIV RNA to between 10 and 40 copies/ml. However there are as yet no data on the significance of detecting HIV at viral loads below 50 copies/ml as a risk for mother-to-child HIV transmission.

In the United Kingdom, 78% of HIV infections among women attending antenatal clinics are with non-B subtypes, 61% being subtype A and 29% subtype C(83). 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(84-86). This appears to be less of an issue, however, with the new generation of commercial viral load assays. Nevertheless, 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. Although rare, some untreated individuals may consistently have an undetectable viral load in conjunction with low CD4 cell numbers(87;88). It has been demonstrated that this is not necessarily assay- or subtype- related and the reason for this discordance remains unclear.

For patients initiating or changing failing therapy, plasma viral load should be monitored 2 weeks after commencing treatment and ideally every 4 weeks thereafter. For patients conceiving on therapy, with undetectable viraemia viral load measurements every 3 months and at 36 weeks' gestation (depending on turnaround time) may be sufficient. Viral blips are known to occur during suppressive therapy and are of uncertain significance but the pregnant patient should be recalled and the assay repeated. The viral load at 36 weeks is important when deciding mode of delivery. Knowing the viral load at delivery is helpful in understanding the rare cases of transmission.

Antiretroviral drug resistance

A baseline resistance assay should be performed on all pregnant women at diagnosis and a further test undertaken following short-term antiretroviral therapy. Ideally, in women taking zidovudine monotherapy, this should be done on the viral load sample taken at delivery. For women who have received HAART, this should be performed on the first viral load sample taken off therapy, ideally within 6 weeks. Any pregnant woman on non-suppressive antiretroviral therapy should have a resistance test conducted(89;90).

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. 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.

There is concern that the use of zidovudine monotherapy in pregnancy may lead to the emergence of drug-resistant virus, possibly compromising the mother's future care. Early studies demonstrated zidovudine-associated resistance mutations in approximately 10–25% of pregnant women, with high level resistance in 6–12%(91-94). However, in these studies maternal viral loads were generally higher and exposure to zidovudine more extensive than would be expected when using zidovudine monotherapy according to these guidelines. In the ACTG 076 trial the prevalence of any mutations associated with decreased susceptibility to zidovudine was only 3% and no high-level resistance was detected(95). Similarly, no mutations were detected among women in Côte d'Ivoire receiving short-course zidovudine monotherapy initiated late in pregnancy(96). A UK study(97) 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, when zidovudine monotherapy was only recommended to selected women. More recently, studies on this cohort have been extended and demonstrated no evidence of minority species resistant to zidovudine(98). The risk of developing zidovudine resistance is therefore likely to be low if monotherapy is restricted to drug-naïve asymptomatic women, with low viral loads and good CD4 cell numbers (see Section 10). In a London study, women starting triple antiretroviral therapy 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(99).

The long half-life of NVP and low genetic barrier contribute to development of resistance and this has implications for its use as a single-dose intervention or in a short-term HAART regimen. In the Ugandan HIVNET 012 study(100) drug-naïve women received a single dose of NVP at the onset of labour and their infants a single dose within 72 hours of delivery. NVP resistance was detected in 19% (21/111) of women at 6 weeks postpartum and was associated with higher baseline viral loads and lower CD4 cell numbers(101). Detectable resistance appeared to be transient, with these mutations no longer found in plasma 12–24 months postpartum. More recent studies have demonstrated resistance in as many as 40% of women following single-dose NVP(102). Following single-dose NVP, resistance is more frequently detected in women with subtype C HIV infection compared with subtypes A and D(103). Resistance to NVP can also occur when a single dose is given to women already receiving combination antiretroviral treatment, the prevalence of the K103N mutation being approximately 15%(104). Resistance developed in a significant proportion

of women receiving a short-term NVP-containing regimen in pregnancy, despite the use of a dual nucleoside tail(105). The high genetic barrier to resistance of boosted PIs and their short plasma half-life make them a more attractive option for START than NNRTIs.

Transmission of drug resistant virus to the infant can occur(106). 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(93;94;107), and between 30% and 40% in others(108;109). Similarly, NVP-resistant virus was detected in 11 of 24 (46%) infected infants in the HIVNET 012 study(101). However, mutations were transient and no longer detected 4–12 months after delivery. The implication of these mutations, and their subsequent ‘fading’, for the further management of these children is uncertain. Although some studies have indicated that drug resistance is not necessarily associated with an increased risk of perinatal transmission(92;93;95;107) there is still insufficient information to define clearly the relationship between drug resistant mutants and mother-to-child transmission.

9. Management of HIV-related complications in pregnancy

The health and survival of the mother is paramount. The investigations of a pregnant woman are essentially no different to normal and should be conducted promptly. The usual precautions relating to X-ray exposure apply whether a woman has HIV or not but unnecessary avoidance of simple investigations can be harmful. MRI may be safer than CT: discuss with your radiologists.

Most treatments of HIV-related disease are the same regardless of whether the woman is pregnant.

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.

BHIVA treatment guidelines of opportunistic infections will soon be available and will include a section on pregnancy.

PCP prophylaxis

In a multicentre retrospective study of 148 infants exposed to antiretroviral therapy *in utero* the risk of congenital malformation was significantly raised in those exposed in the first trimester to folate antagonists used for *Pneumocystis* pneumonia prophylaxis combined with ART(110). 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. Regular administration of even small doses of folic acid (such as found in some multivitamin preparations) appears to negate this additional risk (111). Co-trimoxazole remains the PCP prophylaxis of choice for pregnant women.

10. Antiretroviral therapy in pregnancy: efficacy

More than 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.

The Cochrane Systematic review which was restricted to interventions shown to be effective in randomized controlled trials, concluded that zidovudine monotherapy, NVP monotherapy and delivery by elective Caesarean section (PLCS) appear to be very effective in decreasing the risk of transmission(112) whilst in the 2007 update the authors conclude that 'a combination of zidovudine plus lamivudine given to mothers in antenatal, intrapartum and postpartum periods and to babies for a week after delivery or a single dose of NVP given to mothers in labour and babies immediately after birth may be most effective'(113). This clearly does not reflect current practice but is extremely helpful in drawing attention to the lack of clinical trial data with highly active antiretroviral therapy in pregnancy. The question of efficacy relates to reducing infections in the neonate, maintaining or improving maternal health and preserving maternal therapeutic options.

Evidence of efficacy from monotherapy studies

Zidovudine

The efficacy of zidovudine to reduce mother-to-child transmission of HIV-1 has been demonstrated in several large randomized controlled studies(71;114;115) and supported by epidemiological

surveys(116-119). The efficacy of zidovudine ranges from 67%, when started before the third trimester, administered by intravenous infusion during labour, and given to the neonate for the first 6 weeks of life, to 50% with shorter courses (started at week 36), without a neonatal component, in non-breastfed babies, to 30% with a similar regimen in breastfed babies(120;121). In a non-breastfeeding population the transmission rate with zidovudine monotherapy has been reduced to 6–8%(114;117). As with monotherapy in non-pregnant women zidovudine transiently reduces HIV-1 plasma viraemia and increases CD4 positive lymphocyte counts. In ACTG 076, in which mothers commenced zidovudine 100mg five times daily between weeks 14 and 28 of gestation, therapy was associated with a 0.24 log₁₀ reduction in plasma viraemia at the time of delivery(75)(117). In the Bangkok study, zidovudine 300mg twice daily was commenced at week 36 resulting in a 0.57 log₁₀ reduction in plasma viraemia at delivery. This was considered to account for 80% of the efficacy of zidovudine in reducing transmission(71).

Viral load is an important predictor of transmission and zidovudine reduces transmission at all levels of maternal viraemia. However, in mothers with untreated very high viral load (>100,000 RNA copies/ml) the transmission rate may be >60% and therefore even with a two-thirds reduction in transmission, the risk to the infant would still be high. HAART is therefore recommended for any mother with a viral load >10,000 copies/ml (see also Scenarios). Pre-labour Caesarean section (PLCS) has been demonstrated to reduce transmission by as much as zidovudine (see Section 10). When zidovudine and PLCS were combined, in a cohort of women with all levels of viral load, transmission was further reduced to <1%(122). The ANRS French Perinatal (1997 – 2004) Cohort has an overall transmission rate of 1.3% with no significant difference in transmission rates between HAART, dual and monotherapy but details of mode of delivery for each therapeutic group are not presented (123). In the UK and Ireland, the observed transmission rate in women on ZDVm plus PLCS was 0%. (0/467, 95% upper CI 0.8%). This was not significantly different to the 0.7% transmission rate with HAART plus PLCS (17/2337 95% CI 0.4 – 1.2%) or the 0.7% rate with HAART and a planned vaginal delivery (4/565, 95% CI 0.2 – 1.8%)(4).

NNRTIs

The rapid placental transfer and long half-life of NVP have led to studies of the efficacy of NVP to reduce the risk of mother-to-child transmission of HIV. In HIVNET 012, NVP given to the mother in labour and to the neonate, reduced transmission up to 18 months despite on-going breastfeeding(100;124). The efficacy of this approach was confirmed by the SAINT study(125). The efficacy, low cost and ease of use led to its adoption by the World Health Organization. However, the use of two-dose NVP alone to prevent mother-to-child transmission of HIV is now reserved for only those settings where more intensive interventions are not available because of the development of resistance, which has been shown to impact on the response to subsequent NNRTI-containing HAART(126;127). The use of single-dose NVP (sdNVP) as an emergency in labour may be appropriate in certain situations (see Scenarios) provided sufficient cover of the pharmacological tail is provided.

Since efavirenz also has a plasma half-life that is at least as long as NVP, similar problems with resistance might be anticipated if used as either short-course or single-dose therapy.

Evidence from studies of combination therapy

Dual nucleoside analogue therapy

Whilst cohort data have shown lower rates of transmission with zidovudine plus lamivudine (2.6%) than with zidovudine alone (6.5%)(109), concerns relating to lamivudine resistance outweigh these benefits and this approach is therefore not recommended.

Zidovudine monotherapy with single-dose NVP and 1 week of zidovudine plus lamivudine

The current practice, as advocated by the WHO in resource-limited settings(128), of adding single-dose NVP to short-course zidovudine (from 28/40), reduces transmission to 2% in formula-feeding mothers(129). The high rates of mutations associated with NVP resistance can be considerably reduced if the period of pharmacological activity is covered, as recommended, with zidovudine plus lamivudine for 1 week(130) (see Section 8). Low rates of NVP mutations were also seen when single-dose NVP was given on a background of zidovudine plus lamivudine from 34 weeks(131) but higher rates of lamivudine resistance (8.3%) occurred and the strategy did not significantly improve mother-to-child transmission rates compared to zidovudine monotherapy with single-dose NVP(132). These approaches are not recommended as first-line interventions in the UK.

Combinations with more than two drugs

In the North American Women and Infants Transmission Study (WITS) cohort there has been a reduction in transmission from 7.8% in mother–infant pairs receiving zidovudine monotherapy to 1.1% in mother–infant pairs exposed to triple therapy including a protease inhibitor(5). In PACTG 367 the transmission rate among 3081 pregnant women delivering in North America had fallen from 4.2% in 1998 to 0.5% in 2002. Among women who received no antiretroviral therapy transmission was 18.5%, falling to 5.1% with zidovudine monotherapy, 1.4% with dual NRTIs and 1.3 % with three or more drugs. Of the 1736 women who had plasma viraemia of less than 1000 copies/ml at the time of last measurement prior to delivery, the transmission rate was 0.7%(133).

Data from the ECS demonstrate a reduction in transmission over time periods that can be associated with changing trends in therapy from zidovudine monotherapy for all, dual therapy and finally to HAART. In the period 2001–2003, during which time 92% of mothers received HAART, HIV transmission was reduced to 0.99% [95% confidence interval (CI) 0.32–2.3%](134).

Transmission at less <50 copies HIV RNA/ml plasma at delivery has been reported with a rate of 0.4% (5/1338) in the ANRS French Perinatal Cohort (123) and 0.1% (3/2117) in UK & Ireland cohort(3;4).

In summary, although these studies show a reduction in transmission since the the introduction of HAART, recent data from the UK show no difference in transmission rates, when comparing mothers given zidovudine monotherapy combined with PLCS, according to BHIVA guidelines, and those receiving HAART(3).

Stopping HAART

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 without compromising future maternal therapeutic options. Stopping NVP or efavirenz must be carefully planned with appropriate tails, to allow for their long half-lives.

11. Antiretroviral therapy in pregnancy: toxicity

Maternal toxicity

Information about the safety of drugs in pregnancy is limited. Data are usually from animal studies, anecdotal experience, registries and clinical trials.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Nucleoside analogues 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 postpartum complications of pregnancy(109).

Nucleoside analogues may cause mitochondrial dysfunction as they have varying affinity for mitochondrial DNA γ polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion(135). The relative potency of the nucleoside analogues in inhibiting mitochondrial DNA γ polymerase *in vitro* is highest with zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), zidovudine (ZDV), abacavir (ABC), tenofovir and emtricitabine(136). The mitochondrial toxicity of zidovudine may, however, not be entirely related to mitochondrial DNA γ polymerase inhibition. Lamivudine, abacavir, tenofovir and emtricitabine have been shown to have relatively low toxicity in this regard. Toxicity related to mitochondrial dysfunction has been reported in patients receiving long-term treatment with nucleoside analogues and although this generally resolves with discontinuation of the drug or drugs, fatalities have been reported.

Early in 2001, the US Food and Drugs Administration and the European Medicines Authority advised doctors that they had received reports of three pregnant women who had died of lactic acidosis following treatment with stavudine and didanosine (as part of triple therapy) and a further four cases of lactic acidosis in pregnancy with this combination(137). The use of didanosine plus stavudine in pregnancy should be restricted to woman with resistance or intolerance to other nucleoside analogues and no reasonable alternatives. Monitoring liver function and blood lactate in pregnant women on this combination is therefore recommended.

Protease inhibitors (PI)

Hyperglycaemia, new onset diabetes, exacerbation of existing diabetes mellitus and diabetic ketoacidosis have been reported with administration of protease inhibitors(138;139). 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)(140). In a Spanish cohort of 609 pregnant women with HIV infection the incidence of gestational diabetes (GD) was 7% (higher than expected for the general population). Older age and use of protease inhibitor (OR 2.3 95% CI 1.0–5.3) were associated with GD in a multivariate analysis(141). Higher rates of hyperglycaemia were also seen with nelfinavir (15.6%) than with NVP (8.6%) in a Dutch study(142). However, this has not been found in other cohort reviews(143;144) nor in a recent prospective study comparing 76 women taking PI-based therapy (33% had impaired glucose tolerance) with 73 women on a PI-sparing regimen (26% had impaired glucose tolerance)(145). Thus the data remain inconclusive.

Indinavir and full-dose ritonavir are now rarely prescribed in general HIV care and are not considered further here. Nelfinavir, has been widely prescribed and was well tolerated in 128 pregnant women although gastrointestinal side effects (29.7% versus 6.6%) and hyperglycaemia (15.6% versus 2.2%) were significantly more common compared with non-pregnant women in the same cohort(142). Nelfinavir is no longer available in Europe due to concerns regarding impurities. There are plans to construct a register of children exposed to nelfinavir and women who have taken nelfinavir during pregnancy. Details can be obtained from www.emea.europa.eu , www.rocheuk.com, or www.chiva.org.uk. Data regarding unboosted saquinavir are sparse. Although a significant proportion of mothers [13/42, (31%)] developing abnormal LFTs with ritonavir- boosted saquinavir has been reported all but one were Grade 1/2 and therapy was only changed in five(146). Ritonavir-boosted lopinavir was well tolerated in a retrospective study of 104 mothers in the UK with 96 continuing therapy to delivery. Nausea and vomiting was reported by 26% but <2% discontinued therapy. Grade 1/2 abnormal LFTs were also common (19.2%) with Grade 3 changes in 3.8% but only one patient, with pre-eclampsia, stopped therapy. Hyperglycaemia was uncommon (<2%)(147). Limited data (33 pregnancies) have been presented on atazanavir. Although maternal bilirubin levels were nearly always (92%) elevated (range 4–76 μ mol/l) no infants required phototherapy(148).

Nevirapine

The main concerns with NVP relate to cutaneous and hepatic toxicity. There has been a change to the Summary of Product Characteristics (13th February 2004) which, along with other changes, now states that 'women and patients with higher CD4 cell counts are at increased risk of hepatic adverse events, often associated with rash, especially women with pre-treatment CD4 counts greater than 250 cells/mm³'. Although there is no specific mention of pregnancy, pregnant women are perhaps more likely to match this description than non-pregnant women, especially those choosing short-course therapy. Whether the risk of hepatitis is the same in pregnancy is uncertain but a number of hepatitis-related deaths has been reported in pregnant women taking regimens that include NVP(149) including two cases reported from a cohort of 123 women in Ireland who initiated a nevirapine containing regimen during pregnancy. Treated according to Irish Guidelines for the Management of HIV in pregnancy which recommend that all pregnant women should be treated with HAART(150). both fatalities occurred in women with high CD4 counts (473 – 501 cells/ μ l) and low viral loads (724 – 1895 HIV RNA copies/ml). (151). Neither woman would have initiated nevirapine since the change in SPC. In PACTG 1022 4/17 women discontinued NVP due to toxicity compared with 1/21 randomized to nelfinavir. One patient treated with NVP, whose baseline ALT was 58 U/L, died of fulminant hepatic failure(152). Money *et al.* reported 'major' toxicities in 5/56 women (10.5%) taking NVP during pregnancy compared to one episode of renal calculi among 47 women taking a PI (2%)(153). Conversely Bershoff-Matcha and colleagues reported no serious adverse events among 43 pregnant women compared with 23 among 227 non-pregnant women(154). Natarajan compared 170 women who commenced NVP during pregnancy with 65 pregnant women who had commenced NVP prior to conception. The incidence of rash (7.6%) and hepatitis (4.7%) during the pregnancy was higher in those initiating NVP than in those who had started earlier (rash 3.1%) but alternative causes for the suspected toxicity were found in seven cases and only 10 mothers (5.8%) discontinued NVP. There were no deaths(155). In a study of 126 women commencing NVP-based HAART in Thailand, eight (6.3%) developed hepatitis of whom six discontinued NVP and nine (7.1%) developed a rash of whom six discontinued NVP. No statistically significant difference in frequency of complications was seen in the women commencing NVP-based HAART with a CD4 count greater than 250 cells/mm³ (14.5%) compared with those starting at less than 250 (12%) but the treatment time was shorter in the latter group who started therapy at 28 weeks of gestation(156). In a Thai population that included males,

pregnant women and non-pregnant women, 9.4% starting NVP as part of triple therapy developed liver or skin toxicities; pregnant women with CD4 counts greater than 250 cells/mm³ did not have significantly higher rates(157). Data presented at Conference on Retroviruses and Opportunistic Infections 2007 suggested that in pregnant Thai women, prescription of NVP to women with CD4 cell counts up to 350 remains safe(158). These conflicting data are likely to be due to differences 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. In the Kisumu study in Kenya, in which ZDV, 3TC and NVP are started at 34 weeks gestation, 13/155 (8.4%) mothers had to stop NVP with Grade 2–4 toxicities, but a CD4 count cut-off of 250 cells/mm³ did not discriminate between susceptibility states(159). Therefore, although severe toxicity and fatalities were reported in some pregnant women starting NVP in pregnancy, data from several much larger cohorts(155;158;160) including 563 mothers have not shown that pregnant women are at greater risk.

In conclusion NVP has been widely prescribed and effective in pregnancy and remains a useful component of HAART in pregnancy. Only nelfinavir (as the third drug on a dual NRTI backbone) has been used to a similar degree. There is very little reported experience with other triple therapies in pregnancy. All the studies have shown combination therapy to be effective in reducing mother-to-child transmission and therefore the potential benefits of the intervention must be assessed against the risk of toxicity.

Pregnancy outcome

There are a number of studies, including data from the UK that show a significant association between the use of HAART in pregnancy and pre-term delivery (PTD).

The possibility that protease inhibitor use was associated with an increased risk of PTD had been suggested by Swiss investigators in 1998(161). In an analysis of data from the combined Swiss and European Collaborative Study cohorts, further evidence of an increased rate of pre-term delivery was found in women on combination ART including a PI(162). In the 2004 analysis of this on-going study, a trend towards more pre-term deliveries (in women not delivering by PLCS) has been shown over time, correlating with increased use of combination therapies(163). Data from the UK and Ireland of 4445 pregnancies delivered between 1990 and 2005 showed 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 (or dual therapy)(164) and the association was stronger for more severe pre-term deliveries.

An Italian study suggested that HAART in pregnancy is associated with a reversal of the Th1 to Th2 switch that is a feature of normal pregnancy(165). Two further questions arise: is all HAART equal; and does the timing of initiating therapy matter? A number of studies report a trend towards more PTD with PIs than with NVP-based therapy and this needs further clarification. If PTD is related to changes in cytokine profiles as suggested by Fiore's study of women already taking HAART at conception(165), then initiating HAART in pregnancy might exacerbate this effect. Data from Martin and Taylor suggest that this may be the case, with a much higher rate of PTD (20%) among pregnant women initiating HAART during pregnancy, regardless of indication (i.e. maternal health versus PMTCT) than in women who conceived on HAART (9.5%) or who took ZDVm (5.8%)(166). Finally, it is worth noting that 60% of the PTD was defined as severe, that is delivering prior to week 34. However, in the Amsterdam and Rotterdam (AmRo) study(167) the most striking association was with therapy commenced early or before pregnancy although there was no evidence for this in the study from the UK and Ireland cohort(164).

The experience in North America seems to differ from Europe. Much higher rates of PTD are found in the general population (12.5% in 2004(168)) and in 1989, when fewer than 50% of the mothers received antenatal care, the PTD rate in HIV-positive mothers was 35%(169). This has since fallen to 22% but remains considerably higher than in UK and Ireland (13%). Drug use, symptomatic HIV infection and no antiretroviral therapy were significantly associated with PTD in this cohort of more than 11,000 pregnancies. In a 1998 North American multicentre study of 76 women taking a PI as part of combination therapy during pregnancy there were 15 PTD (<37 weeks) but 60% of the mothers had identifiable risk factors for PTD such as a history of PTD, smoking and substance misuse(170). Among 462 women participating in ACTG studies in 1998–1999 the PTD rate was also 20% but with no significant difference between women exposed to PIs and those not exposed to PIs [relative risk (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)(171). In a meta-analysis of data from several North American cohorts the PTD rate was ~17% with no effect of combination antiretroviral therapy compared with no antiretroviral therapy or monotherapy(172). However, data

submitted voluntarily to the Antiretroviral Pregnancy Register, which mostly includes submissions from North America shows a trend to very low birth weight in babies exposed to three or more drugs *in utero*(173). Recently a North American cohort study did find an association between HAART (three or more effective drugs) and pre-term delivery(174) but only for protease inhibitor containing combinations(169).

Two published studies have found an increased risk of pre-eclampsia in patients taking HAART: this may form part of the risk of pre-term delivery as well as having important maternal and fetal implications(175;176). This contrasts with the lower-than-expected rate of pre-eclampsia in HIV-infected mothers seen in the pre-ART era(177) but was not seen in a Brazilian study in which, despite high rates of HAART use, the rate of pre-eclampsia in HIV-positive women was 0.8% compared with 10.6% in uninfected controls(178).

Whilst the data on impaired glucose tolerance and PIs are inconclusive and the association of HAART with higher rates of pre-eclampsia unsubstantiated, there is accumulating evidence for an increased risk of pre-term delivery and, in particular, severe (<34 or <32 weeks) pre-term delivery in mothers taking HAART. Whilst in some mothers this is unavoidable because of maternal health or high viraemia, in others ZDV monotherapy and PLCS may be a safe option.

Embryonic/fetal toxicity

The Antiretroviral Pregnancy Register contains a summary of relevant mutagenesis, carcinogenesis and teratogenesis data for each licenced antiretroviral (www.apregistry.org). Reports are updated twice a year. The concerns relating to didanosine and efavirenz are discussed below. No other compounds have yet given rise to any concern.

Didanosine

Ever since the patient denominator for first trimester exposure of 200 was reached in January 2005, the incidence of congenital malformations among babies exposed *in utero* to didanosine has been significantly higher than for any other antiretroviral with similar numbers of exposed babies. Numbers of first trimester exposures (259) are still relatively few compared with zidovudine (1643) and lamivudine (1888) but the 95% confidence intervals (3.3–9.4%) remain above the expected rate of 'early' congenital malformations (2.4%). The observed incidence of 5.8% also exceeds that

observed (1%) with second- or third-trimester initiation of therapy although the 95% CI overlap is 0.1%–3.7%. No pattern of congenital malformations has been observed but this does not exclude causation. Until this has been resolved it is reasonable to avoid first-trimester didanosine exposure.

Efavirenz

The concerns relating to efavirenz date back to pre-clinical animal studies that have not been conducted with any other antiretroviral therapy. Twenty cynomolgus macaques were exposed to efavirenz during early pregnancy. Three of the 20 offspring had significant abnormalities at birth: one with anencephaly and unilateral anophthalmia; the second with microphthalmia; and the third with a cleft palate. Consequently efavirenz was classified as class C and it is recommended that efavirenz should not be prescribed to women of child-bearing potential. These data are likely to have heightened awareness of the potential risk of teratogenicity with this compound. In prospectively reported data to the international, but US-dominated, Antiretroviral Pregnancy Register there have to date (January 2007) been only seven defects noted in 281 babies born following first-trimester efavirenz exposure and none has resembled the abnormalities observed in macaques. Efavirenz was, however, reclassified as Class D, indicating an established risk to the human fetus, based on three reports of myelomeningocele and one of Dandy–Walker syndrome to the register. Each was reported retrospectively, that is after the outcome of the pregnancy was known, and therefore the relative risk cannot be calculated as the denominator (total number of exposures) is not known. Two of the reported cases of spina bifida and the case of Dandy–Walker syndrome were reported in aborted fetuses. Since the incidence of spina bifida in the USA is 4.3 per 10,000 live births the expected number of cases of spina bifida in the prospectively reported register (6636 pregnancies) is three, however, to date none has been reported. Two further cases of Dandy–Walker syndrome have since been reported in the prospective arm of the register, and one further case of spina bifida has been reported in the retrospective arm: none of these babies was exposed to an NNRTI. Until more robust data are available it remains advisable to avoid efavirenz for women who may conceive.

Management of women who conceive on efavirenz

There are two issues to consider: the gestational age at presentation; and the plasma half-life of efavirenz. After stopping, it can take up to 3 weeks for efavirenz to clear from the plasma. It is not known whether there is a key period during the first 6 weeks of fetal development when efavirenz

affects CNS development nor the minimal teratogenic dose and given the long half-life of efavirenz it is difficult to speculate on whether discontinuing efavirenz after the diagnosis of pregnancy will reduce the risk of spina bifida. The risk of spina bifida, which cannot yet be quantified, the gestational age, and the pharmacokinetics of efavirenz should therefore be balanced with potential advantages of continuing a fully suppressive regimen especially if options are limited. This should be discussed with any women who conceive whilst taking efavirenz. Discontinuing all therapy is not recommended as this potentially exposes the women to efavirenz monotherapy for up to 3 weeks. The neural tube has closed by 6 weeks and therefore discontinuing efavirenz if the pregnancy is diagnosed after this time will not influence the outcome.

12. Antiretroviral therapy and pregnancy: pharmacokinetics

Physiological changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing. During pregnancy, GI transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease, notably albumin and α_1 acid glycoprotein; renal sodium re-absorption increases; and changes occur in metabolic enzyme pathway in the liver including the CYP450.

A reduced dose of didanosine is usually prescribed combined with tenofovir, but there is increased renal excretion of didanosine in pregnancy. Although this is not considered sufficient to merit dose amendment there are no data on didanosine in pregnancy when prescribed with tenofovir. However, the new European recommendations are that these compounds should not be co-administered, especially in patients with high viral load and low CD4 cell count (Letter to Health Care Professionals from Bristol-Myers Squibb and Gilead 02 March 2005).

The pharmacokinetics of other nucleoside analogue reverse transcriptase inhibitors are generally not affected by pregnancy and dose adjustment is not required(179-184).

Tenofovir concentrations in the third trimester are reduced by about 15% compared to postpartum. Cord blood concentrations are approximately 60% of maternal blood concentrations. The AUC target of $2\mu\text{g}\cdot\text{h}/\text{ml}$ was missed in 5/19 women(185).

NVP has been studied in pregnancy and plasma concentrations are similar to non-pregnant adults(186-188). No dose adjustment is required.

PIs are highly protein-bound and placental transfer in humans appears to be limited. During the third trimester of pregnancy, lopinavir remains 99.04% protein-bound, which means there is 17% more protein-free lopinavir(189).

Nelfinavir concentrations tend to be variable and frequently low(190). Nelfinavir is currently not available in Europe.

The plasma concentrations of saquinavir when prescribed as unboosted soft-gel capsules are generally low(191) but when either the hard-gel capsules(192), soft-gel capsules(193) or new formulation tablets(194) are boosted by co-prescription with ritonavir, plasma concentrations appear to be generally therapeutic and no dose adjustment is routinely required. Interpatient variability during pregnancy is however high(146).

Compared to postpartum concentrations, third-trimester concentrations of lopinavir (lopinavir 400mg/ritonavir 100mg) are reduced by 28%. The protein-free fraction is moderately increased (17%) and at the standard dose, lopinavir appears to be clinically effective with a wide variation in individual plasma trough concentrations. Cohort studies have suggested that the majority of mothers taking the standard adult dose have adequate trough concentrations(195). Furthermore these data relate to the Kaletra™ capsule formulation. Until data from the new tablet formulation are available no dose adjustment is recommended as a routine.

At standard dose, boosted atazanavir concentrations are similar in the third trimester and postpartum(126).

In general, there are still limited data on the currently available PI formulations and a protein-binding effect has been examined only for lopinavir. Given this lack of data and the considerable degree of interpatient variability, therapeutic drug monitoring is recommended for PIs during pregnancy. It should be conducted at steady state (2 weeks or more into therapy) and repeated in the third trimester.

The pharmacokinetics in pregnancy of newer agents such as emtricitabine, tipranavir, darunavir fosamprenavir and maraviroc have not been described. 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 underdosing. Therefore therapeutic drug monitoring in pregnancy should be considered for all all PIs and for new agents where the facility exists.

Penetration of PIs into the genital tract of pregnant women is variable. Indinavir appears to concentrate in the cervico-vaginal secretions whilst lopinavir and saquinavir could not be detected(127). The implications of such data are uncertain.

NRTIs penetrate the genital tract more efficiently. A recent study compared genital tract levels with plasma giving values as follows: emtricitabine 600%, lamivudine 300%, tenofovir 300% and zidovudine 200%(196).

13. Obstetric management of pregnancy and delivery

The management of the HIV-positive pregnant woman aims to minimize the risk of mother-to-child transmission while not increasing maternal or neonatal morbidity. It must be recognized that much of the evidence for obstetric factors contributing to mother-to-child transmission comes from the pre-HAART era. There are very few studies to date examining these issues in the setting of women with a fully suppressed plasma viral load on HAART. As such it is unclear whether a woman with a fully suppressed viral load can be managed as if she were not HIV-infected in all obstetric situations. Until such data are available, it may be prudent to adopt a relatively cautious approach in some circumstances, as reflected by the guidance in this section.

Antenatal care

The importance of confidentiality, a care plan and a multidisciplinary approach to antenatal care is discussed in Section 6.

Periconceptual folic acid supplements are recommended. This is particularly important for those taking co-trimoxazole (the folate antagonist most commonly used for PCP prophylaxis), as maternal folate deficiency is associated with neural tube defects in the fetus.

The dating and anomaly scans should be undertaken according to national guidelines for the general population(197). The issue of teratogenicity from first-trimester exposure to antiretrovirals is discussed elsewhere but it is appropriate for the anomaly scan to be undertaken by the most experienced operator available. Screening for Down's Syndrome should be discussed with all women during the first trimester. Provision of the most specific and sensitive non-invasive tests for Down's Syndrome (nuchal translucency with serum screening) with appropriate counselling is likely to reduce the need for subsequent invasive prenatal diagnostic testing (discussed below).

Early pregnancy problems

Nausea and vomiting

Nausea and vomiting are common in early pregnancy. Symptoms usually begin between 5 and 6 weeks gestation, and in 90% of women these symptoms have resolved by 16 weeks. The incidence of nausea and vomiting may be increased in women taking HAART. Most women are able to adjust the timing of their antiretrovirals to avoid times of nausea.

Hyperemesis gravidarum is a condition characterized by intractable vomiting leading to fluid and electrolyte disturbances and nutritional deficiency. The onset is always in the first trimester. In severe cases, with inadequate treatment, hyperemesis may cause Wernicke's encephalopathy (due to thiamine deficiency), central pontine myelinolysis (due to hyponatraemia or its rapid reversal) and maternal death. Hyperemesis is a diagnosis of exclusion. In HIV-positive women, particularly those taking HAART, a diagnosis of hyperemesis should only be made once acidosis, hepatitis and pancreatitis have been excluded. Management of hyperemesis includes intravenous fluid replacement, correction of electrolyte imbalance, thiamine replacement and antiemetics. There is no reported increase in teratogenic risk with standard antiemetic drugs(198;199). First-line agents include the antihistamines promethazine and cyclizine. Prochlorperazine and metoclopramide may be used as second-line agents, but their use has been associated with extrapyramidal reactions in some young women(198;200). Oral, rectal and systemic routes of

administration should be considered. Controlled interruption of HAART may be the best option in severe cases. There are no known interactions between antiemetics and antiretrovirals.

Bleeding in early pregnancy

Although earlier studies have suggested that HIV infection increases the risk of first trimester pregnancy loss (miscarriage and ectopic pregnancy)¹⁸, more recent studies(201) (202) have not confirmed this. Management of HIV-positive women with bleeding in early pregnancy does not differ from HIV-negative women with similar symptoms and many of these women can be managed in Early Pregnancy Units. The possibility of drug toxicity should be considered in women with abdominal pain.

Prenatal diagnosis

HIV-infected women considering invasive prenatal diagnosis should be counselled in a specialist fetal medicine unit. For those women requiring genetic testing by amniocentesis every effort should be made to avoid inserting the needle through the placenta. Observational studies conducted prior to the widespread use of HAART in pregnancy suggested a possible association between amniocentesis and mother-to-child transmission. However this association has not been demonstrated in more recent studies of women taking HAART(203-205). For women who have started HAART but whose viral load is not yet undetectable, it may be advisable to delay the amniocentesis until the maternal viral load is undetectable if at all possible. In women not already taking HAART, administration of antiretrovirals to cover the procedure is advised. In these cases, the chosen regimen should ideally include agents with good placental transfer. Protease inhibitors cross the placenta only to a very limited degree. If non-nucleoside reverse transcriptase inhibitors (NNRTI) are not already part of the regimen consider adding a single 200mg dose of NVP to other HAART therapy.

Complications of later pregnancy

Problems associated with HIV

There are a number of medical conditions that may arise as a result of HIV infection and that can complicate the pregnancy. Some of these complications are known to increase the risk of mother-to-child transmission.

Pregnancy is a hypercoagulable state and infection with HIV may increase this tendency. The adoption of stringent antithromboembolic precautions is essential if a pregnant HIV-positive woman is hospitalized or undergoes surgery. This will include TED stockings and/or low molecular weight heparin injections.

HIV infection may also be associated with the development of acquired thrombophilias, which in the general population are known to predispose to a range of pregnancy complications such as *in-utero* fetal death, pre-eclampsia and intrauterine growth restriction. Although it is thought that these can be managed in a similar fashion to women with thrombophilias in pregnancy who are not HIV-infected, there are no studies to confirm similar efficacy in the HIV-infected woman.

Nephropathies associated with HIV infection can occur. One of the commonest is IgA nephropathy that results in large amounts of protein being lost in the urine. This will increase the risk of pre-eclampsia and hypertension, and is associated with an increased risk of thromboembolism(206).

Medical disorders of pregnancy

Glucose impairment and pre-eclampsia have been associated with antiretroviral therapy (see Section 11). Both should be managed as per normal obstetric practice.

Obstetric cholestasis (OC) has a complex aetiology, which includes genetic, environmental and endocrinological factors. It is a diagnosis of exclusion but is characterized by pruritis, without rash, with raised serum transaminases and bile acids. It is more common in women who also develop pre-eclampsia. The condition is not thought to be more common in women infected with HIV but the finding of raised transaminases can be confused with the hepatic effects of antiretroviral drugs. OC is associated with maternal liver impairment and fetal morbidity and mortality and positive diagnosis is therefore important.

It may be difficult to distinguish the toxic effect of antiretrovirals from certain medical disorders of pregnancy, such as pre-eclampsia, HELLP syndrome, obstetric cholestasis and acute fatty liver of pregnancy. If these disorders are suspected, additional tests should be undertaken for lactic acidosis, hepatitis and pancreatitis. If there is lactic acidosis (>5mmol/L) consideration should be given to interrupting therapy. Monitor lactic acidemia (2–4.9 mmol/L) carefully. This is most commonly seen in patients taking didanosine or stavudine. The presenting symptoms of lactic

acidosis may be non-specific, but may include gastrointestinal disturbance, fatigue, fever and breathlessness. Close collaboration between the HIV physician and obstetrician is mandatory for any woman who becomes acutely unwell in pregnancy to avoid diagnostic pitfalls.

In the unlikely event of a maternal death a post-mortem should be conducted by a pathologist with experience in maternal death and HIV disease. In the event of a coroner's post-mortem the report should be obtained for audit.

Antepartum haemorrhage

Conditions associated with vaginal bleeding in pregnancy, such as placenta praevia and placental abruption, may increase the risk of mother-to-child transmission. There is no published evidence that helps decision-making regarding delivery, but in general the risks to the mother of delivery or continued blood loss, as well as the risks to the fetus of continued blood loss must be weighed against the risks of mother-to-child transmission and prematurity.

Pre-term labour

The association between antiretroviral therapy and risk of pre-term labour is discussed in Section 11.

Pre-term delivery has been identified as a risk for HIV mother-to-child transmission(207) (208). An HIV-positive woman presenting with threatened pre-term labour (intact membranes) should have a vaginal swab taken for bacteriology. At gestations less than 34 weeks two doses of intramuscular betamethasone 12mg 24 hours apart should be administered in order to enhance fetal lung maturation. This management is no different from that of HIV-negative women. The use of tocolytic agents, which can be used to delay delivery for up to 48 hours, will be determined by considering the risk of prematurity to the neonate compared with the risk of infection (see also Scenarios).

Pre-term pre-labour rupture of membranes at gestations >34 weeks

Pre-term pre-labour rupture of membranes (PPROM) is associated with 40% of pre-term deliveries and can result in significant neonatal morbidity and mortality. For the general population, in the absence of chorioamnionitis or fetal compromise, management is expectant and delivery is considered at 34 weeks (RCOG 2006). At this gestation, the small risk of severe neonatal morbidity

and mortality associated with pre-term delivery is outweighed by the risk to both mother and neonate of chorioamnionitis.

For the HIV-positive woman, all the data on transmission in this setting are from the pre-HAART era where prolonged rupture of membranes and chorioamnionitis were associated with an increased risk of mother-to-child transmission(209). Moreover, the woman may be more susceptible to overwhelming and life-threatening sepsis as a result HIV-related immunosuppression(210-212). In absence of data to the contrary it is recommended that for a mother with HIV infection PPRM after 34 weeks delivery of the baby should be expedited regardless of maternal viral load and therapy. Carefully search for genital infections, start erythromycin and have a low threshold for intravenous broad-spectrum antibiotics.

Pre-term pre-labour rupture of membranes at gestations <34 weeks

When PPRM occurs before 34 weeks consider the advisability of prolonging pregnancy in the light of maternal HAART, viraemia and the presence of any other pregnancy or HIV-related co-morbidities. Start steroids immediately, carefully search for genital infections, start erythromycin and have a low threshold for intravenous broad-spectrum antibiotics. It may be possible to optimize the woman's HAART regimen to reduce the risk of mother-to-child transmission. Maternal single-dose NVP should be strongly considered (even in the presence of NVP-associated resistance (see Section 13) because of the highly efficient transplacental transfer and prolonged plasma concentrations in a neonate that may be unable to take oral post-exposure prophylaxis. Intravenous zidovudine may be considered if the mother has detectable plasma viraemia. All maternal ART must be given regardless of any planned surgery.

Once two doses of steroids have been administered, elective delivery <34 weeks may be considered balancing the risks of severe complications of prematurity and availability of neonatal facilities, with the risk of HIV infection, after multidisciplinary discussion involving the obstetricians, neonatologists and HIV physicians. There have been no randomized controlled trials to inform these decisions.

Term pre-labour rupture of membranes

The transmission risk for women with term PROM taking HAART who have undetectable plasma viraemia is unknown. A meta-analysis of studies conducted before use of HAART in pregnancy

demonstrated a 2% incremental increase in transmission risk for every hour of ruptured membranes up to 24 hours(213). There is evidence of compartmentalization between the genital tract and plasma; genital tract HIV-1 has been detected in women with an undetectable plasma viral load(53;214). It is therefore reasonable to assume that prolonged rupture of the membranes, even in women with undetectable plasma viraemia may be associated with an increased risk of mother-to-child transmission. Although this increased risk is likely to be small it seems prudent that delivery should be expedited. Broad-spectrum intravenous antibiotics (such as a cephalosporin and metronidazole) should be administered stat where there is evidence of chorioamnionitis and may be considered for all mothers planning a vaginal delivery. For those with a fully suppressed viral load, favourable cervix and intending to deliver vaginally, induction of labour may be considered. Where PLCS was planned, HIV is still detectable or successful labour unlikely, early delivery by Caesarean section is recommended (see Scenario 7)

Prolonged pregnancy

The management of prolonged pregnancy is difficult in women infected with HIV. The current recommendation for the general pregnant population is that provided the mother and fetus are well, the fetus will benefit from delivery at beyond 41 weeks gestation(215). The risk of *in utero* fetal death (IUFD) at 41 weeks is estimated at 1 in a 1000 and therefore induction of labour is usually recommended at this stage. Induction of labour is usually achieved using vaginal prostin or artificial rupture of the membranes (ARM) with the addition of a syntocinon infusion if contractions do not then start.

In the HIV-infected woman, it is generally held that early ARM may be associated with an increased risk of mother-to-child transmission, particularly if the maternal plasma viral load is detectable. This is because prolonged rupture of membranes is associated with an increased risk of mother-to-child transmission for women with detectable plasma viraemia (see above) and because early ARM where the membranes are tightly covering the fetal head may cause trauma to the fetal scalp, thereby increasing the risk of exposure to maternal blood and cervico-vaginal secretions. The risk of sudden IUFD must therefore be weighed against both the risks of the method of induction described above, and the increased rate of complications, including emergency Caesarean section, fetal distress, need for epidural anaesthesia and assisted delivery. If the woman is keen to achieve a vaginal delivery, is on optimum HAART, has an undetectable

viral load and favourable cervix then induction of labour may be considered, but it is generally recommended to perform a Caesarean section if spontaneous labour has not ensued prior to 41+ weeks.

Vaginal birth after Caesarean (VBAC)

The general population are now recommended to attempt to deliver vaginally after previous Caesarean section in view of the high rates of successful vaginal delivery and the low risk of scar dehiscence(216). The risk of dehiscence of a lower segment Caesarean scar in labour is of the order of 1 in 250. The probability of a successful vaginal delivery is dependent on current and past obstetric factors. In general, provided the woman is being cared for in a consultant-led maternity unit and the labour properly monitored with rapid recourse to Caesarean section in the face of any difficulty, the outcome of trial of labour for mother and neonate is good, even if scar dehiscence occurs. There are no data for women with HIV infection but prolonged exposure to maternal blood if dehiscence occurs might carry additional transmission risk. The usual criteria for elective vaginal delivery apply.

Management of delivery

Mode of delivery

A decision on mode of delivery should involve the mother, the obstetrician and the HIV physician in a detailed risk assessment. Discussion must take into account maternal plasma viral load, safety and efficacy data on mode of delivery by pre-labour Caesarean section including future pregnancy plans, the efficacy and toxicity of antiretroviral therapy, and the wishes of the mother. Initial studies conducted prior to the use of HAART in pregnancy found a reduction in mother-to-child transmission with elective Caesarean section. A meta-analysis of 15 prospective cohort studies ($n=8533$)(217) and a randomized controlled trial of mode of delivery in Europe ($n=436$)(122) both supported the protective effect of elective Caesarean section, with reductions in mother-to-child transmission of 50% and 70%, respectively.

Although maternal plasma viral load has an almost linear association with the risk of mother-to-child transmission(70), transmission has been reported when maternal viraemia was

undetectable(75;218). In a meta-analysis of seven prospective studies from the US and Europe ($n=1202$) of those with plasma HIV RNA <1000 copies/ml at or around delivery, the transmission rate for mothers taking antiretroviral therapy was 1%, compared with 9.8% for those not taking therapy(74). Caesarean section, either pre-labour or emergency, reduced the risk of mother-to-child transmission by two-thirds, independent of viral load or maternal antiretroviral therapy. 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 low maternal plasma viral loads (74).

Prospective data from the European Collaborative Study group ($n=1983$) also suggested reduction in transmission with elective Caesarean section for women with low plasma viraemia(134). In this study of 4525 mother-child pairs recruited between 1997 and 2004, mother-to-child transmission from 1997-1998, at a time when only a small minority of pregnant women received HAART, was 5.06%. By 2001-2002 when the majority of women received HAART in pregnancy, mother-to-child transmission was 0.99%. However, among the 560 women with undetectable HIV RNA levels (44% with levels of <50 copies/ml), elective Caesarean section was associated with a 93% reduction in the risk of mother-to-child transmission compared with vaginal delivery or emergency Caesarean section (OR, 0.07; CI 0.02-0.31; $P=0.0004$).

In the current era of HAART, it is unclear whether PLCS provides additional benefit if maternal plasma viraemia is undetectable (<50 HIV RNA copies/ml plasma). Data from the UK and Ireland (1990-2004) showed a significantly lower mother-to-child transmission rate in women on HAART who undergo a PLCS (0.7%) compared to women who deliver vaginally (1.9%). The analysis included unplanned as well as planned vaginal deliveries, and was not restricted to women who achieved undetectable viral load(3). In the French Cohort PLCS did not significantly reduce the rate of transmission compared to vaginal delivery if maternal viral load was less than 400 HIV RNA copies/ml(123). In the UK and Ireland cohort (2000-2006) 2117 infants were born to women with an HIV viral load less than 50 copies per ml plasma on HAART. There were 3 infections (0.1%) 2 in infants born by PLCS and 1 in an infant born by planned vaginal delivery(4). These data support the strategy of offering HIV-positive women with uncomplicated pregnancies, on HAART with no detectable viraemia the option of a trial of labour.

Management of Caesarean section

The timing of pre-labour pre-rupture of membrane CS is a balance between the likelihood of transient tachypnoea of the newborn (TTN) and the risks of labour supervening before the scheduled Caesarean section. The general pregnant population is now advised that elective Caesarean section should be performed at 39 weeks when the frequency of TTN is 1 in 300(219). The risk of TTN doubles for every week earlier that delivery occurs. The risks of membrane rupture and labour increase as the pregnancy progresses towards term. Therefore, where the mother is on optimal HAART and the viral load is undetectable, and there are no other reasons for recommending a Caesarean section, it may be reasonable to defer this until 39 weeks. Where there is a detectable viral load or any clinical reason to suppose that the woman will labour early, then earlier Caesarean section will be wise and is usually scheduled at 38 weeks gestation.

If indicated, the zidovudine infusion should start 4 hours before the start of the Caesarean section and continue until the umbilical cord has been clamped.

Although there was a suggestion a number of years ago that the so called 'bloodless Caesarean section' might confer some protection on the fetus(220) there has been no further evidence to substantiate this. However, it would seem to be good practise to keep the surgical field relatively haemostatic and not to rupture the membranes until the head is delivered through the surgical incision, if possible. The cord should be clamped early.

Several studies have suggested that the complications of Caesarean section are higher in women with HIV, with the highest risks in women undergoing emergency Caesarean section. The most frequent reported complication was postpartum fever and this was increased in women with low CD4 counts(221;222). However many of these studies were performed prior to the recommendation that prophylactic antibiotics should be administered intra-operatively to all women undergoing Caesarean section to reduce infectious morbidity. A more recent case-controlled study from the UK, where all HIV-positive women received antiretroviral therapy and prophylactic antibiotics ($n=44$) did not demonstrate any differences in post-operative morbidity(223). This is in keeping with data from a Dutch cohort ($n=143$)(167) and studies from Latin America and the Caribbean, which also showed low rates of postpartum morbidity(224). However, the observation that HIV-infected women may be at increased risk of postpartum morbidity, regardless of mode of delivery, was suggested by a case-control study of women delivering in 13 European centres that

found higher rate of morbidity in HIV-infected women ($n=408$) when compared with non-HIV-infected women(222). HIV-infected women may not, therefore, be suitable for early discharge in the postpartum period.

Management of vaginal delivery

When vaginal delivery is planned, spontaneous onset of labour is preferable to induction (see 'Management of prolonged pregnancy' for considerations around induction of labour). Because of the association of mother-to-child transmission with the duration of membranes rupture, labour must progress normally and the mother and the fetus should be in good condition throughout. Fetal blood sampling and fetal scalp electrodes are contraindicated. Because of the necessity to avoid invasive procedures in the fetus, there should be a low threshold for Caesarean section in the face of slow or difficult labour or concern about fetal condition. Amniotomy should be avoided unless there is slowing of progress of second-stage labour. In this situation the risk of trauma of the fetal scalp is likely to be very small, and there is unlikely to be a lengthy delay between amniotomy and delivery.

If instrumental delivery is required low cavity traction forceps are the instrument of choice as it is generally accepted that they are associated with lower rates of foetal trauma than ventouse. Mid-cavity and rotational deliveries should be avoided.

Postpartum care

Suppression of lactation

Cabergoline 1mg orally stat within 24 hours of birth will assist with suppression of breast-milk production.

Contraception

The importance of contraception should be emphasised particularly as women will not be breast-feeding. The BHIVA guidelines on the management of sexual and reproductive health of people living with HIV infection (2007) are found at <http://www.bhiva.org/cms1191550.asp>

14. Pregnancy in women with HIV-2 infection

First described in 1986, HIV-2 is found mainly in West Africa, the epicentre of the epidemic being Guinea Bissau, where a prevalence of up to 10% has been reported(225) and some areas of Southern India. In Europe, HIV-2 is found in regions with a historical relationship with West Africa, in particular Portugal and France. Although in Europe the number of people with HIV-2 infection is small it is gradually increasing as global migration influences population dynamics. In the UK approximately 130 infections with HIV-2 have been reported to the Health Protection Agency (B. Rice, HPA, personal communication). Although HIV-1 and HIV-2 are related, there are important differences between them that influence pathogenicity, natural history and therapy.

HIV-2 appears to be less readily transmitted than HIV-1 both sexually(226;227) and from mother and child(228-230). HIV-2 appears to have a less aggressive natural history than HIV-1(231;232) . In general the viral load in HIV-2 is lower than that in HIV-1, and high CD4 cell counts are associated with low levels of viral replication(233). High levels of viral replication however are correlated with poor prognosis and are an indication to initiate therapy(234;235).

There is little clinical evidence on which to base treatment strategies for patients with HIV-2. HIV-2 differs from HIV-1 in its susceptibility to antiretroviral therapy and also follows different mutation pathways to develop drug resistance. These factors mean that selection of, and adherence to, the first antiretroviral combination regimen, already crucial for successful treatment of HIV-1 infection, is that much more critical for HIV-2(236) (see Table 5).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have no activity against HIV-2, with the IC⁵⁰ being over 100 fold greater than that for HIV-1(237). Amongst the NRTIs there is a suggestion that zidovudine may have less activity against HIV-2 than HIV-1, although this is so far only from *in vitro* data(238). A variety of polymorphisms exist in the HIV-2 protease gene at positions that in HIV

-1 are associated with reduced drug susceptibility(239). *In vitro* phenotypic analysis of HIV- 2 isolates has shown reduced susceptibility to amprenavir, atazanavir and tipranavir but little difference for lopinavir when compared to HIV-1(240). A poor clinical response has been demonstrated to nelfinavir(241).

Enfurvitide is not effective against HIV-2 (236).

In some circumstances patterns of resistance in HIV -2 that emerge under drug pressure may be the same as those seen in HIV -1(242). However there are significant differences, particularly in NRTI pathways. The multiple resistance NRTI mutation Q151M has been noted to occur with increased frequency in HIV – 2 in response to NRTI therapy(243-245). The pathways by which NRTI resistance occurs in HIV-2 may differ from those of HIV-1 and resistance may develop more rapidly due to other pre-existing mutations(246).

Pregnant women with detectable HIV-2 should be managed using a HAART regimen to which the virus is sensitive.

In the light of the current data on NRTI resistance pathways, albeit limited, zidovudine monotherapy should not be used in women with HIV-2. If the mother has a high CD4 cell count (>500 cells/mm³) and a consistently undetectable HIV-2 viral load, drug therapy may not be indicated and the possible risks and benefits of this approach should be discussed with the mother.

The risk to the baby from breast milk is probably lower than for HIV-1 but it is advisable to avoid this method of feeding.

Infants born to infected women should ideally be monitored for HIV-2 proviral DNA and samples should be referred to a specialist laboratory (see below). Determining loss of HIV-2 antibodies by 18 months of age is also recommended.

Mode of delivery.

If the CD4+ lymphocyte counts is >500 cells/mm³ and the untreated HIV-2 viral load below the limit of detection (BLD), consider SVD. Similarly if viral load BLD on HAART, consider SVD. If viral load not BLD or CD4+ <500 cells/mm³ plan for PLCS at 38 weeks.

Laboratory investigation and monitoring for HIV-2 in pregnancy

Making the correct diagnosis is crucial as therapy will differ significantly if HIV-2 is present. Not all laboratories differentiate between HIV-1 and HIV-2 so it is important that any patient who may have been at risk of HIV-2 has the appropriate investigations performed.

At the time of writing in the UK HIV-2 viral load assays are only carried out by:

Prof Deenan Pillay/Dr Bridget Fern

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; email: d.pillay@ucl.ac.uk

HIV-2 genotyping can be performed by:

Dr Erasmus Smit, Consultant Virologist

West Midlands Public Health Laboratory, Health Protection Agency, Birmingham Heartlands
Hospital, Bordesley Green East, Birmingham B9 5SS, UK

Tel: 0121 424 1239; Fax: 0121 772 6229; email: erasmus.smit@heartofengland.nhs.uk

The UK HIV-2 reference laboratory is based at the HPA in Colindale and is lead by:

Ms Jennifer Tosswill

Health Protection Agency, Sexually Transmitted and Blood Borne Virus Laboratory, 61 Colindale
Avenue, London NW9 5HT, UK

Tel: 020 8327 6274; email: jennifer.tosswill@hpa.org.uk

The laboratories should be contacted in advance of sending specimens to discuss appropriate samples and the conditions for transporting them.

15. HIV and hepatitis B and C co-infections

Mother-to-child transmission of HCV

All women with HIV should be screened for both hepatitis B and C infection. Women with very low CD4 cell counts may not produce a serological response to hepatitis C virus (HCV) and molecular assays to detect HCV RNA may be considered in this circumstance.

In women who are infected with the hepatitis C virus (HCV) there is a low rate of transmission of HCV from mother to infant and current estimates indicate that up to 6% of women will infect their child(247-249). The timing and route of transmission is unclear and it is not known whether transmission is transplacental or during delivery. HCV plasma viral load is associated with transmission; women with undetectable viraemia are highly unlikely to transmit. HCV viraemic mothers, (HCV+/HIV-) have an increased transmission rate of up to 10%(248;250). 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 (247;251). These data arise from relatively small-scale, retrospective studies and the findings have not been confirmed. Breastfeeding is not thought to increase the risk of infection(247;249;251-253).

In women who are HCV and HIV co-infected, transmission is increased to up to 15%, with higher rates in those who are HCV viraemic (248;248;249;252;254). Pappalardo's meta-analysis shows an increased odds ratio for HCV transmission of 2.82 (95% CI 1.78–4.45) if the mother is co-infected with HIV(255). Effective control of HIV is associated with a reduction in the rate of HCV transmission although the mechanisms of this improvement are unclear(256;257). No studies to assess the benefits of surgical, rather than vaginal, delivery have been performed in HIV/HCV co-infected women. In view of the reduced mother-to-child transmission of HCV with elective Caesarean in HIV-negative women, and the reduced mother-to-child transmission of HCV with effective control of HIV, it would seem prudent to recommend HAART and consider PLCS for all HIV and HCV co-infected mothers.

Guidelines on the management of adults with HIV/HCV co-infection *per se* can be obtained from the BHIVA website. <http://www.bhiva.org/guidelines/2004/HCV/index.html>

Diagnosis of HCV infection in children

In view of the increased risk of HCV infection in children born to women who are co-infected with HIV, testing for HCV is recommended for all infants born to dually infected mothers. The optimal timing and nature of the test that should be used is unclear. However, transmission of maternal antibodies is almost invariable and therefore antibody testing is unreliable until the infant is 15–18 months old. Testing for viraemia during the first few months of life may not reliably identify chronically infected children and some studies suggest that a proportion of infants who are originally HCV RNA positive will clear virus without intervention (247;251). 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(258;259).

Mother-to-child transmission of 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(258) and materno-fetal transmission of HBV has been greatly reduced in developed countries by effective vaccination programs. Materno-fetal transmission of HBV is related to the level of HBV viraemia. In general women who are HBeAg positive have a high incidence of transmission of HBV to their infants (90%) and the risk is reduced in women who are HBeAg negative (40%)(260). However, women who are HBeAg negative with high level hepatitis B viraemia may have an increased incidence of materno-fetal transmission, although the magnitude of the increased risk and the precise level of viraemia at which the risk becomes significant is not known. Hepatitis B viral DNA quantification is therefore recommended for all HbsAg-positive mothers. A Chinese study has demonstrated a reduction in vertical HBV transmission where mothers received either lamivudine or hyperimmune globulin, compared to no treatment(261). Further studies to define the optimal treatment of maternal disease as well as to prevent transmission are required.

HIV may increase the serum HBV DNA levels and it is plausible that co-infection will increase the rate of HBV transmission but this has not been shown. A small study from Tanzania suggested that

co-infection did not increase the risk of transmission but an increase in the rate of transmission could not be excluded(262).

In pregnant women with HIV/HBV co-infection it is recommended to use a HAART regimen that includes agents active against both HBV and HIV. Lamivudine, emtricitabine and tenofovir are active against both HBV and HIV. As there has been most experience with the use of lamivudine in pregnancy, HIV and HBV co-infected mothers should probably be treated using a regimen containing tenofovir and lamivudine plus a third agent. Guidelines on the management of adults with HIV/HBV co-infection per se can be obtained from the BHIVA website (www.bhiva.org).

Diagnosis of HBV infection in children

Infants born to HBV-positive mothers in the UK should receive active HBV vaccination at birth, 1 month, 2 months, and 12 months of age. Infants born to mothers with high risk of infectivity should also receive Hepatitis B immunoglobulin at birth (no national consensus -consult local hospital policy). At 15–18 months of age infants should be screened for HBsAg to confirm they have not been infected and HBsAb to confirm that they have responded to their vaccination.

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.

16. Management of infants born to HIV-infected mothers

(See Tables 3 and 4 for quick reference guides to infant antiretroviral regimens and infant dosing.) 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 weeks of life. The range of different combinations of ART to which neonates are being exposed is constantly increasing. Neonatal drug metabolism is generally slower than that of older infants or children, and premature neonates have even less efficient metabolism(263). Neonatal dosing regimens have been developed for most of the nucleoside analogues, for the NNRTI NVP, and for the PI nelfinavir (Table 4) although the latter is currently not available in Europe (Nov 2007). Studies of dosing regimens for other drugs (e.g. lopinavir/ritonavir and tenofovir) are in process. Adequate neonatal blood levels are difficult to achieve with nelfinavir and there is little experience of other PIs. A recent population

pharmacokinetic study of ritonavir-boosted lopinavir including six neonates suggested that on standard doses (300mg/m² BD) neonatal trough levels on twice-daily dosing may be too low(264-267). Where ritonavir-boosted lopinavir liquid is required for neonatal post exposure prophylaxis, consideration should be given to a TDS regime (300mg/m² TDS) and therapeutic drug monitoring should where possible be undertaken (further studies are underway). See CHIVA website for dosing updates (www.chiva.org.uk).

In contrast to the PIs, NVP efficiently crosses the placenta (see below) and is well absorbed by the neonate (268) (269). Neonatal metabolism of NVP is induced where there has been antenatal *in utero* exposure(187;188); if this drug is given to the neonate, when the mother has taken it for 3 (or more) days, the full dose of 4mg/kg per day should be started at birth, rather than the induction dose of 2mg/kg per day (Table 3). Owing to the long half-life of NVP, when used in combination therapy for the infant, NVP should be stopped 2 weeks before the other drugs to reduce the risk of monotherapy exposure and development of NNRTI resistance(186).

The only ART available for intravenous (IV) use in sick and/or premature neonates, unable to take oral medication, is ZDV(270;271). Reduced oral and IV dosing schedules for premature infants have only been developed for ZDV (table 3,4) (271).

When to use monotherapy for the infant as post-exposure prophylaxis

Where a low transmission risk mother chooses ZDV monotherapy with Caesarean section delivery, then the infant should also receive ZDV monotherapy.

Where a mother on combination therapy delivers with a viral load of <50 copies/ml, 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. Zidovudine should not be given to an infant born to a mother who is receiving stavudine because of the theoretical negative competitive interaction. Monotherapy with NVP 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 as discussed previously(101).

When to use combination antiretroviral therapy for the infant as post-exposure prophylaxis

With regard to prevention of mother-to-child transmission of HIV, there have been very few studies of combination therapy in neonates and no published studies regarding the efficacy of triple combinations. Dual combination ART to the neonate (ZDV+3TC versus ZDV) had additional benefit over single-drug treatment (in historical controls) in terms of reduction of transmission when mothers were also receiving dual ART(109). A randomized African study that compared short-course (1 week) treatment to the infant with either ZDV+NVP or NVP also demonstrated superiority of two drugs (see below)(272). However, in the randomized African SAINT study, no significant difference in transmission rate was demonstrated in short-course treatment with either ZDV+3TC or NVP after perinatal treatment to the mother(125).

There are three situations where triple combination PEP for neonates is advisable:

1. **Post delivery prophylaxis:** where the mother is found to be HIV-infected only after delivery
2. **Unplanned delivery:** e.g. prematurely prior to starting ART; or after a late presentation when details of maternal HIV parameters may not be available
3. **Persistent maternal viraemia on HAART:** e.g. due to poor adherence or viral rebound with resistance

Two studies have examined the first situation where due to late diagnosis of the mother treatment could only be given to the infant after birth. In a US cohort study a reduced risk of transmission, compared with no intervention, was observed in infants commenced on ZDV monotherapy provided this was started within 48 hours of birth. (119). In a randomized African study of after-birth prophylaxis, babies born to mothers presenting at delivery received either single-dose NVP or single-dose NVP + a week of ZDV(272). Of the babies who were HIV negative on testing at birth, 34 (7.7%) who received NVP + ZDV and 51 (12.1%) who received NVP alone were subsequently infected ($P=0.03$) – 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 post-exposure prophylaxis cases, where the level of blood/body fluid exposure is likely to be much less.

For infants born to ART-naïve women, ZDV, 3TC and NVP is the combination therapy regimen with most experience. Infants born to non-naïve mothers may require other combinations, especially if there is a possibility of ART resistance (seek expert advice).

Resistance testing should be carried out in the mother in such a situation, although this will only give information in retrospect, and choice of treatment will have to be made on a best-guess basis with the history of drug exposure and any previous resistance data in the mother. If the infant is found to be infected, then the first HIV-positive sample should also be tested for the resistance pattern of the transmitted virus.

Treating premature infants: loading the infant with antiretroviral therapy before birth

Although premature infants are at most risk of HIV infection they are also the most difficult to treat with PEP. Most infants born at less than 30–32 weeks gestation will not be able to feed orally for the first few days, with the only licensed IV treatment available to them being ZDV. Therefore, where possible, the infant should be loaded with ART before delivery, via the maternal circulation across the placenta. Most PIs do not cross the placenta in significant concentrations, NRTIs have concentrations of 60–100% in cord blood, so mothers should always continue their medication right up until delivery. A single dose of NVP given to the mother at least 2 hours before delivery will be present in the infant circulation for up to 7 days(273). Tenofovir may also have a prolonged half-life in the neonate, and this is under investigation.

Even if the mother is receiving a PI-based regimen, a single additional dose of NVP may be given to load the fetal circulation, thus the neonate will receive at least ZDV and NVP for the first 5–7 days of life. In the NVP-naïve mother, to prevent development of resistance, the maternal washout period of NVP should be covered with an appropriate 'tail' of antiretroviral therapy.

The premature neonate is at risk of necrotising enterocolitis if oral feeding is commenced too soon or increased too rapidly, Whether very early oral administration of antiretrovirals can exacerbate this is not known, but in general oral drugs should only be given along with the establishment of oral feeds(274). Once the infant is successfully oral feeding, IV ZDV should be changed to oral.

When to start and duration of antiretroviral treatment for neonates

Neonatal post- exposure prophylaxis should be commenced as soon as possible after birth, certainly within 4 hours, and this is particularly important where the mother has not received any antiretroviral therapy (see above). In the PACTG 076 study ZDV was administered for 6 weeks after birth and this subsequently became standard of care(114). 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 ZDV from 28 weeks gestation(115). In the UK, neonates are treated for 4 weeks in line with post-exposure prophylaxis guidelines in other situations(275).

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. However, there may be others not yet recognized(276). Teratogenicity is most likely to be a problem with first-trimester exposure to ART +/- other drugs. All currently licensed antiretroviral therapies (except efavirenz, which has recently been re-classified D) are classified either B or C for use in pregnancy by the FDA. All women who receive ART in pregnancy should be registered anonymously and prospectively with the Antiretroviral Pregnancy Registry (www.apregistry.com), which is updated twice a year. To date, a slight increase in overall congenital abnormalities above the background rate has only been reported for didanosine, however no specific fetal abnormalities have been identified with this or any other drugs (see section 11). Detailed fetal anomaly scanning around 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(277). So far, no adverse growth or developmental effects of ART exposure have been demonstrated in children(278;279). Mitochondrial toxicity after perinatal ART exposure, with two deaths from

encephalopathy, was first reported in uninfected infants from the prospectively followed French cohort(280). Deaths have not been identified in other large cohorts(281-284). However, laboratory analysis of mitochondrial DNA has demonstrated abnormalities in infants born to ART-treated mothers and this is an area of ongoing investigation(285). In the long-term follow up of the infants from the 076 study, two ZDV-exposed children were shown to have unexplained retinopathy and cardiomyopathy, which could potentially be related to mitochondrial dysfunction(279). A long-term follow up study of health and development in about 700 ART exposed children to 3–5 years of age, by annual parental questionnaire, in the UK did not demonstrate any specific health problems(286).

in the UK did not demonstrate any specific health problems(287) . However, although parents were generally supportive of continuing follow up for these children (288), in practice this was difficult and incomplete due to family mobility, concerns about confidentiality, and poor attendance for follow-up appointments.

In a separate initiative, data on infected and uninfected infants reported to the NSHPC (see below) are linked to routinely collected ONS data, a process known as “flagging”. In the event of a cancer or death registration for any of these children this will be reported back to the NSHPC and linked with information on prenatal exposure. Ninety-five percent of HIV-exposed infants born 2001–2004 in England or Wales had been flagged by the end of 2005, and at that time no cancers had been notified (289).

Short term

Short-term acute mitochondrial toxicity may rarely present in the newborn period, exacerbating the metabolic stress of delivery. A small number of sick infants have been reported with severe lactic acidosis, multi-system failure and anaemia, not attributable to any other cause, all have recovered with supportive care(290). Elevated lactic acid levels have also been found in asymptomatic ART exposed infants(291). Neonatal anaemia and neutropaenia is reported in infants exposed to NRTIs, this may be worse where there is exposure to combination therapy, or more prolonged treatment(109). Transfusion is rarely required and most children appear to respond to discontinuation of marrow suppressive therapy. However, a more recent study of over 4000 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(292). 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(293). Whether different combinations of ART may be more or less deleterious to the neonate is not known.

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

Laboratory diagnosis of HIV infection in non-breastfed infants

The gold standard test for HIV infection in infancy is HIV DNA PCR on peripheral blood lymphocytes(294), although some studies are now demonstrating equal/increased early sensitivity with amplification of viral RNA(295). As many infants are infected intrapartum and blood HIV levels may still be very low, HIV DNA is not amplified from all infected infants at birth. Indeed a positive HIV DNA PCR result within 72 hours of birth has previously been taken as evidence of intra-uterine transmission(296). Within the first weeks of life the sensitivity of the test increases dramatically and by 3 months of age at least 95% of non-breastfed 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(297;298).

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 breastfed, then parents can be informed that the child is not HIV infected. Evidence from the French perinatal cohort demonstrated that neonatal ART, especially if more than one drug, can delay the detection of both HIV DNA and RNA in the infant(299). For this reason, the second HIV DNA PCR is collected at 6 weeks of age, after 2 weeks off PEP.

For infants at high risk of infection an additional early HIV-DNA PCR maybe undertaken at 2–3 weeks of age. If this is found to be positive this investigation should be immediately repeated on a

further sample to ensure rapid confirmation of the diagnosis and to enable the establishment of combination antiretroviral treatment to try to avoid the development of HIV encephalopathy.

Loss of maternal antibodies is subsequently confirmed at 18 months of age. Ideally an HIV antibody test should be used to confirm loss of maternal antibodies rather than a combined HIV antibody-antigen test. The newer combined tests are highly sensitive and may give a positive HIV result until up to 2 years of age(300).

If an infant is found to be HIV infected after perinatal ART exposure then the mother and infant should have urgent HIV resistance testing to delineate the reasons for treatment failure and to help guide further treatment.

A managed network for children with HIV in the UK

Where an infant is found to be HIV infected, an urgent referral to the local specialist clinic should be made so that early commencement of combination ART can be started. HIV services for children in the UK are now organized in managed networks (CHINN). The details of the CHIN Network and contact details for local paediatricians can be found in the CHINN report at <http://www.chiva.org/> (301).

Prophylaxis, immunisations and clinical monitoring

Primary *Pneumocystis* pneumonia (PCP) in infants with HIV remains a disease with a high mortality and morbidity(302). 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 primary immunisation schedule at 2,3, and 4 months, except that BCG vaccine should not be given until the infant is confirmed uninfected, with two negative HIV DNA PCRs off ART. (See Section 10 for further information on HBV).

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 the infant or mother is unwell.

Child protection

Rarely, pregnant mothers refuse treatment for their own HIV as well as interventions to reduce the risk of transmission to their unborn infant. Whether for social, religious, or other reasons, mothers who have been reluctant to accept interventions may be able to where each aspect of the intervention package is dealt with separately (maternal ART, delivery, infant ART, infant feeding). This step-by-step approach has helped women to gradually make difficult personal changes to their birth plans. The input of the multidisciplinary team is crucial to support these women as they are often the most isolated and unsupported.

Despite all efforts, where the multidisciplinary team is unable to influence a mother's views antenatally, then a pre-birth planning meeting with social services should be held. The mother should be informed that it is the paediatrician's role to advocate on behalf of the child's well being and therefore to prevent, where possible, HIV infection. If the mother continues to refuse any intervention package, then legal permission should be sought at birth to treat the infant for 4 weeks with combination post-exposure prophylaxis and in addition breastfeeding should be strongly discouraged. Preparation of the legal case may be lengthy and time consuming; useful documentation can be obtained for colleagues who have already undertaken this.

Reporting and long-term follow up

It is the responsibility of clinicians caring for women with HIV and their children to report them prospectively to the National Study of HIV in Pregnancy and Childhood (NSHPC). Reports should also be made to the International Drug Registry antenatally. See instructions below.

National Study of HIV in Pregnancy and Childhood (NSHPC)

This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, based at the UCL Institute of Child Health, London. Diagnosed pregnant women are reported prospectively through a British HIV Association and Children's HIV Association

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 reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, or in the case of some units with large caseloads direct to the NSHPC. For further information see the NSHPC website www.nshpc.ucl.ac.uk or e-mail nshpc@ich.ucl.ac.uk

National Study of HIV in Pregnancy and Childhood (NSHPC)

This is the UK and Ireland surveillance system for obstetric and paediatric HIV, based at the Institute of Child Health, London. Diagnosed pregnant women are reported prospectively 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 reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health. In the case of some units with large caseloads reporting is direct to the NSHPC. For further information see the NSHPC website or e-mail nshpc@ich.ucl.ac.uk

Website: <http://www.ucl.ac.uk/paediatric-epidemiology/nsh/nshpc.html>

Antiretroviral Pregnancy Registry

Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA

In UK call Tel: 0800 5913 1359; Fax: 0800 5812 1658;

For forms visit: www.apregistry.com

17. Infant feeding and HIV transmission during breastfeeding

Worldwide, breastfeeding is an important route of HIV transmission from mother to child. In the UK, where safe infant feeding alternatives are available and free for women in need, HIV-infected women are advised not to breastfeed their infants. Postnatally, mothers should be advised that although ART is likely to reduce free virus in the plasma and cell-associated virus in breast milk the presence of HIV-1 DNA remains unaffected and may therefore constitute a transmission risk(303).

Risk of HIV transmission via breastfeeding

The only randomized clinical trial of breast versus formula feeding to date, was undertaken in Nairobi and confirmed the substantial risk of transmission through breastfeeding (304). HIV-infected pregnant women, none of whom had received antiretroviral prophylaxis during pregnancy, were allocated to either breast ($n=212$) or formula ($n=213$) feeding, and median duration of breastfeeding was 17 months. Adherence to assigned feeding modality was 96% in the breastfeeding arm and 70% in the formula arm. The cumulative probability of HIV infection at 2 years of age was 36.7% in breastfed infants and 20.5% in formula fed. The estimated absolute rate of transmission through breastfeeding over two years was 16.2%, doubling the overall rate of transmission to 39% at 2 years of age.

The cumulative rates of transmission through breastfeeding observed from PMTCT trials, are in line with the results from the randomized trial, with an 10–14% increase in breastfed infants infected between 4–6 weeks and 18–24 months of age (124;125;305-307). 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 a negative diagnostic test at, or after, 4 weeks of age, followed by a subsequent positive test result. The overall rate of transmission was 24% and of the 993 infected children, the timing of acquisition was early in 314 (31.4%), late in 225 (23.1%) and unknown in 454 (45.4%). The mean duration of breastfeeding was nearly 7 months, and the median 4 months. There was a continued risk of transmission throughout the breastfeeding period, which was approximately constant over time. 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 (308).

Factors associated with breastfeeding transmission of HIV-1

RNA viral load in milk is generally lower than in plasma, and frequently below the detection limit of current assays. In a study in South Africa(309;310), 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(309). Milk viral load was below the limit of detection of the HIV RNA polymerase chain reaction (PCR) assay (<200 copies/ml) in a

substantial proportion of samples. Low maternal CD4 cell count ($<200/\mu\text{L}$) during pregnancy and raised Na/K ratio (a marker of sub-clinical mastitis) were significantly associated with increased milk RNA viral load at all times(310). Thus women with more advanced HIV are more at risk of breast-milk transmission.

Many women with HIV in the UK would prefer to breastfeed their infants if it was safe to do so. Results of randomized controlled trials of breastfeeding in mothers on combination antiretroviral therapy, currently underway in a number of African countries, are thus awaited with interest. In the meantime exclusive formula feeding remains the recommended method for infant feeding in the UK.

Appendix 1. 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 <32/40 gestation Naive	<10,000 copies per ml	ZDV monotherapy starting between 20–32/40	Unlikely to be <50 copies per ml	PLCS at 38 wks + IV ZDV	ZDV for 4 weeks	Stop	1b A
		or START (PI based) commencing between 20–32/40	<50 copies per ml	PLCS at 39 weeks or SVD Oral HAART See Scenario 4	ZDV for 4 weeks	Stop	III B
1b	>10,000 copies per ml	START (PI based) commencing between 20–32/40	>50 copies per ml	See Scenario 4	See Scenario 4	Stop ideally when undetectable	IV C
		HAART after 1st trimester	<50 copies per ml	PLCS at 39 weeks or SVD Oral HAART See Scenario 4	ZDV for 4 weeks	Stop	III B
2 Mother needs HAART according to BHIVA Guidelines <32/40 gestation Naive	Any	HAART after 1st trimester	>50 copies per ml	See Scenario 4	See Scenario 4	Stop ideally when undetectable	IV C
			<50 copies per ml	PLCS at 39 weeks or SVD Oral HAART See Scenario 4	ZDV for 4 weeks (or other monotherapy component of HAART regimen) See Scenario 4	Continue	III B

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
3a	<50 copies per ml	Continue	<50 copies per ml	PLCS at 39 weeks or SVD Oral HAART	ZDV or other monotherapy component of mother's HAART for 4/52	Continue	III B
3b	>50 copies per ml	Genotype and change to best option (expert advice)	>50 copies per ml	See Scenario 4	See Scenario 4	Reassess	IV C
4	N/A	Genotype and change to best option if possible (expert advice)	>50 copies per ml	PLCS 38/40 + I.V. ZDV if no ZDV resistance on most recent genotype Consider additional sdNVP	Combination PEP	If on START – discontinue (cover NVP tail) If on HAART – continue	IV C
5	Any	Commence HAART	<50 copies >50 copies per ml or no result	Scenario 2 PLCS at 38/40 + oral HAART + IV ZDV Consider sdNVP	ZDV 4/52 Combination PEP	If baseline CD4 suggests mother needs HAART – continue	IV C
6	Threatened pre-term delivery and / or pre-term ROM			Vaginal swab for bacteriology & start two doses im steroids 24 hours apart if <34 weeks			IV C la A

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
6a	Any	Commence HAART with NVP. Urgent CD4 cell count or Stat NVP plus PI-based HAART if CD4 >250		Consider Emg CS weighing up gestational age with viral load for 6a, 6b & 6c	Combination PEP but seek expert advice	If baseline CD4 suggests mother needs HAART – continue	IV C
6b	>50 copies per ml	Expert advice Add sdNVP and review HAART		As 6a Add IV ZDV where VL is >50copies/ml	Combination PEP Seek expert advice		IV C
6c	<50 copies per ml	Continue prescription Consider stat dose NVP if HAART not NNRTI based if <34 weeks		As 6a	(Monotherapy component of mother's regimen) for 4 weeks	Continue HAART but ensure cover NNRTI	IV C
7							
7a	Any	Commence HAART with NVP. urgent CD4 cell count	N/A	Caesarean ASAP (but not less than 2 hours after NVP) Give NVP then set up IV ZDV	Combination PEP Seek expert advice	Review maternal CD4 and continue if needed. Cover NVP tail if stopping	IV C
7b	>50 copies/ml	As per 6b	N/A	As 7a	Combination PEP Seek expert advice	Optimize maternal HAART	IV C

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
7c Mother on HAART	<50 copies/ml	Continue oral dosing	N/A	Induce vaginal delivery or Caesarean ASAP	Monotherapy for 4 weeks	Continue	IV C
8 Mother diagnosed after delivery	Any	N/A	N/A	N/A	Combination PEP for 4 weeks	Manage as non-pregnant	IV C
9 Presentation in labour HIV status unknown. Point of care HIV test Unconfirmed HIV-positive Treatment Naïve	Unknown	Stat NVP and PI-based HAART plus IV ZDV	N/A	Active management of labour Emerg CS 2 hours post sd-NVP if not about to deliver	Combination PEP for 4 weeks	As per BHIVA Guidelines for established infection if mother HIV positive. Cover NNRTI stop if CD4 >250	IV C

Table 1a. Evidence of the efficacy of antiretroviral therapy to reduce the risk of mother-to-child transmission of HIV infection. Studies of antiretroviral therapy to prevent mother-to-child transmission in non-breastfeeding population.

Study name	Countries	Study size	Treatment components			Age HIV assessed	Transmission rates (%)	Percentage reduction (P)
			Prepartum (Initial gestation, weeks)	Intrapartum (IV/Oral)	Postpartum (weeks)			
ACTG 076/ ANRS 024(114)	France	402	14–34	IV	6	18 months (antibody)	22.6 placebo	66.3% (0.00006)
	USA		ZDV 100mg 5 x daily	ZDV	ZDV		7.6 ZDV	
Bangkok Trial(71)	Thailand	392	36	Oral	Nil	6 months DNA PCR	18.9 placebo	50% (0.006)
			ZDV 300mg bd	ZDV			9.4 ZDV	
PHPT(115) Long/long arm	Thailand	1437	ZDV 300mg bd	ZDV	ZDV	180 days DNA PCR	6.7	57.6% cf short/short interim (0.004)
			28	Oral	6			
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(179)	Soweto	197	34–36			6 weeks	6 weeks	6 weeks	Equivalence
			ZDV 300mg bd d4T 40mg bd ddl 200mg bd d4T & ddl	ZDV d4T ddl d4T & ddl	ZDV d4T ddl d4T & ddl	ZDV d4T ddl d4T & ddl	DNA PCR	6.3 4.2 1.9 2.0	between ZDV and d4T combined with ddl
PMCT-2(129)	Thailand	1844	28 week ZDV	Oral ZDV SD-NVP SD-NVP Placebo	Oral ZDV SD-NVP SD-NVP Placebo	1 week ZDV SD-NVP v Placebo		1.9 2.8 6.5	

ZDV, zidovudine; d4T, stavudine; ddl, didanosine; SD-NVP, single-dose NVP

Table 1b. Studies of antiretroviral therapy to prevent mother-to-child transmission in breastfeeding populations.

Study name	Countries	Study size	Treatment components			Age HIV assessed	Transmission rates (%)	Percentage reduction (P)
			Prepartum (Initial gestation week)	Intrapartum (IV/Oral)	Postpartum (weeks)			
RetroCI(120)	Côte D'Ivoire	280	36 ZDV 300mg bd	Oral	Nil	DNA PCR 3 months 6 months 12 months 18 months 24 months	Placebo v ZDV 26.1 v 16.5 26.1 v 16.9 28.5 v 18.5 30.1 v 21.6 30.1 v 22.1	37 % (0.07) 35% 35% 28% 27% (<0.5)
DITRAME(311)	Burkina Faso, Côte d'Ivoire	431	36 ZDV 300mg bd	Oral	1 week maternal	6 months 15 months	27.5 v 18 30.6 v 21.5	35% 30%
PETRA(312)	RSA, Tanzania Uganda	1802	36 ZDV 300mg bd	Oral	Yes	6 weeks 18 months	17.2 v 8.6 26.6 v 20.7	50% (0.001) 22% (0.07)
			3TC 150mg bd	Oral	Yes	6 weeks 18 months	17.2 v 10.8 26.6 v 24.4	37% (0.02) 8% (0.5)
			Nil	Oral	Nil	6 weeks 18 months	17.2 v 17.7 26.6 v 25.7	-3% (0.8) 3% (0.8)
HIVNET 012(313)	Uganda	626	Nil	ZDV 300mg stat + 3hrly v NVP 200mg stat	ZDV 7 days v NVP stat 48 <72 hrs	ZDV v NVP 6-8 weeks 12 months	ZDV v NVP 20.0 v 11.8 24.1 v 15.7	41% (0.006) 35%
SAINT ⁽¹²⁵⁾	RSA	1307	Nil	Oral ZDV + 3TC v NVP	1 week	8 weeks	ZDV+3TC v NVP 10.8 v 14	Equivalence

ZDV, zidovudine; NVP, NVP; 3TC, lamivudine.

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

	Transmission rate (%)		Odds ratio (95% CI)	Transmission rate (%)		Odds ratio (95% CI)	Transmission Rate		Odds ratio (95% CI)
	PLCS	SVD & other MOD		PLCS & ZDV *	SVD, other MOD & ZDV*		PLCS & advanced maternal disease **	SVD, other MOD & advanced maternal disease**	
Relative efficacy of PLCS									
Meta-analysis 15 cohorts pre 1997 US & Europe N = 8533(217)	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 ⁽¹²²⁾ 1993-98 N = 436	Allocated to PLCS 1.8 (3/170) Actual CS (ELCS +EMCS)	Allocated to SVD 10.5 (21/200) Actual SVD	OR (95% CI) 0.2 (0.1-0.6) OR (95% CI)	Allocated to PLCS +ZDV* 0.8 (1/119) Actual CS +ZDV (ELCS +EMCS)	Allocated to SVD +ZDV 4.3 (5/117) Actual SVD +ZDV	OR (95% CI) 0.2 (0-1.7) OR (95% CI)	Allocated to PLCS + CD4 <200 0 (0/16) Actual CS + CD4 <200 (ELCS +EMCS)	Allocated to SVD + CD4 <200 14.3 (2/14) Actual SVD + CD4 <200	NS
	3.4 (7/203)	10.2 (17/167)	0.4 (0.2-0.9)	2.1 (3/144)	3.3 (3/92)	0.6 (0.1-3.2)	0 (0/20)	20 (2/10)	NS

PLCS, pre-labour Caesarean section; SVD, spontaneous vaginal delivery; MOD, mode of delivery; *, full 076 protocol with antepartum, intrapartum, and postpartum ZDV; **, advanced maternal disease – an AIDS diagnosis and / or CD4 <200/<14%; NS, not significant by Fisher's exact test.

Table 3. Antiretroviral studies in infants with doses and combinations. (* change of dose from previous BHIVA guidelines).

Drug	Dose	Mono/combo	Study	New dose	Comments / Side effects
ZDV (ZDV / ZDV) (Retrovir)	Oral Term (>34 wks) 4mg/kg BD 2mg/kg QDS Prem (30– 34 wks) 2mg/kg BD for 2 weeks then 2mg/kg TDS for 2 weeks. Prem (<30weeks) 2mg/kg BD for 4 weeks Intravenous	Combo (+ 3TC) Mono Mono Mono Mono Mono	Moodley 2001 Boucher 1993 Capparelli 2003 Capparelli 2003 Boucher 1993 Capparelli 2003	* new * new * new	Anaemia, neutropaenia, more common with combination therapy in mother and infant. In French Study of ZDV+3TC small proportion of infants either required transfusions or early stop of therapy ZDV and d4T should not be administered together in view of theoretical risk of negative interaction
	Term 1.5mg/kg QDS Prem 1.5mg/kg BD 2mg/kg BD	Combo (all with ZDV)	Moodley 2001 Mandelbrot 2001 Moodley 2003		Anaemia, neutropaenia (but less common than with ZDV), more common with combination therapy in mother and infant.
Lamivudine (3TC) (Epivir)	2mg/kg BD	Combo (all with ZDV)	Moodley 2001 Mandelbrot 2001 Moodley 2003		Anaemia, neutropaenia (but less common than with ZDV), more common with combination therapy in mother and infant.
Didanosine (ddl) (Videx)	60mg/m ² BD 100mg/m ² OD	Mono Combo (with d4T + NEL)	Wang et al, 1999 Rongkavilit, 2001	* new * new	Difficult to separate dosing from feeding, and ddl much better absorbed on an empty stomach. May cause GI symptoms. Variable absorption in neonate
Stavudine (d4T) (Zerit)	1mg/kg BD	Combo (with ddl + NEL)	Rongkavilit, 2001		ZDV and d4T should not be administered together in view of theoretical risk of negative interaction
Abacavir (ABC) (Ziagen)	2mg/kg BD	Mono	Johnson, 2000		Hypersensitivity reaction not been noted in infants (only small numbers treated)
NVP	Daily Dosing Regime	Mono	Shetty JAclmmDsynd	* new	<u>Daily Dosing Regime from HIVNET 023</u>

(NVP / NEV) (Viramune)	200mg to mother in labour, then 2mg/kg OD for 1 st week, then 4 mg/kg OD for 2 nd week (see table 4) Single-dose regime 200mg to mother in labour, then one 2mg/kg dose at 48-72 hrs from birth	Mono	2003 Guay, 1999	(breastfeeding prophylaxis study). Single-dose regime should be avoided as high risk of development of resistance in mother and infant
Nefinavir (NEL/ NFV) (Viracept) NB: no longer available	50-75mg/kg BD 15 /30/45mg/kg BD 90 mg/kg/day (total dose)	Combo (with ZDV+3TC) Combo (with ddl+d4T) Combo (with ddl+d4T)	NICHD/HPTN 040/P1043 Bryson, 2000 Rongkavilit, 2002 Faye, 2002	* new Ongoing, RCT of different regimes for PEP for infants born to mothers with antenatally untreated HIV In this study, insufficient dosing at all 3 doses PENTA 7 Study in HIV pos young infants, highly variable PK, with poor viral suppression
Co-trimoxazole (septrin)	900mg/ m ² OD Mon/Wed/Fri <6 months 120mg OD Mon/Wed/Fri 6-12 months 240mg OD Mon/Wed/Fri	PCP prophylaxis	Simmonds, 1995	May cause rash, bone marrow suppression. Give to infants born to mothers with a higher risk of transmission

Table 4. Suggested treatment for newborn infants as PEP for HIV (All treatment is for 4 weeks).

Scenario	Infant treatment	Comments/suggested doses
Mother on ZDV monotherapy + PLCS+IV ZDV in labour	Monotherapy ZDV	Well term infant, ZDV 4mg/kg BD (see Table 3 for prem / sick infant doses)
Mother on HAART VL<50: HAART contains ZDV	ZDV Monotherapy	Well term infant, ZDV 4mg/kg BD (see Table 3 for prem / sick infant doses)
History of ZDV resistance	Use the NRTI with most experience in mother's regime: 3TC>d4T>ABC>ddl	3TC 2mg/kg BD; d4T 1mg/kg BD; ABC 2mg/kg BD; ddl 100mg/m ² OD. If possible, avoid ddl due to feeding restriction
Mother presents with VL>50 and no previous ART exposure (e.g. premature labour / ROM; presentation at term with no ART etc)	Combination therapy ZDV+3TC+NVP	Well term infant, ZDV 4mg/kg BD (see Table 3 for prem / sick infant doses) + 3TC 2mg/kg BD + NVP 2mg/kg OD 1 st week and NVP 4mg/kg OD 2 nd week (use NVP 4mg/kg OD for 2 weeks if the mother has received >3days NVP). Stop NVP after 2 weeks, in view of long half-life. Continue other NRTIs for full 4 weeks.
Mother presents with VL>50 and previous ART exposure (e.g. premature labour / ROM; presentation at term)	Combination therapy Seek expert advice	Will need 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 breastfeeding.	Well term infant, ZDV 4mg/kg BD (see table 3 for prem / sick infant doses) + 3TC 2mg/kg BD + NVP 2mg/kg OD 1 st week and NVP 4mg/kg OD 2 nd week (use NVP 4mg/kg OD for 2 weeks if the mother has received > 3days NVP). Stop NVP after 2 weeks, in view of long half-life. Continue other NRTIs for full 4 weeks.
Premature or unlikely to tolerate oral feeds Maternal VL <50 Maternal VL >50 or unknown	ZDV monotherapy IV Add maternal NVP (at least 2 hours prior to delivery if possible)	Switch to oral when tolerating feeds

Table 5. Expected utility of licensed antiretroviral drugs for HIV-2. Modified from Parkin and Shapiro (314)

Drug	Consider for treatment of HIV-2	Comments
Nucleoside analogue RTI	NOT AS MONO or DUAL THERAPY	
Abacavir	Yes	
Didanosine	Use with caution	Low-level innate resistance in SIV and some HIV-2?
Emtricitabine	Yes	Based on similar resistance profile to Lamivudine
Lamivudine	Yes	
Stavudine	Use with caution	
Tenofovir	Yes	Only NRTI active against Q151M-containing virus
Zalcitabine	Use with caution	Low potency
ZDV	Yes	Not as monotherapy. Expect Q151M after failure
NNRTI		
Efavirenz	No	Innate resistance
NVP	No	Innate resistance
Protease inhibitors		
Fosamprenavir, Amprenavir	No	May be active in combination with low-dose ritonavir
Atazanavir	No	Inactive <i>in vitro</i> against HIV-2
Indinavir	Yes	(with ritonavir)
Lopinavir	Yes	(with ritonavir)
Nelfinavir	No	Low-level resistance; poor clinical response; do not expect D30NHIV
Ritonavir	Yes/No	Use with caution. Low-level resistance; low potency
Saquinavir	Yes	
Tipranavir	Yes	
Darunavir		
Fusion inhibitors		
Enfurvitide	No	Innate resistance susceptibility threshold not defined

Table 6. Classification of levels of evidence and grades of recommendations.

Classification of evidence levels

- Ia Evidence obtained from meta-analysis of randomized clinical trials
- Ib Evidence obtained from at least one randomized clinical trial
- IIa Evidence obtained from at least one well-designed controlled study without randomization
- 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 randomized 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 randomized 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*)

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