

## **British HIV Association guidelines for the management of HIV infection in pregnant women 2012**



NHS Evidence has accredited the process used by the British HIV Association (BHIVA) to produce guidelines. Accreditation is valid for five years from July 2012 and is applicable to guidance produced using the processes described in the British HIV Association (BHIVA) Guideline Development Manual. More information on accreditation can be viewed at [www.evidence.nhs.uk](http://www.evidence.nhs.uk)

# British HIV Association guidelines for the management of HIV infection in pregnant women 2012

## Writing Group Members

**Dr GP Taylor**

*Reader in Communicable Diseases, Section of Infectious Diseases, Imperial College London, UK (Vice Chair)*

**Ms P Clayden**

*UK Community Advisory Board representative/HIV treatment advocates network, London, UK*

**Dr J Dhar**

*Consultant in Genitourinary Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK*

**Mrs K Gandhi**

*Specialist HIV Pharmacist, Heart of England NHS Foundation Trust, Birmingham, UK*

**Dr Y Gilleece**

*Consultant Physician in HIV and Genitourinary Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK*

**Dr K Harding**

*Consultant Obstetrician, Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK*

**Dr P Hay**

*Reader and Honorary Consultant, St George's Healthcare NHS Trust, London, UK*

**Ms J Kennedy**

*Consultant Midwife, Homerton University Hospital NHS Foundation Trust, London, UK*

**Dr N Low-Beer**

*Consultant Obstetrician and Gynaecologist, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK*

**Dr H Lyall**

*Chief of Service for Paediatrics and Consultant Paediatrician in Infectious Diseases, Imperial College Healthcare NHS Trust, London, UK*

**Dr A Palfreeman**

*Consultant in Genitourinary Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK*

**Dr P Tookey**

*Senior Lecturer and Principal Investigator National Study of HIV in Pregnancy and Childhood, UCL Institute of Child Health, London, UK*

**Dr S Welch**

*Consultant in Paediatric Infectious Diseases, Heart of England NHS Foundation Trust, Birmingham, UK*

**Dr E Wilkins**

*Consultant Physician in Infectious Diseases and Director of the HIV Research Unit, North Manchester General Hospital, Manchester, UK*

**Dr A de Ruiter**

*Consultant Physician in Genitourinary Medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chair)*

## Table of contents

- 1.0 Scope and purpose
  - 1.1 Guideline development process
  - 1.2 Patient involvement
  - 1.3 Dissemination and implementation
  - 1.4 Guideline updates and date of next review
- 2.0 Recommendations and auditable outcomes
  - 2.1 Recommendations
  - 2.2 Auditable outcomes
- 3.0 Introduction
  - 3.1 UK prevalence of HIV in pregnancy and risk of transmission
  - 3.2 HIV infection in children
  - 3.3 Antenatal HIV screening
  - 3.4 Reporting and long-term follow-up
  - 3.5 National Study of HIV in Pregnancy and Childhood
- 4.0 Screening and monitoring of HIV-positive pregnant women
  - 4.1 Screening
  - 4.2 Laboratory monitoring of HIV-positive pregnant women
- 5.0 Use of antiretroviral therapy in pregnancy
  - 5.1 Conceiving on highly active antiretroviral therapy
  - 5.2 Naïve to highly active antiretroviral therapy: mother needs antiretroviral therapy for herself
  - 5.3 Naïve to highly active antiretroviral therapy: mother does not need highly active antiretroviral therapy for herself
  - 5.4 Late-presenting woman not on treatment
  - 5.5 Elite controllers
  - 5.6 Stopping antiretroviral therapy postpartum
- 6.0 HIV and hepatitis virus coinfections
  - 6.1 Hepatitis B virus
  - 6.2 Hepatitis C virus
- 7.0 Obstetric management
  - 7.1 Antenatal management
  - 7.2 Mode of delivery
  - 7.3 Management of spontaneous rupture of membranes
  - 7.4 Use of intrapartum intravenous infusion of zidovudine
- 8.0 Neonatal management
  - 8.1 Infant post-exposure prophylaxis
  - 8.2 *Pneumocystis pneumonia* prophylaxis
  - 8.3 Immunization
  - 8.4 Infant feeding
  - 8.5 Infant testing
  - 8.6 Laboratory diagnosis of HIV infection in non-breastfed infants
  - 8.7 Child protection
- 9.0 Psychosocial issues
- 10.0 Acknowledgements and conflicts of interest
- 11.0 References
- Appendix 1: Summary of the modified GRADE system
  - A1.1 References
- Appendix 2: Systematic literature search
  - A2.1 Questions and PICO criteria
  - A2.2 Search 1: safety and efficacy of antiretrovirals in pregnancy
  - A2.3 Search 2: hepatitis viruses coinfection
  - A2.4 Search 3: delivery, fetal monitoring and obstetric issues

A2.5 Search 4: paediatric issues

A2.6 Search 5: investigations and monitoring in pregnancy

Appendix 3: Search protocols (main databases search)

A3.1 Search 1: when to initiate antiretroviral therapy

A3.2 Search 2: hepatitis coinfection

A3.3 Search 3: fetal monitoring and obstetric issues

A3.4 Search 4: paediatric issues

A3.5 Search 5: investigations and monitoring in pregnancy

Appendix 4

A4.1 Antiretroviral therapies for which sufficient numbers of pregnancies with first trimester exposure have been monitored to detect a two-fold increase in overall birth defects

A4.2 Advisory Committee Consensus

## 1.0 Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of human immunodeficiency virus (HIV)-positive pregnant women in the UK. The scope includes guidance on the use of antiretroviral therapy (ART) both to prevent HIV mother-to-child transmission (MTCT) and for the welfare of the mother herself, guidance on mode of delivery and recommendations in specific patient populations where other factors need to be taken into consideration, such as coinfection with other agents. The guidelines are aimed at clinical professionals directly involved with, and responsible for, the care of pregnant women with HIV infection.

### 1.1 Guideline development process

The British HIV Association (BHIVA) revised and updated the Association's guideline development manual in 2011 ([www.bhiva.org/GuidelineDevelopmentManual.aspx](http://www.bhiva.org/GuidelineDevelopmentManual.aspx); see also Appendix 1). BHIVA has adopted the modified GRADE system for the assessment, evaluation and grading of evidence and the development of recommendations. Full details of the guideline development process including selection of the Writing Group and the conflict of interest policy are outlined in the manual.

The guidelines were commissioned by the BHIVA Guidelines Subcommittee who nominated the Chair of the Writing Group and deputy. They then nominated a Writing Group of experts in the field based on their knowledge, expertise and freedom from conflicts of interest.

The scope, purpose and guideline topics were agreed by the Writing Group. Questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist. Details of the search questions and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendices 2 and 3. The literature searches for the 2012 guidelines covered the period up until September 2011 and included abstracts from selected conferences. For each topic and healthcare question, evidence was identified and evaluated by Writing Group members with expertise in the field. Using the modified GRADE system (see Appendix 1), members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading

the strength of recommendations. All Writing Group members received training in use of the modified GRADE criteria before assessing the evidence.

Owing to the lack of data from randomized controlled trials (RCTs) in several important areas the Writing Group were unable to assign high grades (in areas such as mode of delivery); however, they have made recommendations on best practice where decisions need to be made on the balance of available evidence. Recommendations are summarized and numbered sequentially within the text.

The guidelines were published online for public consultation and external peer review was commissioned, comments from which resulted in minor revision before final approval by the Writing Group.

### 1.2 Patient involvement

BHIVA views the involvement of patient and community representatives in the guideline development process as both important and essential. The Writing Group included a patient representative who was involved in all aspects of guideline development.

### 1.3 Dissemination and implementation

The following measures have been/will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and the journal *HIV Medicine*.
- Publication in *HIV Medicine*.
- Shortened version detailing concise summary of recommendations.
- E-learning module accredited for CME.
- Educational slide set to support local and regional educational meetings.
- National BHIVA audit programme.

### 1.4 Guideline updates and date of next review

The guidelines will be next fully updated and revised in 2014. However, the Writing Group will continue to meet regularly to consider new information from high-quality studies and publish amendments and addendums to the current recommendations before the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

## 2.0 Recommendations and auditable outcomes

### 2.1 Recommendations

#### 2.1.1 Section 4: screening and monitoring of HIV-positive pregnant women

##### 4.1 Screening

- 4.1.1 Sexual health screening is recommended for pregnant women newly diagnosed with HIV. Grading: 1B
- 4.1.2 For HIV-positive women already engaged in HIV care who become pregnant sexual health screening is suggested. Grading: 2C
- 4.1.3 Genital tract infections should be treated according to BASHH guidelines. Grading: 1B

##### 4.2 Laboratory monitoring of HIV-positive pregnant women

- 4.2.1 Newly diagnosed HIV-positive pregnant women do not require any additional baseline investigations compared with non-pregnant HIV-positive women other than those routinely performed in the general antenatal clinic. Grading: 1D
- 4.2.2 HIV resistance testing should be performed before initiation of treatment (as per *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*), except for late-presenting women. Post short-course treatment a further resistance test is recommended to ensure that mutations are not missed with reversion during the off-treatment period. Grading: 1D
- 4.2.3 In women either who conceive on highly active antiretroviral therapy (HAART) or who do not require HAART for their own health there should be a minimum of one CD4 cell count at baseline and one at delivery. Grading: 2D
- 4.2.4 In women who commence HAART in pregnancy a viral load (VL) should be performed 2–4 weeks after commencing HAART, at least once every trimester, at 36 weeks and at delivery. Grading: 1C
- 4.2.5 In women commencing HAART in pregnancy liver function tests (LFTs) should be performed as per routine initiation of HAART and then at each antenatal visit. Grading: 1C
- 4.2.6 In the event that a woman who has initiated HAART during pregnancy has not achieved a plasma VL of <50 HIV RNA copies/mL at 36 weeks the following interventions are recommended: Grading: 1C
- Review adherence and concomitant medication.
  - Perform resistance test if appropriate.
  - Consider therapeutic drug monitoring (TDM).
  - Optimize to best regimen.
  - Consider intensification.

#### 2.1.2 Section 5: Use of antiretroviral therapy in pregnancy

##### 5.1 Conceiving on highly active antiretroviral therapy

- 5.1.1 It is recommended that women conceiving on an effective HAART regimen should continue this even if it contains efavirenz or does not contain zidovudine. Grading: 1C
- Exceptions are:
- (i) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and previous antiretroviral (ARV) history) one or more agents that cross the placenta. Grading: 2D
  - (ii) The combination of stavudine and didanosine should not be prescribed in pregnancy. Grading: 1D

##### 5.2 Naïve to highly active antiretroviral therapy: mother needs antiretroviral therapy for herself

- 5.2.1 Women requiring ART for their own health should commence treatment as soon as possible as per *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012* ([www.bhiva.org/PublishedandApproved.aspx](http://www.bhiva.org/PublishedandApproved.aspx)). Grading: 1A

- 5.2.2 Although there is most evidence and experience in pregnancy with zidovudine plus lamivudine, tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable nucleoside backbones. Grading: 2C
- 5.2.3 In the absence of specific contraindications, it is recommended that the third agent in HAART should be efavirenz or nevirapine (if the CD4 cell count is <250 cells/ $\mu$ L) or a boosted PI. Grading: 1C
- 5.2.4 No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses with the exception of darunavir, which should be dosed twice daily. Grading: 1C  
Consider third trimester TDM particularly if combining tenofovir and atazanavir. Grading: 1C  
If dosing off licence consider switching to standard dosing throughout pregnancy or regular TDM. Grading: 1C
- 5.3 Naïve to highly active antiretroviral therapy: mother does not need highly active antiretroviral therapy for herself*
- 5.3.1 All women should have commenced ART by week 24 of pregnancy. Grading: 1C
- 5.3.2 Although there is most evidence and experience in pregnancy with zidovudine plus lamivudine, tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable nucleoside backbones. Grading: 2C
- 5.3.3 In the absence of specific contraindications, it is recommended that HAART should be boosted-PI-based. The combination of zidovudine, lamivudine and abacavir can be used if the baseline VL is <100 000 HIV RNA copies/mL plasma. Grading: 1C
- 5.3.4 Zidovudine monotherapy can be used in women planning a caesarean section (CS) who have a baseline VL <10 000 HIV RNA copies/mL and CD4 cell count of >350 cells/ $\mu$ L. Grading: 1A
- 5.3.5 Women who do not require treatment for themselves should commence temporary HAART at the beginning of the second trimester if the baseline VL is >30 000 HIV RNA copies/mL. (Consider starting earlier if VL >100 000 HIV RNA copies/mL.) Grading: 1C
- 5.4 Late-presenting woman not on treatment*
- 5.4.1 A woman who presents after 28 weeks should commence HAART without delay. Grading: 1B
- 5.4.2 If the VL is unknown or >100 000 HIV RNA copies/mL a three- or four-drug regimen that includes raltegravir is suggested. Grading: 2D
- 5.4.3 An untreated woman presenting in labour at term should be given a stat dose of nevirapine (Grading: 1B) and commence fixed-dose zidovudine with lamivudine (Grading: 1B) and raltegravir. Grading: 2D
- 5.4.4 It is suggested that intravenous zidovudine be infused for the duration of labour and delivery. Grading: 2C
- 5.4.5 In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir (to the treatment described in 5.4.2) to further load the baby. Grading: 2C
- 5.4.6 Women presenting in labour/with rupture of membranes (ROM)/requiring delivery without a documented HIV result must be recommended to have an urgent HIV test. A reactive/positive result must be acted upon immediately with initiation of the interventions for prevention of MTCT (PMTCT) without waiting for further/formal serological confirmation. Grading: 1D
- 5.5 Elite controllers*
- 5.5.1 Untreated women with a CD4 cell count  $\geq$ 350 cells/ $\mu$ L and VL <50 HIV RNA copies/mL (confirmed on a separate assay):  
Can be treated with zidovudine monotherapy or with HAART (including abacavir/lamivudine/zidovudine). Grading: 1D  
Can aim for a vaginal delivery. Grading: 1C  
Should exclusively formula feed their infant. Grading: 1D
- 5.6 Stopping ART postpartum*
- 5.6.1 The discontinuation of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART postpartum should be according to BHIVA adult guidelines. Grading: 1C
- 5.6.2 ART should be continued in all pregnant women who commenced HAART with a history of an AIDS-defining illness or with CD4 cell count <350 cells/ $\mu$ L as per adult treatment guidelines. Grading: 1B
- 5.6.3 ART should be continued in all women who commenced HAART for MTCT with a CD4 cell count of between 350 and 500 cells/ $\mu$ L during pregnancy that are coinfecting with hepatitis B virus (HBV) or hepatitis C virus (HCV) in accordance with adult treatment guidelines. Grading: 1B

- 5.6.4 ART can be continued in all women who commenced HAART for MTCT with a CD4 cell count of between 350 and 500 cells/ $\mu$ L during pregnancy. Grading: 2C
- 5.6.5 ART should be discontinued in all women who commenced HAART for MTCT with a CD4 cell count of  $>500$  cells/ $\mu$ L unless there is discordance with her partner or co-morbidity as outlined in Section 6. Grading: 2B

### 2.1.3 Section 6: HIV and hepatitis virus coinfections

#### 6.1 Hepatitis B virus

- 6.1.1 On diagnosis of new HBV infection, confirmation of viraemia with quantitative HBV DNA, as well as hepatitis A virus (HAV), HCV and hepatitis delta virus (HDV) screening and tests to assess hepatic inflammation and function are recommended. Grading: 1C
- 6.1.2 LFTs should be repeated at 2 weeks after commencing HAART to detect evidence of hepatotoxicity or immune reconstitution inflammatory syndrome (IRIS) and then monitored throughout pregnancy and postpartum. Grading: 1C
- 6.1.3 In the immediate period after discontinuing drugs with anti-HBV activity, LFTs and HBV DNA should be monitored frequently. Grading: 1C
- 6.1.4 Where pegylated interferon or adefovir is being used to treat HBV in a woman who does not yet require HIV treatment who discovers she is pregnant, treatment should be switched to a tenofovir-based HAART regimen. Grading: 1C
- 6.1.5 As there is no evidence of any adverse effect on maternal or neonatal health if women become pregnant while taking ART active against HBV these should be continued. Grading: 1C
- 6.1.6 In all HAV non-immune HBV coinfecting women HAV vaccine is recommended, after the first trimester, as per the normal schedule (0 and 6–12 months) unless the CD4 cell count is  $<300$  cells/ $\mu$ L when an additional dose may be indicated. Grading: 1D
- 6.1.7 Tenofovir and emtricitabine should form the backbone of an ART regimen in naïve patients with wild-type HIV/HBV infection and no contraindication to either drug. Grading: 1B
- 6.1.8 If tenofovir is not currently part of HAART, it should be added. Grading: 1B
- 6.1.9 Lamivudine/emtricitabine may be omitted from the ARV regimen and tenofovir given as the sole anti-HBV agent if there is clinical or genotypic evidence of lamivudine/emtricitabine resistant HBV. Grading: 1C
- 6.1.10 Lamivudine or emtricitabine should not be used as the only active drug against HBV in HAART because of the likelihood of emergent HBV resistance to these agents. Grading: 1B
- 6.1.11 Emtricitabine has potential antiviral benefits over lamivudine, is co-formulated with tenofovir and appears to be equally safe during pregnancy and hence is the preferred option to be given with tenofovir in coinfection. Grading: 2D
- 6.1.12 Where the CD4 cell count is  $<500$  cells/ $\mu$ L HAART should be continued postpartum if HBV coinfection exists because of the increased risk of HBV progressive disease. Grading: 1B
- 6.1.13 Where the CD4 cell count is  $>500$  cells/ $\mu$ L and there is no other indication to treat HBV, consideration should be given to continuing anti-HBV treatment postpartum with HAART incorporating tenofovir and emtricitabine. Grading: 2C
- 6.1.14 If a decision is taken to discontinue therapy postpartum, careful monitoring of liver function is imperative. Grading: 2D
- 6.1.15 Where the CD4 cell count is  $>500$  cells/ $\mu$ L and there is HBV viraemia and evidence of liver inflammation or fibrosis, HAART containing tenofovir and emtricitabine should be continued. Grading: 2C
- 6.1.16 Hepatitis flares that occur after HAART cessation should be treated by resumption of active anti-HBV treatment before significant liver dysfunction occurs. Grading: 2D
- 6.1.17 In the absence of obstetric complications, normal vaginal delivery can be recommended, if the mother has fully suppressed HIV VL on HAART. Grading: 2C
- 6.1.18 Neonatal immunization with or without hepatitis B immunoglobulin (HBIG) should commence within 24 h of delivery. Grading: 1A



## 6.2 Hepatitis C virus

- 6.2.1 On diagnosis of new HCV infection, confirmation of HCV viraemia with quantitative VL and genotype, assessment of hepatic inflammation and function and concomitant liver disease should be performed. Grading: 1C
- 6.2.2 LFTs should be repeated at 2 weeks after commencing HAART to detect evidence of ARV hepatotoxicity or IRIS and then monitored throughout pregnancy and postpartum. Grading: 1C
- 6.2.3 Coinfected mothers with HCV should not be treated for HCV with pegylated interferon with or without ribavirin and all women who discover they are pregnant while receiving treatment should discontinue both pegylated interferon and ribavirin immediately. Grading: 1B
- 6.2.4 In all non-immune HCV coinfecting women after the first trimester, vaccination against HBV is recommended: Grading: 2C
- 6.2.5 HAV vaccine is recommended as per the normal schedule (0 and 6-12 months), unless the CD4 cell count is <300 cells/ $\mu$ L when an additional dose may be indicated Grading: 2C
- 6.2.6 In the absence of obstetric complications, normal vaginal delivery can be recommended if the mother is receiving HAART. Grading: 2C
- 6.2.7 Where the CD4 cell count is <500 cells/ $\mu$ L, HAART should be continued if active HCV coinfection exists because of the increased risk of progressive HCV-related liver disease. Grading: 1B
- 6.2.8 Where the CD4 cell count is >500 cells/ $\mu$ L and there is no HCV viraemia or fibrosis, HAART should be discontinued. Grading: 2C
- 6.2.9 Where the CD4 cell count is >500 cells/ $\mu$ L and there is HCV viraemia and evidence of liver inflammation or fibrosis, continuing HAART is preferable because of a benefit on fibrosis progression. Grading: 2B
- 6.2.10 Where the CD4 cell count is between 350 and 500 cells/ $\mu$ L and there is no evidence of viraemia, inflammation or fibrosis, continuing HAART is preferable if the patient displays a preference to do so. Grading: 2C

## 2.1.4 Section 7: obstetric management

### 7.1 Antenatal care

- 7.1.1 Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status. Grading: 1D
- 7.1.2 The combined screening test for trisomy 21 is recommended as this has the best sensitivity and specificity and will minimize the number of women who may need invasive testing. Grading: 2C
- 7.1.3 Invasive prenatal diagnostic testing should not be performed until after the HIV status of the mother is known and should be ideally deferred until HIV VL has been adequately suppressed. Grading: 1C
- 7.1.4 If not on treatment and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence HAART to include raltegravir and be given a single dose of nevirapine 2-4 h before the procedure. Grading: 1D
- 7.1.5 External cephalic version (ECV) can be performed in women with HIV. Grading: 2D

### 7.2 Mode of delivery

- 7.2.1 Vaginal delivery is recommended for women on HAART with an HIV VL <50 HIV RNA copies/mL plasma at gestational week 36. Grading: 1C  
 For women taking HAART, a decision regarding recommended mode of delivery should be made after review of plasma VL results at 36 weeks.  
 For women with a plasma VL of <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, a planned vaginal delivery is recommended.  
 For women with a plasma VL of 50-399 HIV RNA copies/mL at 36 weeks, pre-labour CS (PLCS) should be considered, taking into account the actual VL, the trajectory of the VL, length of time on treatment, adherence issues, obstetric factors and the woman's views.  
 Where VL is  $\geq$ 400 HIV RNA copies/mL at 36 weeks, PLCS is recommended.
- 7.2.2 In women in whom a vaginal delivery has been recommended and labour has commenced, obstetric management should follow the same guidelines as for the uninfected population. Grading: 1C

- 7.2.3 Vaginal birth after CS (VBAC) should be offered to women with a VL <50 copies/mL. Grading: 1D
- 7.2.4 Delivery by PLCS is recommended for women taking zidovudine monotherapy irrespective of plasma VL at the time of delivery (Grading: 1A) and for women with VL >400 HIV RNA copies/mL regardless of ART (see Recommendation 7.2.1) with the exception of elite controllers (see Section 5.5). Grading: 1D
- 7.2.5 Where the indication for PLCS is PMTCT, PLCS should be undertaken at between 38 and 39 weeks' gestation. Grading: 1C
- 7.3 Management of spontaneous rupture of membranes*
- 7.3.1 In all cases of term pre-labour spontaneous ROM, delivery should be expedited. Grading: 1C
- 7.3.2 If maternal HIV VL is <50 HIV RNA copies/mL immediate induction of labour is recommended, with a low threshold for treatment of intrapartum pyrexia. Grading: 1C
- For women with a last measured plasma VL of 50–999 HIV RNA copies/mL, immediate CS should be considered, taking into account the actual VL, the trajectory of VL, length of time on treatment, adherence issues, obstetric factors and the woman's views. Grading: 1C
- 7.3.4 If maternal HIV VL is  $\geq 1000$  RNA copies/mL plasma immediate CS is recommended. Grading: 1C
- 7.3.5 The management of prolonged premature ROMs (PPROM) at  $\geq 34$  weeks is the same as term ROM except women who are 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines. Grading: 1C
- 7.3.6 When PPRM occurs at <34 weeks. Grading: 1C
- Intramuscular steroids should be administered in accordance with national guidelines
- Virological control should be optimized
- There should be multidisciplinary discussion about the timing and mode of delivery
- 7.4 Use of intrapartum intravenous infusion of zidovudine*
- 7.4.1 Intrapartum intravenous zidovudine infusion is recommended in the following circumstances: Grading: 1C
- For women with a VL >10 000 HIV RNA copies/mL plasma who present in labour, or with ROMs or who are admitted for planned CS
- For untreated women presenting in labour or with ROMs in whom the current VL is not known. Grading: 1C
- In women on zidovudine monotherapy undergoing a PLCS intravenous zidovudine can be considered. Continued oral dosing is a reasonable alternative. Grading: 1B
- 2.1.5 Section 8: neonatal management*
- 8.1 Infant post-exposure prophylaxis*
- 8.1.1 Zidovudine monotherapy is recommended if maternal VL is <50 HIV RNA copies/mL at 36 weeks' gestation or thereafter before delivery (or mother delivered by PLCS while on zidovudine monotherapy). Grading: 1C
- 8.1.2 Infants <72 h old, born to untreated HIV-positive mothers, should immediately initiate three-drug therapy for 4 weeks. Grading: 1C
- 8.1.3 Three-drug infant therapy is recommended for all circumstances other than Section 8.1.1 where maternal VL at 36 weeks' gestation/delivery is not <50 HIV RNA copies/mL. Grading: 2C
- 8.1.4 Neonatal post-exposure prophylaxis (PEP) should be commenced very soon after birth, certainly within 4 h. Grading: 1C
- 8.1.5 Neonatal PEP should be continued for 4 weeks. Grading: 1C
- 8.2. Pneumocystis pneumonia prophylaxis*
- 8.2.1 Pneumocystis pneumonia (PCP) prophylaxis, with co-trimoxazole, should be initiated from age 4 weeks in:
- HIV-positive infants. Grading: 1C
  - Infants with an initial positive HIV DNA/RNA test result (and continued until HIV infection has been excluded). Grading: 1C
  - Infants whose mother's VL at 36 weeks gestational age or at delivery is >1000 HIV RNA copies/mL despite HAART or unknown (and continued until HIV infection has been excluded). Grading: 2D

### 8.3 Immunization

- 8.3.1 Infants born to HIV-positive mothers should follow the routine national primary immunization schedule. Grading: 1D

### 8.4 Infant feeding

- 8.4.1 All mothers known to be HIV positive, regardless of ART, and infant PEP, should be advised to exclusively formula feed from birth. Grading: 1A
- 8.4.2 In the very rare instance where a mother who is on effective HAART with a repeatedly undetectable VL chooses to breastfeed, this should not constitute grounds for automatic referral to child protection teams. Maternal HAART should be carefully monitored and continued until 1 week after all breastfeeding has ceased. Breastfeeding, except during the weaning period, should be exclusive and all breastfeeding, including the weaning period, should have been completed by the end of 6 months. Grading: 1B
- 8.4.3 Prolonged infant prophylaxis during the breastfeeding period, as opposed to maternal HAART, is not recommended. Grading: 1D
- 8.4.4 Intensive support and monitoring of the mother and infant are recommended during any breastfeeding period, including monthly measurement of maternal HIV plasma VL, and monthly testing of the infant for HIV by polymerase chain reaction (PCR) for HIV DNA or RNA (VL). Grading: 1D

### 8.5 Infant testing

- 8.5.1 HIV DNA PCR (or HIV RNA testing) should be performed on the following occasions: Grading: 1C
- During the first 48 h and before hospital discharge.
  - 2 weeks post infant prophylaxis (6 weeks of age).
  - 2 months post infant prophylaxis (12 weeks of age).
  - On other occasions if additional risk (e.g. breast-feeding).
- 8.5.2 HIV antibody testing for seroreversion should be done at age 18 months Grading: 1C

### 2.1.6 Section 9 psychosocial issues

- 9.1 Antenatal HIV care should be delivered by a multidisciplinary team (MDT), the precise composition of which will vary. Grading: 1D

## 2.2 Auditable outcomes

Proportion of pregnant women newly diagnosed with HIV having a sexual health screen.

Proportion of newly diagnosed women, requiring HAART for their own health, starting treatment within 2 weeks of diagnosis.

Proportion of women who have commenced ART by beginning of week 24 of pregnancy.

Proportion of women with a baseline HIV VL >30 000 RNA copies/mL plasma and who do not require treatment for themselves commencing temporary HAART at the beginning of the second trimester (by beginning of 16 weeks' gestation).

Proportion of women presenting in labour/with ROM/requiring delivery without a documented HIV result having an urgent HIV test result documented and this reactive/positive result acted upon immediately with initiation of the interventions to PMTCT without waiting for further/formal serological confirmation.

Proportion of women with HBV coinfection who have LFTs performed 2 weeks after commencing HAART to detect evidence of ARV hepatotoxicity or IRIS.

Proportion of women with HCV coinfection who have LFTs performed 2 weeks after commencing HAART to detect evidence of ARV hepatotoxicity or IRIS.

Proportion of women who have invasive prenatal diagnostic testing performed before their HIV status is known.

Proportion of emergency CS performed and their indication.

Proportion of infants <72 h old, born to untreated HIV-positive mothers, initiating three-drug therapy within 2 h of delivery.

Proportion of routine neonatal PEP commenced within 4 h of delivery.

Proportion of infants born to HIV-positive mothers who have HIV antibody testing for seroreversion performed at age 15–24 months.

### 3.0 Introduction

One of the major successes in the management of HIV-positive patients has been the PMTCT of HIV-1. With the widespread implementation of routine antenatal screening for HIV-1, transmission of HIV-1 from mother to child is now a rare occurrence in the UK. Despite few recent RCTs regarding the use of ART in pregnancy or obstetric intervention, practice continues to evolve. This is largely informed by observational data, theoretical considerations and expert opinion.

At the outset, the aim of the Writing Group was to make these guidelines as clinically relevant and as practical as possible. The Writing Group drew up a list of questions reflecting day-to-day practice and queries. It was acknowledged that the level of evidence for many of these topics was poor but recognized that there was a need to provide guidance. These guidelines have expanded on all areas relevant to the clinical care of HIV-positive pregnant women. The guidelines are intended to inform and aid healthcare workers in the management of pregnant women with HIV. They are not intended to be prescriptive or restrictive and it is recognized that situations will arise where the optimum management may deviate from these recommendations and new data will emerge to better inform practice.

A particular focus has been obstetric management. An increasing number of women are aiming for and achieving a vaginal delivery but the rate of emergency CSs has increased. It is hoped that the recommendations contained within these guidelines will enable a further increase in the proportion of vaginal deliveries and a reduction in the number of emergency CSs.

Linked to this is the proposed starting gestation for women temporarily taking HAART in pregnancy, which has been brought forward depending on baseline VL. It is anticipated that this will result in a larger proportion of women achieving a VL <50 HIV RNA copies/mL by 36 weeks' gestation, thereby allowing them to plan for a vaginal delivery.

Additional guidance has been provided with regard to conception on HAART, the choice of specific drugs or drug classes and the management of women with HBV or HCV coinfection. For the first time these guidelines have addressed the issue of continuation of HAART post delivery in women with a baseline CD4 cell count >350 cells/ $\mu$ L.

The paediatric section provides further guidance on infant PEP, drug dosing and safety. It is clear that there exists an urgent need for paediatric syrup preparations for

a wider variety of ARV drugs because the current options, particularly in the case of maternal viral resistance, are limited.

In key areas, the National Study of HIV in Pregnancy and Childhood (NSHPC) informs the management of HIV in pregnancy through the comprehensive data collection, collation and analysis, and the need to interrogate the data continues as practice changes.

#### 3.1 UK prevalence of HIV in pregnancy and risk of transmission

Prevalence of HIV infection among women giving birth in the UK is monitored through an unlinked anonymous survey based on residual neonatal dried blood spots. This has been in place in London since 1988, other selected English regions since 1990 and Scotland between 1990 and 2008. The survey provides an estimate of overall HIV prevalence in women giving birth regardless of whether or not they have been diagnosed. Nationally, estimated prevalence increased gradually during the 1990s, more rapidly between 2000 and 2005, and has since stabilized. In 2009 the survey covered over 400 000 births, and estimated HIV prevalence was 2.2 per 1000 women giving birth (1 in every 449). Prevalence in London was about 1 in 350 in 2000, rising to 1 in 250 by 2003 and has been relatively stable since then. In the rest of England, about 1 in 3500 women giving birth was HIV positive in 2000, rising to 1 in 700 by 2006, and remaining stable since then. In Scotland prevalence increased from about 1 in 2150 in 2000 to 1 in 1150 in 2008 [1,2].

The majority of HIV-positive pregnant women are from sub-Saharan Africa with prevalence stable between 2004 and 2007 at about 2–2.5% among sub-Saharan African mothers giving birth in London, and slightly higher at 3–3.5% among sub-Saharan women giving birth elsewhere in England. Although prevalence among UK-born women giving birth remained low at about 0.46 per 1000 women (1 in 2200) in 2009, a gradual increase has been seen since 2000 when it was 0.16 per 1000.

In the UK, the rate of HIV MTCT from diagnosed women was 25.6% in 1993, at which time interventions were virtually non-existent [3]. Between 2000 and 2006, with high uptake of interventions, the overall transmission rate from diagnosed women was 1.2%, and <1% among women who had received at least 14 days of ART. Among more than 2000 women who had received HAART and delivered with an undetectable VL, there were only three transmis-

sions, an MTCT rate of 0.1% [4]. These very low transmission rates persist. A small proportion of HIV-positive women remain undiagnosed at delivery in the UK, which probably means that currently about 2% of all HIV-exposed infants (born to diagnosed and undiagnosed women) are vertically infected [1].

By 2010, over 98% of all diagnosed women received some form of ART before delivery: the proportion of those who were taking zidovudine monotherapy dropped from about 20% in 2002–2003 to <5% since 2006, and only about 2% in 2009–2010. Over the same period the proportion of women delivering by elective CS declined from about two-thirds to just over one-third, while vaginal deliveries increased from <15% of all deliveries to almost 40%. Although planned vaginal delivery is now common for women who are on HAART with undetectable VL close to delivery, the increase in planned vaginal deliveries may have contributed to a rise in reported emergency CS, from about 20% to 25% [5].

Between 2005 and 2010 between 1100 and 1300 children were born each year in the UK to diagnosed HIV-positive women. Since virtually all diagnosed women in the last decade have taken ART to reduce the risk of MTCT, almost all of these children are uninfected. However, this means there are, in 2011, over 11 000 HIV-exposed uninfected children in the UK whose mothers conceived on combination ART (cART), or started ART during pregnancy [5].

### 3.2 HIV infection in children

The number of children diagnosed with vertically acquired HIV infection in the UK increased from about 70 a year in the early 1990s to a peak of 152 in 2004, and declined to 82 in 2009 [6]. During the last decade, about two-thirds of newly diagnosed children were born abroad. Owing to the increasing prevalence of maternal infection, combined with increasing maternal diagnosis rates and decreasing MTCT rates, the estimated number of infected children born in the UK has remained stable over the last decade, at about 30–40 a year. More than 300 children have also been reported, mostly in the early years of the epidemic, with non-vertically acquired infection, the majority from blood or blood products.

Among HIV-positive children with follow-up care in the UK and Ireland, the rate of AIDS and mortality combined declined from 13.3 cases per 100 person years before 1997 to 2.5 per 100 person years in 2003–2006 [7]. With improving survival, the median age of children in follow-up increased from 5 years in 1996 to 12 years in 2010, by which time over 300 young people had transferred to adult care [8]. Pregnancies in vertically infected young women are now occurring [9].

### 3.3 Antenatal HIV screening

Before the widespread implementation of the routine offer and recommendation of antenatal HIV screening in the UK, detection rates before delivery were poor. In the mid-1990s only about one-third of infected pregnant women were diagnosed, and most of those were aware of their infection status before they became pregnant [10]. In England, the routine offer and recommendation policy was implemented in 2000, and similar policies were subsequently adopted elsewhere in the UK. By the end of 2003, virtually all maternity units had implemented the antenatal screening policy, and over two-thirds had achieved >80% uptake, with about one-third reaching the 90% target [11]. Standards for monitoring antenatal screening were revised and updated in 2010 [12]. National uptake of antenatal HIV screening was reported to be 95% in 2008, up from 89% in 2005, and all regions reported at least 90% [13].

Between 2000 and 2004 the majority of HIV-positive women diagnosed before delivery were identified through antenatal screening. However, since 2005 the situation has reversed and in 2010 about three-quarters of women diagnosed before delivery were already aware of their infection before they conceived, many of them diagnosed in a previous pregnancy [5].

Nevertheless, some HIV-positive women remain undiagnosed at delivery, leading to potentially avoidable cases of MTCT. Since 2000, about 10 transmissions from diagnosed women have been recorded each year in the UK, against a background of increasing prevalence. However, another 20–30 UK-born children are also diagnosed each year, at various ages, whose mothers were not known to have been infected at the time of their birth [5].

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 before delivery [14]. About half of those undiagnosed women had declined antenatal testing. A smaller proportion had tested negative: these women presumably seroconverted in pregnancy, or while they were still breastfeeding.

In 2009, the National Screening Committee considered the introduction of a routine repeat screening test in the third trimester to identify seroconversions in pregnancy, but concluded that a universal re-offer should not be introduced at that time. However, it was reiterated that women who declined the initial offer should be re-offered screening at about 28 weeks' gestation, and that repeat tests could be offered to any woman who was thought to be at continuing risk of infection, and to any woman who requested a second or subsequent test [12].

### 3.4 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 NSHPC. Aggregated data tables from the UK and Ireland of ARV exposure and congenital malformations are regularly sent to the Antiretroviral Pregnancy Registry (APR). Individual prospective reports should also be made to the APR antenatally with postnatal follow-up.

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](http://www.apregistry.com)

Child Health, University College London. HIV-positive children and children born to HIV-positive 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. Diagnosed pregnant women are reported prospectively through a parallel reporting scheme run under the auspices of the Royal College of Obstetricians and Gynaecologists. Longer-term data on infected children are subsequently collected through the Collaborative HIV Paediatric Study (CHIPS). For further information see the NSHPC website (<http://www.nshpc.ucl.ac.uk>), the CHIPS website (<http://www.chipscohort.ac.uk>) or email NSHPC ([nshpc@ich.ucl.ac.uk](mailto:nshpc@ich.ucl.ac.uk)).

### 3.5 National study of HIV in pregnancy and childhood

This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, based at the Institute of

## 4.0 Screening and monitoring of HIV-positive pregnant women

### 4.1 Screening

4.1.1 Sexual health screening is recommended for pregnant women newly diagnosed with HIV. Grading: 1B

4.1.2 For HIV-positive women already engaged in HIV care that become pregnant sexual health screening is suggested. Grading: 2C

4.1.3 Genital tract infections should be treated according to BASHH guidelines. Grading: 1B

There are few data regarding the prevalence of genital infections in HIV-positive women in the UK [15]. At present, the majority of pregnant HIV-positive women in the UK come from, and mostly acquired HIV in, sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV-positive population, can be high [16]. Data from the unlinked anonymous survey of newborn infant dried blood spots show that, while the prevalence of HIV infection among pregnant women born in sub-Saharan Africa has remained relatively stable in recent years, there has been a fourfold increase in prevalence among women born in Central America and the Caribbean rising from 0.21% in 2000 to 0.78% in 2009 [2]. A high prevalence of genital infections in women of Afro-Caribbean origin has been reported [17].

The diagnosis and treatment of genital infections in any individual have clear benefits in terms of both 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, HBV and syphilis, asymptomatic HIV-uninfected pregnant women in the UK are not routinely screened for genital infections. In HIV-positive pregnant women, additional considerations are the potential effects of the presence of a genital infection on MTCT of HIV-1. This could occur through an increase in the HIV-1 VL in the genital tract and/or the presence of chorioamnionitis. In addition, certain infections may be linked to premature birth, an event that occurs more frequently in HIV-positive women when compared with HIV-uninfected women.

VL in cervicovaginal specimens has been shown to correlate with HIV-1 MTCT [18]. Genital tract VL will usually mirror the plasma VL [19], but there is increasing evidence of compartmentalization of HIV-1 between the plasma and genital tract. Genital tract HIV-1 has been detected in women with an undetectable plasma VL [20,21] and

genetic diversity of virus from the two compartments has been reported [22]. A number of factors may be responsible for this, including differential drug penetration into body compartments and the presence of genital tract infections. With increasing numbers of women in the UK aiming for and achieving a vaginal delivery an increasing number of fetuses are exposed to the cervicovaginal secretions of HIV-positive women. The clinical significance of this is not clear. Data from the UK and Ireland [4] and France [23] showing no difference in MTCT associated with mode of delivery in women with an undetectable VL provide some reassurance that potential discordance may not be clinically relevant but further research is warranted.

It has long been recognized that genital infections, in particular ulcerative diseases, are associated with an increased risk of sexual transmission of HIV [24,25]. This may be a consequence of an increase in local HIV replication resulting in a higher VL in genital secretions, secondary to the presence of specific microorganisms, and/or ulceration and inflammation [26,27]. Organisms associated with bacterial vaginosis (BV) have been shown to stimulate HIV expression *in vitro* [28,29]. A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis [30].

A study from Zimbabwe has shown a correlation between herpes simplex virus type 2 (HSV-2) antibody status and HIV-1 MTCT [31]. A study from Thailand of perinatal cervicovaginal lavages showed that HSV-2 shedding was associated with increased risk of intrapartum HIV transmission and that the effect was independent of perinatal cervicovaginal lavage and plasma HIV VL. However, this study was carried out in the context of either zidovudine monotherapy from 36 weeks or placebo [32]. 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 valaciclovir 500 mg twice a day further reduced genital HIV replication in those women with residual HIV shedding despite HAART [33]. A study from the USA reported greater rates of HSV-2 shedding at delivery in HSV-2 seropositive women with HIV compared with HIV-negative women, 30.8% *vs.* 9.5% (RR 3.2, 95% CI 1.6–6.5) [34]. Future studies are needed to evaluate whether valaciclovir can

reduce the risk of HIV MTCT during late pregnancy, the intrapartum period and breastfeeding.

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [35,36]. Chorioamnionitis, prolonged ROMs and premature birth have all been associated with MTCT of HIV and may be interlinked [37–39]. However, a Phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission showed no benefit in reducing MTCT in the context of single-dose nevirapine prophylaxis [40].

Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with BV, including *Ureaplasma urealyticum* [41,42]. A strong association between BV and premature delivery has been reported [43,44]. 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 MTCT of HIV [42]. A study in which mothers received zidovudine from 34 weeks of pregnancy reported that maternal fever >38 °C and BV were associated with *in utero* transmission of HIV with 2.6-fold and 3-fold risks, respectively [45]. It is not known how applicable this is in settings where mothers receive HAART from earlier in pregnancy.

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 [43,44]. However, the available evidence cannot rule out a small benefit in pregnancy outcome associated with the screening and treatment of BV. The latest Cochrane analysis concludes that there is little evidence that screening and treating all HIV-1-uninfected pregnant women with asymptomatic BV will prevent preterm delivery (PTD) and its consequences. However, there is some suggestion that treatment before 20 weeks' gestation may reduce the risk of PTD [46].

In HIV-1-uninfected women, data regarding the effect of screening for and treating BV on premature delivery are conflicting. As outlined above, in HIV-positive pregnant women, there are additional considerations regarding the potential effect of genital infections on MTCT of HIV-1, but these data are largely from the pre-HAART era. In the setting of full virological suppression on HAART, it is unclear to what extent, if any, the presence of any genital infection will contribute to HIV MTCT. Newly diagnosed HIV-positive pregnant women should be screened for sexually transmitted infections as per the routine management of newly diagnosed patients [47]. For pregnant HIV-1-positive women already engaged in HIV care, in the absence of RCTs but for the reasons

outlined above, the Writing Group suggests screening for genital tract infections, including evidence of BV. This should be done as early as possible in pregnancy and consideration should be given to repeating this at about 28 weeks. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the BASHH guidelines ([www.bashh.org/guidelines](http://www.bashh.org/guidelines)), followed by a test of cure. Partner notification should take place where indicated, to avoid reinfection.

With regard to cervical cytology, HIV-positive pregnant women should be managed as per Guidelines for the NHS Cervical Screening Programme 2010 [48]. Routine cytology should be deferred until after delivery, but if follow-up cytology or colposcopy is advised because of a previously abnormal result, then this should be undertaken.

## 4.2 Laboratory monitoring of HIV-positive pregnant women

**4.2.1 Newly diagnosed HIV-positive pregnant women do not require any additional baseline investigations compared with non-pregnant HIV-positive women other than those routinely performed in the general antenatal clinic. Grading: 1D**

**4.2.2 HIV resistance testing should be performed before initiation of treatment (as per *BHIVA guidelines for the treatment of HIV-1 positive adults with anti-retroviral therapy 2012*; [www.bhiva.org/PublishedandApproved.aspx](http://www.bhiva.org/PublishedandApproved.aspx)), except for late-presenting women. Post short-course treatment a further resistance test is recommended to ensure that mutations are not missed with reversion during the off-treatment period. Grading: 1D**

In the case of late-presenting women, HAART, based on epidemiological assessment of resistance, should be initiated without delay and modified once the resistance test is available.

**4.2.3 In women who either conceive on HAART or who do not require HAART for their own health there should be a minimum of one CD4 cell count at baseline and one at delivery. Grading: 2D**

**4.2.4 In women who commence HAART in pregnancy a VL should be performed 2–4 weeks after commencing HAART, at least once every trimester, at 36 weeks and at delivery. Grading: 1C**

Performing a VL test at 2 weeks allows for a more rapid assessment of adherence and may be of particular benefit in a late-presenting woman.

**4.2.5 In women commencing HAART in pregnancy, LFTs should be performed as per routine initiation of HAART and then at each antenatal visit. Grading: 1C**

Hepatotoxicity may occur because of the initiation of HAART and/or the development of obstetric complications



such as obstetric cholestasis, pre-eclampsia, HELLP syndrome and acute fatty liver. Close liaison with the obstetric team is recommended.

*Failure to suppress*

**4.2.6 In the event that a woman who has initiated HAART during pregnancy has not achieved a plasma VL of <50 copies/mL at 36 weeks the following interventions are recommended: Grading 1C**

- Review adherence and concomitant medication.
- Perform resistance test if appropriate.

- Consider TDM.
- Optimize to best regimen.
- Consider intensification.

For a woman who conceives on HAART that is not fully suppressive or loses virological control during pregnancy, these interventions should be undertaken as soon as possible. If treatment failure occurs when the infant is likely to be delivered prematurely and may be unable to take medication enterally, intensification should consist of therapies that readily cross the placenta such as double-dose tenofovir, raltegravir and single-dose nevirapine.

## 5.0 Use of antiretroviral therapy in pregnancy

### 5.1 Conceiving on highly active antiretroviral therapy

5.1.1 It is recommended that women conceiving on an effective HAART regimen should continue this even if it contains efavirenz or does not contain zidovudine. Grading: 1C

Exceptions are:

(i) PI monotherapy should be intensified to include (depending on tolerability, resistance and previous ARV history) one or more agents that cross the placenta. Grading: 2D

(ii) The combination of stavudine and didanosine should not be prescribed in pregnancy. Grading: 1D

Despite the lack of licence for the use of ART in pregnancy, with the exception of zidovudine in the third trimester, there is global consensus that women who conceive on effective HAART should continue this throughout the pregnancy. Where the risk of treatment failure due to reduced or intermittent drug exposure with hyperemesis gravidum exceeds the risk of treatment interruption the Writing Group recommends the latter option although there are no data that specifically address this issue.

The APR provides the best data on teratogenicity and first trimester ART exposure. This prospective database records rates of congenital birth defects in babies born to women with first-trimester exposure to ART in comparison with background rates of congenital birth defects and second and third trimester-only exposures to the same compounds. The congenital malformation rate observed in babies exposed to a specified drug is reported once a minimum of 200 prospective first-trimester exposures to an individual ARV have been reported. In prospectively reported cases, zidovudine, lamivudine and ritonavir have been shown to have congenital malformation rates within the expected range and a congenital malformation rate >1.5-fold higher than the general population has been excluded. Among other currently used agents (abacavir, tenofovir, emtricitabine, lopinavir, atazanavir, nevirapine and efavirenz) there are now more than 200 prospective reports of first-trimester exposure with no signal of increased risk (and a greater than twofold higher rate than in the general population has been excluded) [49].

There are insufficient data to recommend routinely switching from efavirenz to another agent. The earlier recommendation that efavirenz be avoided in women who may conceive [50] was based on preclinical animal studies that had not been conducted on any other ART, the FDA

reclassification of efavirenz to category D and the paucity of human data. Three of 20 offspring of cynomolgus macaques exposed to efavirenz in the first trimester had significant abnormalities at birth: one had anencephaly and unilateral anophthalmia; the second microphthalmia; and the third a cleft palate [51]. Subsequently four anecdotal cases of myelomeningocele and two of Dandy Walker syndrome were reported following human first-trimester efavirenz exposure. No prospective data were available, causation was not proven and a lack of data on the number of cases reported compared with the number of exposures meant that the relative risk of the putative association could not be calculated.

Based on the emerging prospective data in which no evidence of human teratogenicity has been seen, the Writing Group consider that there are insufficient data to support the former position and furthermore recommend that efavirenz can be both continued and commenced (see below) in pregnancy.

The data considered were:

- Antiretroviral Pregnancy Registry [49].

Sufficient numbers of first trimester exposures of efavirenz have been monitored to detect at least a twofold increase in risk of overall birth defects and no such increase has been detected to date. A single case of myelomeningocele and one case of anophthalmia have been prospectively reported in live births. There have been six retrospective reports of findings consistent with neural tube defects, including myelomeningocele. It is important to note that not all HIV pregnancies are reported to the APR, as reporting is voluntary. A web and literature search reveals two case reports of myelomeningocele associated with first-trimester efavirenz exposure [52,53].

- Data from the IeDEA West Africa and ANRS Databases, Abidjan, Cote d'Ivoire, found no significant increased risk of unfavourable pregnancy outcome in women with first trimester exposure to efavirenz ( $n = 213$ ) compared with nevirapine ( $n = 131$ ) apart from termination, which was more common with efavirenz [54].
- In 2010, a systematic review and meta-analysis of observational cohorts reported birth outcomes among women exposed to efavirenz during the first trimester [55]. The primary endpoint was a birth defect of any kind with secondary outcomes, including rates of spontaneous abortions, termination of pregnancy, stillbirths and PTD.

Sixteen studies met the inclusion criteria, 11 prospective and five retrospective. Nine prospective studies reported on birth defects among infants born to women with efavirenz exposure (1132 live births) and non-efavirenz-containing regimens (7163 live births). The analysis found no increased risk of overall birth defects among women exposed to efavirenz during first trimester compared with exposure to other ARV drugs. There was low heterogeneity between studies and only one neural tube defect was observed with first-trimester efavirenz exposure, giving a prevalence of 0.08%. Furthermore, the prevalence of overall birth defects with first-trimester efavirenz exposure was similar to the ranges reported in the general population. This meta-analysis, which included the data from the APR and the leDEA and ANRS databases, has been updated to include published data to 1 July 2011. The addition of 181 live births reported from five studies together with the updated report from the APR resulted in a revised incidence of neural tube defects in infants exposed to efavirenz during the first trimester of 0.07% (95% CI 0.002–0.39) [56].

- Two publications have reported higher rates of congenital birth defects associated with efavirenz, Brogly *et al.* (15.6%) [57] and Knapp *et al.* (12.8%) [58]. The Writing Group considers these rates to be inflated. Recruitment occurred prenatally but also up to 12 months of age, which could confer recruitment bias. Although the overall study numbers were large, the number of efavirenz exposures used as the denominator in the final analyses of first-trimester exposure was small, 32 and 47, respectively. There was no difference in the anomaly rate found with no exposure *vs.* any exposure in first/second/third trimester. In addition, no pattern of anomalies specific to efavirenz was described by these studies: patent foramen ovale ( $n = 1$ ); gastroschisis ( $n = 1$ ); polydactyly ( $n = 1$ ); spina bifida cystica ( $n = 1$ ); plagiocephaly ( $n = 1$ ); Arnold Chiari malformation ( $n = 1$ ); and talipes ( $n = 1$ ). The reporting of two cases of congenital malformation was duplicated in the two studies. The paper by the NISDI Perinatal Study Group [59], which was used as a comparator by Knapp *et al.* to support their findings, reported similar overall congenital anomaly rates of 6.16% and accepted reports up to 6 months of age. Adjustment of the congenital anomaly rate by the authors to those noted within 7 days, as reported by the APR (2.7%) and the non-HIV background rate (2.8%), gives a similar rate of 2.4% and is consistent with reported rates in the UK (3.1% for first trimester and 2.75% for second/third trimester-only ARV exposure) [60].

Thus, it is the recommendation of the Writing Group, based on current evidence, that efavirenz can be used in preg-

nancy without additional precautions and considerations over and above those of other ARTs.

Non-pregnant adults in the UK are now rarely prescribed zidovudine as part of HAART. Despite the proven efficacy of zidovudine in PMTCT, particularly in the pre-HAART era [61], there are no data to support routinely switching to zidovudine, or adding zidovudine to a combination of ARVs that is suppressing HIV replication to <50 HIV RNA copies/mL plasma. Analysis of data combined from two observational studies, the European Collaborative Study (ECS) and the UK and Ireland NSHPC, has shown no difference in pregnancy outcomes between zidovudine-based and zidovudine-sparing HAART [62]. Risk of PMTCT is determined by maternal VL, whether ART is taken in pregnancy and the time on therapy before delivery. With regard to the latter, therapy for more than 14 days is associated with significantly lower transmission rates than shorter periods [4]. Data from the French cohort, confirm very low transmission rates in mothers who have conceived on treatment (0%; 95% CI 0–0.3% if VL <50 HIV RNA copies/mL at delivery) [63]. However, as newer therapies become established, the degree of transplacental transfer of the components of combination therapy should be considered.

While ritonavir-boosted PI therapy can maintain suppression of VL, PMTCT would be almost entirely dependent on antiviral activity within the mother. With minimal transplacental transfer, the low to undetectable drug concentrations in the fetus provide no periexposure protection. In PHPT-5, the addition of boosted lopinavir to zidovudine monotherapy from 28 weeks' gestation was no better than maternal zidovudine with or without single-dose nevirapine provided neonatal nevirapine was administered [64]. The Writing Group therefore recommends that, where possible, patients who conceive on PI monotherapy should have their regimen intensified with an agent that crosses the placenta.

Didanosine administered with stavudine is contraindicated in pregnancy due to the risk of maternal lactic acidosis [65].

## 5.2 Naïve to highly active antiretroviral therapy: mother needs antiretroviral therapy for herself

### 5.2.1 Women requiring ART for their own health should commence treatment as soon as possible as per *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012* ([www.bhiva.org/PublishedandApproved.aspx](http://www.bhiva.org/PublishedandApproved.aspx)). Grading: 1A

When considering the optimal time to start HAART, theoretical considerations for avoiding medication during pregnancy, and first trimester in particular, must be considered in light of increasing safety data on first-trimester

exposure to ART, risk to maternal health (and fetal exposure to opportunistic infections), risk of MTCT and time required to achieve an undetectable VL by the time of delivery. Where the mother is at risk of, or has presented with an opportunistic infection, initiation of HAART should not be delayed. Where treatment is indicated based on CD4 cell count only, deferring treatment to the start of the second trimester is reasonable, particularly if the patient is experiencing nausea and/or vomiting of pregnancy.

**5.2.2 Although there is most evidence and experience in pregnancy with zidovudine plus lamivudine, tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable nucleoside backbones. Grading: 2C**

Most data on the efficacy of HAART in pregnancy are based on a three/four-drug combination, including a zidovudine/lamivudine backbone. Where treatment has been started at, or before, 28 weeks these studies have demonstrated transmission rates of 1% or less [4,63,66, 67]. The adult prescribing guidelines now recommend tenofovir/emtricitabine or abacavir/lamivudine as first-line therapy based on safety, tolerability and efficacy (*BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*; www.bhiva.org/PublishedandApproved.aspx). No studies have compared the safety and efficacy of the three, fixed-dose, dual nucleoside/nucleotide combinations that constitute the backbone of HAART, in pregnancy. Zidovudine-based and zidovudine-sparing regimens are equally safe and efficacious (see Section 5.1: Conceiving on HAART). Based on their antiviral efficacy in non-pregnant adults, transplant transfer and mode of action, it is unlikely that these newer combinations will be less effective than zidovudine/lamivudine as part of HAART in pregnancy.

**5.2.3 In the absence of specific contraindications, it is recommended that the third agent in HAART should be efavirenz or nevirapine (if the CD4 cell count is <250 cells/ $\mu$ L) or a boosted PI. Grading: 1C**

The choice of third agent should be based on safety, tolerability and efficacy in pregnancy. Based on non-pregnant adults, *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012* (www.bhiva.org/PublishedandApproved.aspx) recommended an NNRTI, with efavirenz preferred to nevirapine, or a boosted PI of which lopinavir or atazanavir have been most widely prescribed. For the pregnant woman, there is more experience with nevirapine as efavirenz has until recently been avoided in pregnancy. The Writing Group consider there to be insufficient evidence to recommend the avoidance of efavirenz in the first trimester of pregnancy, and include efavirenz in the list of compounds that may be initiated during pregnancy. Despite the well-documented cutaneous, mucosal and hepatotoxicity with

nevirapine at higher CD4 T-lymphocyte counts, nevirapine remains an option for women with a CD4 T-lymphocyte count <250 cells/ $\mu$ L. Nevirapine is well tolerated in pregnancy, with several studies suggesting this to be the case even above the stated CD4 cell count cut-off [68–71]; has favourable pharmacokinetics in pregnancy [72–74] and has been shown to reduce the risk of MTCT even when given as a single dose in labour, alone or supplementing zidovudine monotherapy or dual therapy [75–77].

Despite some concerns regarding diabetes, PTD (see below) and pharmacokinetics during the third trimester (discussed separately) several ritonavir-boosted PIs have been shown to be effective as the third agent in HAART in pregnancy (lopinavir [66,78], atazanavir [79], saquinavir [80,81]). In the European Collaborative Study, time to undetectable VL was longer in women initiating PI-based HAART; however, in this study 80% of these women were taking nelfinavir [82]. In a more recent study, treatment with a boosted PI resulted in more rapid viral suppression (to <50 HIV RNA copies/mL) than nevirapine, except in the highest VL quartile [83]. In another multicentre study nevirapine-based HAART reduced VL more rapidly during the first 2 weeks of therapy than PI-based HAART with nelfinavir, atazanavir or lopinavir, but time to undetectable was influenced by baseline VL rather than choice of HAART [84]. The role of newer PIs (e.g. darunavir), integrase inhibitors and entry inhibitors in the treatment-naïve pregnant patient has yet to be determined; therefore other, more established, options should preferentially be initiated.

#### *HIV, protease inhibitor therapy and preterm delivery*

The data on the association of HAART and PTD are conflicting. Some studies implicate boosted PIs, others do not. The data are summarized below.

The association between HAART and PTD was first reported by the Swiss Cohort in 1998 [60,85], and subsequently by a number of other European studies, including three analyses from the ECS [60,86–88]. Analysis of the NSHPC UK and Ireland data in 2007 found there to be a 1.5-fold increased risk of PTD when comparing women on HAART with those on mono- or dual therapy [89].

Several large studies from the USA have not found an association between HAART and PTD [90,91]. In two further studies, one multicentre study from the Pediatric Spectrum of HIV Disease cohort and one single-centre study, an association between PTD and HAART was found only if HAART included a PI [92,93]. Two of the earlier ECS reports had also noted that the increased risk of PTD in patients on HAART was particularly marked in patients on PI-containing HAART [86,88]. However, a US meta-analysis in 2007 did not find an association between PTD and PI-containing HAART [94], and analysis of the NSHPC

UK and Ireland data, although finding the increased risk of PTD in women on HAART, similarly did not find a difference when comparing PI- and NNRTI- based regimens [89]. In addition, an analysis of data on over 10 000 women reported to the APR from 1989 to 2010 did not find a significant increase in PTD in women with PI exposure with lower pre-existing risk [95]. Over 85% of these reports to the APR came from the USA.

Most studies that have looked at the relationship between the timing of HAART initiation and PTD have found that the risk was increased in those either conceiving on HAART or taking it early in pregnancy (in the first trimester) [86,88,94,96]. However, the NSHPC UK and Ireland study did not find an association between timing of HAART initiation and PTD [89]. One single-centre UK study found the risk to be increased in those initiating HAART in pregnancy compared with those conceiving on treatment [97].

A 2010 USA study attempted to overcome the potential confounding factors associated with timing of HAART initiation by looking only at women starting HAART in pregnancy and comparing PI-containing with non-PI-containing regimens and did not find an association between PI-containing regimens and PTD [98]. In this study, 72% of the 777 women received a PI-based regimen, and in 47% of those, the PI was nelfinavir, with 22% on lopinavir/ritonavir. Further comparison between nelfinavir and the ritonavir-boosted lopinavir was unfortunately not possible. A 2011 study from the ANRS reported an association between HAART and PTD and in the 1253 patients initiating a PI-based regimen, those on ritonavir-based PI regimens were significantly more likely to deliver prematurely when compared with those on a non-boosted PI regimen (HR 2.03; 95% CI 1.06–3.89) [99].

The conflicting findings of these largely observational studies make it difficult to draw definitive conclusions. Importantly, a history of previous PTD, one of the most significant risk factors for subsequent PTD, is rarely, if ever collected.

Additionally, there may be fundamental differences between cohorts precluding reliable comparison. For example, the USA has the highest background PTD rate of any industrialized country, peaking at 12.8% in 2006 [100].

Two randomized studies have now been published, both looking at the use of different ARV regimens in breastfeeding populations, primarily in relation to HIV MTCT. The Mma Bana study from Botswana randomly allocated 560 women at 26–34 weeks' gestation, with CD4 cell counts >200 cells/ $\mu$ L to receive either lopinavir/ritonavir plus zidovudine/lamivudine (PI group) or abacavir/zidovudine/lamivudine (NRTI group). The PTD rates were significantly higher in the PI group (21.4% *vs.* 11.8%;  $P = 0.003$ ) [101].

A second study, the Kesho Bora Study randomly allocated 824 women at 28–36 weeks' gestation, again with CD4 cell counts >200 cells/ $\mu$ L to receive lopinavir/ritonavir and zidovudine/lamivudine or zidovudine monotherapy twice daily plus a single dose of nevirapine at the onset of labour. There was no difference in the PTD rate between the two groups (13% with PI *vs.* 11% with zidovudine monotherapy/single-dose nevirapine) [102].

The randomized studies above are two of few studies that have been able to look at individual PIs. One additional analysis from the APR of 955 live births exposed to lopinavir/ritonavir reported a PTD rate of 13.4% [103]. A retrospective study from the UK reported a PTD rate of 10% in 100 women taking ritonavir-boosted atazanavir in pregnancy, of whom 67% had conceived on their regimen [79].

The data regarding HAART, individual components of HAART and PTD remain conflicting. Some studies suggest that PIs, in particular ritonavir-boosted PIs, are associated with an increased risk of PTD but this is not confirmed by others. There is a need for a randomized study of sufficient power to explore these issues further and the Promoting Maternal and Infant Survival Everywhere (PROMISE) study (NCT01061151), with 6000 women either randomly allocated to a PI-based combination regimen or zidovudine monotherapy will hopefully provide some answers to these important questions.

**5.2.4 No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses with the exception of darunavir, which should be dosed twice daily. Grading: 1C**

**Consider third-trimester TDM particularly if combining tenofovir and atazanavir. Grading: 1C**

**If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM. Grading: 1C**

Physiological changes that occur even during the first trimester of pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing. Gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and there are accompanying increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease, notably albumin and  $\alpha_1$  acid glycoprotein; renal sodium reabsorption increases; and changes occur in the metabolic enzyme pathway in the liver, including changes in cytochrome P450. Caution should be exercised if women fall pregnant on unlicensed doses and consideration given to performing TDM to assess trough levels, or reverting to licensed dosing, often twice per day, during pregnancy.

The pharmacokinetics of most NRTIs (zidovudine [104], stavudine [105], lamivudine [106], abacavir [107]) are not

significantly affected by pregnancy and dose adjustment is not required. Renal excretion of didanosine is increased in pregnancy, but dose alteration is probably not required [108]. Tenofovir concentrations in the third trimester were reported to be reduced by about 15% compared with postpartum, but trough levels are adequate [109] although in a population-based study of tenofovir use, pregnant women appear to have 39% more clearance than non-pregnant women [110]. Higher rates of treatment failure during pregnancy with tenofovir-containing combinations have not been reported. A single, double dose of tenofovir administered shortly before delivery resulted in plasma concentrations similar to those observed in non-pregnant adults following a standard 300 mg dose and adequate levels in the neonate [111] (see Section 8: Neonatal management). New data on emtricitabine show that while third-trimester concentrations are lower than postpartum the absolute concentrations achieved during pregnancy are adequate and dose adjustment is not required [112].

Among the NNRTIs, nevirapine has been extensively studied in pregnancy and plasma concentrations are similar to those in non-pregnant adults [72,74]. No dose adjustment is required when using licensed doses. There are no data on the prolonged release formulation of nevirapine in pregnant women. Efavirenz 600 mg daily has been reported in one study of 25 pregnant women to result in third-trimester plasma concentrations that were similar to 6–12-week postpartum concentrations in the same women. Cord blood to maternal blood ratio was 0.49 resulting in transplacental concentrations in the therapeutic range [113]. There are currently no data on the pharmacokinetics of efavirenz and rilpivirine in pregnant women.

PIs are highly protein-bound and placental transfer in humans appears to be limited. During the third trimester of pregnancy, small reductions in protein binding can significantly increase free drug levels. For example, the protein binding of lopinavir reduces marginally to 99.04%, which results in 17% more unbound lopinavir [114]. It is therefore difficult to interpret the significance of studies that show reduced total plasma levels, with an increased likelihood of trough levels below the target during pregnancy. Compared with postpartum concentrations, third-trimester concentrations of lopinavir (lopinavir 400 mg/ritonavir 100 mg) 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. A study using the tablet formulation concluded that women taking three tablets bd (lopinavir 600 mg/ritonavir 150 mg) achieved similar area under the curve (AUC) levels to non-pregnant adults taking the standard dose of two tablets bd [115]. The improved bioavailability of the tablet formulation is also

found in pregnant women and this, together with the impact of pregnancy on changes in protein binding, increases the protein-free fraction in the third trimester [116]. Cohort studies have suggested that the majority of mothers taking the standard adult dose, even with the capsule formulation, have adequate trough concentrations and achieve an effective virological response [117].

The plasma concentrations of saquinavir achieved with the tablet formulation when boosted by ritonavir appear to be generally therapeutic and no dose adjustment is routinely required. Interpatient variability during pregnancy is, however, high [80,118].

A study from Italy reported similar third-trimester and postpartum atazanavir concentrations at standard 300 mg dose with 100 mg ritonavir once daily [119]. However, recently third-trimester 24 h AUC concentrations 28% lower than postpartum concentrations were reported from North America. Third trimester concentrations of atazanavir in women taking tenofovir were lower still, being approximately 50% of the postpartum values of women on atazanavir without tenofovir, and 55% of women in the study taking tenofovir failed to achieve the target atazanavir concentration. The study authors therefore recommended that it may be necessary to increase the dose of atazanavir to 400 mg (when given with ritonavir 100 mg once daily) during the third trimester [120]. Data from the Europe-based PANNA study also reveals a 33% reduction in third-trimester AUC and  $C_{last}$  atazanavir concentrations compared with postpartum. However, all drug concentrations measured, including with coadministered tenofovir, were above the recommended minimum plasma concentration for wild-type virus [121]. When prescribed with zidovudine/lamivudine, plasma concentrations achieved with atazanavir 300 mg plus ritonavir 100 mg once daily are only 21% less (by AUC) than historic controls while trough concentrations were reported to be comparable with these controls. Increasing the dose of atazanavir to 400 mg daily during the third trimester increased trough concentrations by 39% and doubled the risk of hyperbilirubinaemia [122]. A case note review of 155 women in London receiving atazanavir did not report virological failure during pregnancy despite 96% receiving standard dosing of 300 mg with ritonavir 100 mg. TDM was rarely performed and mostly if virological control was considered suboptimal [79].

For darunavir, a study from the USA reported reduced troughs and  $AUC_{24h}$  with once-daily dosing in pregnancy, while dosing twice a day produced levels more comparable with those in non-pregnant individuals [123]. They concluded that twice-daily dosing should be used in pregnancy and higher doses may be required. For women receiving darunavir/ritonavir 800/100 mg the mean trough level

(C<sub>24h</sub>) in the third trimester and postpartum was 1.37 (0.15–3.49) µg/mL and 2.59 (<0.09–3.96) µg/mL respectively. Similar findings have been reported from the PANNA network with subtherapeutic trough concentrations reported with once-daily 800/100 mg dosing and no detectable darunavir in any of the cord blood samples [121], and therefore twice-daily dosing of darunavir in pregnancy is recommended.

Fosamprenavir was studied at a dose of 700 mg with ritonavir 100 mg bd [124]. The mean trough levels (C<sub>24h</sub>) in the third trimester and postpartum were 1.46 (0.66–2.33) µg/mL and 2.24 (1.17–5.32) µg/mL, respectively. The investigators observed that HIV replication was well suppressed for all subjects at delivery and did not recommend routine dose adjustment. Maternal and cord blood concentrations were above mean protein-binding-adjusted IC<sub>50</sub> (0.146 µg/mL) for wild-type virus.

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, TDM for PIs during pregnancy can be considered, but not recommended in the absence of studies that show improved outcomes. If performed, it should be conducted at steady state (2 weeks or more into therapy) and repeated in the third trimester.

A study of 10 pregnant women taking raltegravir 400 mg twice daily found adequate trough levels in all 10, although levels were very variable and lower than postpartum [125], while in another study of five women third trimester concentrations were no lower than postpartum and in the two cord blood samples studied, the cord blood to maternal blood ratio was >1.0 [126]. No dose adjustment of raltegravir in pregnancy is required.

The pharmacokinetics of enfuvirtide in pregnancy, as well as newer agents such as tipranavir and maraviroc, have not been described. It is worth noting that enfuvirtide does not cross the placenta [127]. There is an urgent need for extensive investigation of the pharmacokinetics of ART in pregnant women to ensure efficacy, to reduce toxicity and to prevent the emergence of resistance through inadvertent underdosing. Therefore, TDM in pregnancy should be considered for 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 cervicovaginal secretions while lopinavir and saquinavir could not be detected [128]. The implications of such data are uncertain. NRTIs penetrate the genital tract more efficiently. One study compared genital tract levels with plasma giving values as follows: emtricitabine 600%, lamivudine 300%, tenofovir 300% and zidovudine 200% [129].

**5.3 Naïve to highly active antiretroviral therapy: mother does not need highly active antiretroviral therapy for herself**

**5.3.1 All women should have commenced ART by week 24 of pregnancy. Grading: 1C**

In both the UK and Ireland and the French cohorts, transmission events were significantly associated with starting treatment later in the pregnancy. In the French cohort the median duration of treatment was 9.5 weeks among women who transmitted compared with 16 weeks for non-transmitters ( $P < 0.001$ ) [23]. In the NSHPC, non-transmitters initiated treatment at 25.9 weeks (IQR 22.4–28.7) compared with transmitters who started at 30.1 weeks (IQR 27.4–32.6) ( $P < 0.001$ ) [4].

**5.3.2 Although there is most evidence and experience in pregnancy with zidovudine plus lamivudine, tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable nucleoside backbones. Grading: 2C**

**5.3.3 In the absence of specific contraindications, it is recommended that HAART should be boosted-PI based. The combination of zidovudine, lamivudine and abacavir can be used if the baseline VL is <100 000 HIV RNA copies/mL plasma. Grading: 1C**

The prolonged half-life of NNRTIs makes them less suitable as part of a short course of treatment for PMTCT only. Therefore, boosted PIs are preferred. Questions relating to PTD and pharmacokinetics in the third trimester are addressed separately. A fixed-dose combination of zidovudine, lamivudine and abacavir is an option in this setting.

In an RCT in pregnant women with a CD4 cell count >200 cells/µL (with no VL restriction) zidovudine, lamivudine and abacavir (NRTI-only group) were compared with zidovudine plus lamivudine combined with ritonavir-boosted lopinavir (PI group). Therapy was initiated at 26–34 weeks' gestation and continued postpartum for 6 months during breastfeeding. By delivery, 96% in the NRTI-only group and 93% in the PI group had achieved VLs <400 HIV RNA copies/mL plasma despite baseline VLs >100 000 in 15% and 13%, respectively, with significantly more women in the NRTI-only group achieving VL <50 at delivery (81%) than in the PI group (69%). Overall, the HIV MTCT rate was 1.1% by the end of the breastfeeding period with no significant difference in transmission rates between the arms, although the study was not powered to address transmission and more transmissions were reported in the NRTI-only arm [66]. PTD (see Recommendation 5.2.3) was less common in the NRTI-only arm (15%) compared with the PI arm (23%), although this did not reach statistical significance. A fixed-dose combination of zidovudine, lamivudine and abacavir is generally well tolerated, with a low pill burden and easily discontinued.

In non-pregnant patients, higher rates of treatment failure have been reported with the combination of zidovudine, lamivudine and abacavir compared with other HAART combinations when the baseline VL is >100 000 HIV RNA copies/mL plasma (*BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*; www.bhiva.org/PublishedandApproved.aspx). Although these groups are not comparable, the Writing Group recommend restricting the use of zidovudine, lamivudine and abacavir for PMTCT to women with baseline VLs <100 000 HIV RNA copies/mL plasma.

#### **5.3.4 Zidovudine monotherapy can be used in women planning a CS who have a baseline VL <10 000 HIV RNA copies/mL and CD4 cell count >350 cells/ $\mu$ L. Grading: 1A**

Data on the efficacy of zidovudine monotherapy for PMTCT are well known: a 67% reduction, in ACTG 076, in transmission to 8.3% (treatment initiated 14–28 weeks, non-breastfeeding, low CS rate, baseline CD4 cell count >200 cells/ $\mu$ L) [61], a 50% reduction in a Thai study to 9.4% (mean treatment only 25 days and oral zidovudine during labour) [130]; 0.8% transmission for women treated with zidovudine monotherapy and assigned to PLCS in the Mode of Delivery study [131]. Since 2000, BHIVA guidelines have recommended zidovudine monotherapy plus PLCS for women with CD4 cell counts above the prescribed threshold for initiating HAART and with an untreated VL <10 000 HIV RNA copies/mL plasma, based on these and other data and on the published relationship between VL and transmission [132]. No transmissions were observed in the UK and Ireland among the 464 pregnancies managed by zidovudine monotherapy and PLCS between 2000 and 2006 reported to the NSHPC. The median delivery VL in these women was 400 (IQR 61–1992) HIV RNA copies/mL [4].

#### **5.3.5 Women who do not require treatment for themselves should commence temporary HAART at the start of the second trimester if the baseline VL is >30 000 HIV RNA copies/mL plasma. (Consider starting earlier if VL > 100 000 HIV RNA copies/mL.) Grading: 1C**

VL data also influence recommendations relating to mode of delivery (see below). Major determinants of the probability of achieving a VL <50 HIV RNA copies/mL plasma by the time of delivery are the baseline untreated VL and the time available to achieve this target. In the Mma Bana study, VLs <400 HIV RNA copies/mL plasma were achieved by the time of delivery in 96% (lopinavir/ritonavir-based) to 100% (abacavir/lamivudine/zidovudine) of mothers with baseline VL <1000 HIV RNA copies/mL plasma and in 86% (lopinavir/ritonavir-based) to 90% (abacavir/lamivudine/zidovudine) if baseline VL >100 000 HIV RNA copies/mL. When therapy was initiated at 31–34 weeks, only 78% of mothers on PI-based therapy

had achieved this target [66]. Data from a UK multi-centre study retrospectively analysing therapy outcomes in pregnant women initiating HAART at a median gestation of 23 weeks demonstrate very low rates of complete suppression in women with a baseline VL in the upper quartile (>32 641 HIV RNA copies/mL) with only 46% achieving <50 HIV RNA copies/mL by 36 weeks' gestation (the data point used to make most delivery management decisions) and this fell to 37% for VLs >100 000 HIV RNA copies/mL [133]. For all VLs >10 000 HIV RNA copies/mL, treatment initiation later than 20.3 weeks' gestation was associated with significantly less likelihood of successful VL suppression. To address this, the Writing Group recommend that HAART should be commenced at the start of the second trimester, or as soon as possible thereafter, in women with a baseline VL >30 000 HIV RNA copies/mL plasma.

### **5.4 Late-presenting woman not on treatment**

#### **5.4.1 A woman who presents after 28 weeks should commence HAART without delay. Grading: 1B**

Late presentation after 28 weeks and before the onset of labour occurs less frequently since the introduction of the routine offer and recommendation of antenatal HIV screening. With improved turnaround times for VL testing, a woman presenting beyond 28 weeks may still be managed with a view to a possible vaginal delivery if she commences HAART and achieves a VL <50 HIV RNA copies/mL by 36 weeks. Where women present between 24 and 28 weeks, the advantages of more detailed assessment and tailoring of the regimen should be weighed against the advantages of initiating HAART immediately. The turnaround time for CD4 cell counts, VL and viral resistance tests will impact on this choice.

#### **5.4.2 If the VL is unknown or >100 000 copies/mL a three- or four-drug regimen that includes raltegravir is suggested. Grading: 2D**

Where the VL is unknown or >100 000 HIV RNA copies/mL, a fourth drug, raltegravir, may be added to this regimen. Raltegravir has significantly higher first- and second-phase viral decay rates when used as monotherapy (*vs.* efavirenz) or in combination with other ARVs [134,135]. It is important to note that no adequate or well-controlled studies of raltegravir have been conducted in pregnant women. Pharmacokinetic data presented in Recommendation 5.2.4 indicate that no dose change is required in the third trimester.

#### **5.4.3 An untreated woman presenting in labour at term should be given a stat dose of nevirapine 200 mg (Grading: 1B) and commence fixed-dose zidovudine with lamivudine (Grading: 1B) and raltegravir. Grading: 2D**



**5.4.4 It is suggested that intravenous zidovudine be infused for the duration of labour and delivery. Grading: 2C**

A single dose of nevirapine, regardless of CD4 cell count (even if available), should be given immediately as this rapidly crosses the placenta and within 2 h achieves, and then maintains, effective concentrations in the neonate for up to 10 days [73,136]. HAART should be commenced immediately with fixed-dose zidovudine and lamivudine and with raltegravir as the preferred additional agent because it also rapidly crosses the placenta [137]. Intravenous zidovudine can be administered for the duration of labour and delivery [138]. If delivery is not imminent, CS should be considered. If delivery occurs <2 h post-maternal nevirapine, the neonate should also be dosed with nevirapine immediately.

**5.4.5 In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir (to the treatment described in Recommendation 5.4.2) to further load the baby. Grading: 2C**

If the mother is drug naïve, take baseline bloods for CD4 cell count and VL if not known, and commence HAART as per Recommendation 5.4.2. Nevirapine and raltegravir should be included in the regimen as they cross the placenta rapidly (see above).

In addition, double-dose tenofovir has been shown to cross the placenta rapidly to preload the infant and should be considered where the prematurity is such that the infant is likely to have difficulty taking PEP in the first few days of life [139].

**5.4.6 Women presenting in labour/ROM/requiring delivery without a documented HIV result must be recommended to have an urgent HIV test. A reactive/positive result must be acted upon immediately with initiation of the interventions to PMTCT without waiting for further/formal serological confirmation. Grading: 1D**

If the mother's HIV status is unknown due to lack of testing, a point of care test should be performed. Women who have previously tested negative in pregnancy but who have ongoing risk for HIV should also have a point of care test if presenting in labour. If the test is positive (reactive), a confirmatory test should be sent but treatment to prevent MTCT should commence immediately. Where point of care test is not available, laboratory-based serology must be performed urgently, including out of hours, and the result acted upon as above. Baseline samples for CD4 cell count, VL and resistance should be taken. Treatment should be commenced immediately as per Recommendation 5.4.3 above. Triple therapy should be given to the neonate (see Section 8: Neonatal management).

## 5.5 Elite controllers

**5.5.1 Untreated women with a CD4 cell count  $\geq 350$  cells/ $\mu$ L and a VL <50 HIV RNA copies/mL (confirmed on a separate assay):**

- Can be treated with zidovudine monotherapy or with HAART (including abacavir/lamivudine/zidovudine). Grading: 1D
- Can aim for a vaginal delivery. Grading: 1C
- Should exclusively formula feed their infant. Grading: 1D

Elite controllers are defined as the very small proportion of HIV-positive individuals who, without treatment, have undetectable HIV RNA in plasma as assessed by more than one different VL assay on more than one occasion. It is estimated that 1-in-300 HIV-positive individuals are elite controllers [140].

In the absence of data from RCTs on elite controllers, recommendations are based on RCT and observational data on all pregnant HIV-positive women.

In the original zidovudine monotherapy study (ACTG 076) the transmission rate if maternal VL was <1000 HIV RNA copies/mL was 1% (range 0–7%) [61]. Treatment reduced transmission even among women with low or undetectable HIV VL, suggesting that the effects of treatment were not all related to decreasing maternal viraemia but may also be related to reducing HIV in the genital tract and/or peri-exposure prophylaxis of the infant by placental transfer of zidovudine. A meta analysis of transmission outcomes in several major USA and European studies also demonstrated that an HIV VL <1000 HIV RNA copies/mL at delivery was associated with a relatively low risk of transmission and that ARV prophylaxis offered additional clinically significant protection [141]. Zidovudine has been shown to reduce cervicovaginal shedding of HIV [18] and there are no data to suggest that HAART is more effective than zidovudine at reducing cervicovaginal shedding in women with a plasma HIV VL <50 copies/mL. Therefore, zidovudine monotherapy is an option in this setting. There are no data to support the use of intravenous zidovudine infusion during labour in elite controllers. HAART may provide more reassurance about prevention of MTCT but will also expose both mother and infant to more potential drug toxicities. The choice of HAART is as per Recommendation 5.3.3.

Data on the mode of delivery in elite controllers are sparse and limited to case reports [142]. The benefits of PLCS at various levels of viraemia are discussed in Section 7.2 (Mode of delivery). There are no data to support the use of PLCS for PMTCT when the VL is <50 HIV RNA

copies/mL in women on ART. The Writing Group therefore recommends vaginal delivery for all elite controllers on ART.

## 5.6 Stopping antiretroviral therapy postpartum

**5.6.1** The discontinuation of NNRTI-based HAART postpartum should be according to *BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012* ([www.bhiva.org/PublishedandApproved](http://www.bhiva.org/PublishedandApproved)). Grading: 1C

The literature comparing strategies for stopping ART in pregnant women is limited and therefore no alternative recommendation, compared with non-pregnant women, is made.

**5.6.2** ARV therapy should be continued in all pregnant women who commenced HAART with a history of an AIDS-defining illness or with a CD4 cell count <350 cells/ $\mu$ L as per adult treatment guidelines. Grading: 1B

Available RCT data to address the question as to whether one should continue or stop HAART in women receiving it to prevent MTCT and not for their own health are sparse and have limited applicability to current ART treatment practices. What information there is comes from early RCTs with zidovudine monotherapy [143] with or without HIV immunoglobulin [144] and from observational studies with their inherent weaknesses [145–148]. Nevertheless, concerns have been raised regarding the discontinuation of ARVs postpartum in light of results from CD4-guided interruption studies (SMART [149] and TRIVICAN [150] in particular) although interruption of ART given for PMTCT after delivery is not completely analogous. In both these studies, which were halted prematurely because of the significantly worse outcome in the CD4-guided interruption arm, lower CD4 cell count thresholds for resumption of therapy were used than would be currently based on clinical treatment guidelines. Moreover, these CD4-based treatment RCTs (SMART and TRIVICAN) and the major cohort studies (NA-ACCORD [151], ART-CC [152]) either excluded or did not collect data on pregnant women.

Hence, these recommendations extrapolate data used to inform internationally accepted treatment guidelines for all adults as well as incorporating evidence available from the limited data for postpartum drug management. In addition, observations on the collated evidence of the deleterious effect of direct virus infection, and indirect inflammatory response and its correlation to CD4 cell count, allow tentative conclusions to be made on the potential for this to be prevented by cART.

To answer the question as to whether one should continue or stop cART in patients receiving it to prevent MTCT with a CD4 cell count >400 cells/ $\mu$ L, a randomized

study (the HAART Standard Version of PROMISE) Study NCT00955968], is now recruiting: results of this interventional trial are not expected for several years.

**5.6.3.** ART should be continued in all women who commenced HAART for PMTCT with a CD4 cell count of between 350 and 500 cells/ $\mu$ L during pregnancy who are coinfecting with HBV or HCV in accordance with the *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012* ([www.bhiva.org/PublishedandApproved.aspx](http://www.bhiva.org/PublishedandApproved.aspx)). Grading: 1B

There is evidence that continuing ART in patients coinfecting with HBV or HCV reduces co-morbidity progression. For HBV, there is the additional requirement of viral suppression from antiviral drugs (emtricitabine, lamivudine, tenofovir) and the risk of a flare of hepatitis if discontinued (see Section 6.2 Hepatitis C).

**5.6.4** ART can be continued in all women who commenced HAART for PMTCT with a CD4 cell count of between 350 and 500 cells/ $\mu$ L during pregnancy. Grading: 2C

On the basis of the above cohort data the Department of Health and Social Services (2011) [153] and International AIDS Society (2010) guidelines [154] for treating adults have now altered their recommendation and advise treating all adults with a CD4 cell count <500 cells/ $\mu$ L. Moreover, two recent retrospective reviews in women discontinuing ART postpartum found an increased risk of death or opportunistic infection among women stopping therapy after delivery. The Tennessee study reviewed patients who discontinued therapy postpartum (mean nadir CD4 cell count 332 cells/ $\mu$ L) in an observational cohort of mothers from 1997 to 2008 [145]. Despite being a small cohort ( $n = 123$ ), the findings indicated an increased rate of AIDS-defining events and death, and non-AIDS-defining events and death, were more frequent in those discontinuing ( $n = 54$ ) than in those continuing ( $n = 69$ ), although this was not statistically significant. This is the only study that has examined the use of HAART on clinical outcomes in women with high CD4 cell counts. However, there were many potential confounders. In a further retrospective study on mothers discontinuing therapy between 1997 and 2005 [147], more opportunistic infections and deaths were found in those who discontinued; however, this was a small, uncontrolled review where 46% had previous ART exposure and 36% a pre-ART CD4 cell count of <350 cells/ $\mu$ L. Lastly, in a large cohort of women who were enrolled in South America and followed up for 6–12 weeks after discontinuation of ART given to prevent MTCT, significant falls in the CD4 cell percentage were seen as would be expected [146].

Other studies have shown no detrimental effects on disease progression in discontinuing treatment postnatally.

Data from ACTG 185 [144] through 18 months postpartum and from follow-up of women enrolled in the ACTG 076 study [155] suggest that for many women with CD4 cell counts  $>350$  cells/ $\mu\text{L}$ , limited exposure to zidovudine monotherapy does not have an impact on disease progression or response to later therapy. However, again these studies enrolled a heterogeneous group of women many of whom had CD4 cell counts  $<350$  cells/ $\mu\text{L}$  who received zidovudine monotherapy during pregnancy. More persuasively, among women with CD4 cell counts  $>350$  cells/ $\mu\text{L}$  followed in the Women and Infants Transmission Study (WITS) cohort, there were no significant differences in CD4 cell count or disease progression at 1 year among those who did or did not continue ART after delivery [148]. Finally, in an audit to document postpartum disease-free survival of HIV-positive women taking ART during pregnancy, 40% of mothers (nadir CD4 cell count median 317 cells/ $\mu\text{L}$ ) given cART to prevent MTCT and who subsequently discontinued, went on to commence treatment after a median of 33 months [156]. However, this was a heterogeneous group with 13% of mothers having CD4 cell counts  $<200$  cells/ $\mu\text{L}$  and the majority having counts between 201 and 500 cells/ $\mu\text{L}$  (66%) at commencement of cART. Nevertheless, the study did demonstrate that short-term exposure to cART during pregnancy did not jeopardize future response to treatment.

It is uncertain whether untreated HIV infection or the discontinuation of cART with virological suppression when the CD4 cell count is 350–500 cells/ $\mu\text{L}$  has detrimental effects but it is conceivable that treatment at this stage may

prevent future morbidity. In view of this, where patient preference is to continue therapy and the physician believes there is no potential contraindication, in particular poor adherence postpartum, we believe the patient should be allowed to continue treatment. The randomized PROMISE study should provide a definitive answer to this question.

Recent data indicate a 96% reduction in transmission between heterosexual discordant couples if the infected partner is treated with HAART [157]. Therefore, a woman with a baseline CD4 cell count  $>350$  cells/ $\mu\text{L}$  and an HIV VL  $>50$  HIV RNA copies/mL can be offered continued therapy with HAART in this setting.

**5.6.5. ART should be discontinued in all women who commenced HAART for PMTCT with a CD4 cell count  $>500$  cells/ $\mu\text{L}$  unless there is discordance with her partner or co-morbidity as outlined in Section 6 (HIV and hepatitis virus coinfections). Grading: 2B**

Only one cohort study has demonstrated benefit in starting therapy in adults who have a CD4 cell count  $>500$  cells/ $\mu\text{L}$  (NA-ACCORD) [151]: specifically, this was not observed in the ART-CC analysis [152]. In addition, several small CD4-guided interruption studies using a higher threshold than SMART of commencing below 350 cells/ $\mu\text{L}$  (TRISTAN [158], STACCATO [159]) and seroconversion treatment studies have not shown significant clinical benefit with fixed courses of early treatment [160]. Lastly, durable CD4 cell count benefits have been demonstrated in women receiving short-term ART to prevent MTCT when initiating  $>500$  cells/ $\mu\text{L}$  indicating no short-term harm in this strategy and possible benefits [161].

## 6.0 HIV and hepatitis virus coinfections

### 6.1 Hepatitis B virus

The combination of HIV, chronic HBV infection and pregnancy presents unique management questions. Referral to the local designated specialist should be undertaken to ensure that all aspects of care are addressed, including: the effects of HBV/HIV on pregnancy; effects of pregnancy on the course of coinfection; drug management for both HBV and HIV; and PMTCT for both viruses. The prevalence of HBV coinfection in pregnant women tends to reflect that of the adult population (Europe/Africa 4–10%) [162–165] and is 40% higher than that found in the general population (HIV positive *vs.* HIV uninfected: RR 1.40; 95% CI 1.16–1.69) [165]. Up to one-third of hepatitis B surface antigen (HBsAg) are wild type [hepatitis B e antigen (HBeAg)-positive] and, depending on region, up to 6% are coinfecting with HDV. Rates of HBV/HIV coinfection vary with race and ethnicity so that changing immigration patterns in Western countries with traditionally low prevalence may significantly influence rates at a regional level (e.g. 6% among Asian women in the USA *vs.* 0.6% in white women) [166]. The same is true for injection drug use (prevalence <0.1% in north-west Europe compared to 1–4% in southern Europe) and sexual transmission (prevalence higher in men who have sex with men). Although plausible because of higher levels of HBV DNA in coinfecting women, there is no evidence of increased MTCT in coinfection over mono-infection. The impact of pregnancy on women with HBV mono-infection is small. There appears to be no worsening of liver disease in the majority of women, although case reports of hepatic exacerbations/fulminant hepatic failure have been reported; alanine transferase (ALT) levels tend to fall, HBeAg seroconversion occurs in a small minority and may be associated with liver dysfunction, and HBV DNA levels may rise by as much as one log<sub>10</sub>. The impact of HBV infection on pregnancy appears negligible. By contrast, the effect of HIV on HBV disease progression includes: higher levels of HBV replication (HBV DNA levels and proportion HBeAg-positive); higher mortality when compared to HIV or HBV mono-infection; higher rate of chronicity (20–80% compared with 3–5% in HIV-negative with risk increasing with lower CD4 cell counts at the time of HBV acquisition); lower ALT levels; higher rate of hepatoma; lower rate of spontaneous loss of HBeAg or HBsAg and seroconversion to anti-hepatitis B e antibody and anti-hepatitis B surface antibody

(HBsAb); faster progression to cirrhosis; and higher incidence of lamivudine resistance [167].

**6.1.1 On diagnosis of new HBV infection, confirmation of viraemia with quantitative HBV DNA, as well as HAV, HCV and HDV screening and tests to assess hepatic inflammation and function are recommended. Grading: 1C**

**6.1.2 LFTs should be repeated at 2 weeks after commencing HAART to detect evidence of hepatotoxicity or IRIS and then monitored throughout pregnancy and postpartum. Grading: 1C**

**6.1.3 In the immediate period after discontinuing drugs with anti-HBV activity, LFTs and HBV DNA should be monitored frequently. Grading: 1C**

In a pregnant HIV-positive woman, newly diagnosed with HBV (HBsAg-positive on antenatal screening or diagnosed preconception), baseline hepatitis B markers (hepatitis B core antibody/HBeAg status) and level of the virus (HBV DNA), degree of inflammation and synthetic function (ALT, aspartate transaminase, albumin, INR), assessment of fibrosis, and exclusion of additional causes of liver disease (e.g. haemochromatosis, autoimmune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) immunization as well as for HDV coinfection (HDV serology). Fibroscan is contraindicated during pregnancy, so where there is suspicion of advanced liver disease, ultrasound scanning should be performed. It is important where cirrhosis is found to be present that there is close liaison with the hepatologist because of a significantly increased rate of complications: additionally, acute liver failure can occur on reactivation of HBV disease if anti-HBV treatment is discontinued [168]. However, in the absence of decompensated disease and with HAART incorporating anti-HBV drugs and close monitoring, most women with cirrhosis do not have obstetric complications from their HBV infection.

Because of the risk of ARV-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat LFTs at 2 weeks post-initiation of cART. Through pregnancy, it is routine to monitor LFT tests at each antenatal clinic appointment as a marker for potential obstetric complications (HELLP, pre-eclampsia, acute fatty liver, etc.), particularly in the final trimester. Finally, in those diagnosed late and not receiving HBV treatment incorporated into HAART, LFT flares may be seen shortly after delivery, which in some relates to HBeAg seroconversion and reappearance or a marked increase in HBV DNA levels. Where

acute HBV has been diagnosed, there are no data to support management and each case needs to be managed with specialist advice. Data suggest that lamivudine, as part of HAART, does not completely protect against the development of acute HBV infection, although it is unknown whether this is also the case with tenofovir with or without lamivudine/emtricitabine. Although there is a theoretical risk of high HBV DNA levels and the linked association with increased risk of transmission combined with the potential for acute hepatitis and threat to maternal and fetal health, the presumption would be that this would be abrogated by the patient already being on HAART incorporating tenofovir and either emtricitabine or lamivudine.

**6.1.4 Where pegylated interferon or adefovir is being used to treat HBV in a woman who does not yet require HIV treatment and who discovers she is pregnant, treatment should be switched to a tenofovir-based HAART regimen. Grading: 1C**

If a woman on pegylated interferon becomes pregnant, it should be discontinued and changed to a tenofovir-based HAART regimen because of the antiproliferative effect of the drug. Few data are available on the risk of congenital malformation with first trimester exposure to the newer therapies telbivudine (FDA category B) and entecavir (FDA Category C). The outcome of the pregnancy should be reported to the Interferon Pregnancy and Antiretroviral Pregnancy Registries.

**6.1.5 As there is no evidence of any adverse effect on maternal or neonatal health if women become pregnant while taking ART active against HBV, treatment should be continued. Grading: 1C**

For tenofovir, emtricitabine and lamivudine, APR [49] and the Development of Antiretroviral Therapy Study (DART) have not identified any increased risk in prevalence or any specific pattern of anomaly, even when administered in the first trimester. Hence, when a patient becomes pregnant on an anti-HBV viral agent as part of their HAART (tenofovir, lamivudine or emtricitabine), as for HIV management, HAART should be continued. This is because the potential risk to the fetus from drug exposure is outweighed by that of a hepatitis flare or liver disease progression if the drug(s) were to be discontinued in addition to HIV virological rebound and risk of MTCT. Because entecavir has activity against HIV, it is not recommended unless given with active HAART in a coinfecting patient. Moreover, it has been found to have significant carcinogenic potential in animal studies and therefore its use as an antiviral drug for HBV during pregnancy should be avoided. Lamivudine has been extensively used, as has tenofovir and to a lesser extent emtricitabine, for the treatment of HIV mono-infection during pregnancy, and lamivudine and telbivudine have been used in HBV mono-

infected pregnant women and all have been found to be safe. There are limited data on adefovir use in pregnancy and it is not recommended. Where it is being used in a woman for management of HBV but who does not require HIV treatment, this should be switched to tenofovir incorporated into her HAART regimen. In the context of coinfection during pregnancy where HAART is indicated, there is unlikely to be a situation where it would be used instead of tenofovir. There is no evidence of any adverse effect on maternal health if women become pregnant while taking tenofovir, lamivudine or emtricitabine: these drugs are recommended as NRTI choices in national [169] and international guidelines [154].

**6.1.6 In all HAV non-immune HBV coinfecting women, HAV vaccine is recommended after the first trimester as per the normal schedule (0 and 6–12 months) unless the CD4 cell count is <300 cells/ $\mu$ L, when an additional dose may be indicated. Grading: 1D**

Immunization for HAV uses inactivated vaccines. Data for HAV vaccine in pregnancy are limited. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HAV immunization, including in HBV coinfecting pregnant women [170,171]. For HAV vaccines, patients with higher CD4 cell counts and on HAART generally show improved responses to vaccination. HIV-positive persons with CD4 cell counts <300 cells/ $\mu$ L should receive three doses of HAV vaccine over 6–12 months instead of the standard two.

**6.1.7 Tenofovir and emtricitabine should form the backbone of an ART regimen in naive patients with wild-type HIV/HBV infection and no contraindication to either drug (Grading: 1B).**

**6.1.8 If tenofovir is not currently part of HAART it should be added. Grading: 1B**

**6.1.9 Lamivudine/emtricitabine may be omitted from the ARV regimen and tenofovir given as the sole anti-HBV agent if there is clinical or genotypic evidence of lamivudine/emtricitabine resistant HBV. Grading: 1C**

**6.1.10 Lamivudine or emtricitabine should not be used as the only active drug against HBV in HAART because of the likelihood of emergent HBV resistance to these agents. Grading: 1B**

**6.1.11 Emtricitabine has potential antiviral benefits over lamivudine, is coformulated with tenofovir, and appears to be equally safe during pregnancy and hence is the preferred option to be given with tenofovir in coinfection. Grading: 2D**

All HBV/HIV coinfecting women should receive HAART containing tenofovir with emtricitabine or lamivudine treatment during pregnancy, unless contraindicated. Although lamivudine and emtricitabine are potent anti-HBV agents, monotherapy is associated with a high likeli-

hood of HBV resistance in coinfecting persons and hence therapy with either of these drugs, without a second anti-HBV active drug, is not recommended. Tenofovir is effective at suppressing HBV DNA in mono- and coinfecting patients and may induce HBeAg seroconversion although, as for other antivirals, this may be less likely in coinfection. HBV resistance is extremely rare and combination with lamivudine or emtricitabine has been demonstrated to be effective at suppressing HBV DNA and may induce HBeAg seroconversion. Combining lamivudine/emtricitabine with tenofovir may also reduce the risk of breakthrough HBV viraemia [169].

Emtricitabine is structurally similar to lamivudine but has a longer half-life and selects for resistance for both HBV and HIV less rapidly and less often. Although not currently approved for HBV treatment, it induces a sharp reduction of HBV DNA in both mono- and coinfecting patients. In one RCT of coinfecting patients naïve to antivirals, combining emtricitabine with tenofovir has been shown to be more effective than emtricitabine alone (median time-weighted average concentration decrease was  $-5.32 \log_{10}$  IU/mL in the tenofovir/emtricitabine group *vs.*  $-3.25$  IU/mL in the emtricitabine group:  $P=0.036$ ) [172]. Further studies comparing emtricitabine/lamivudine with lamivudine alone produced similar results [173]. In addition, the PROMISE study includes a substudy examining pregnant women with CD4 cell counts  $>350$  cells/ $\mu$ L randomly allocated to either tenofovir/emtricitabine or zidovudine/lamivudine and lopinavir/ritonavir with outcome measures of pregnancy HBV VLs, HBV transmission, pregnancy outcomes, and postpartum ALT and HBV VL. Lamivudine/emtricitabine-resistant strains will respond to tenofovir.

LFT results should be monitored frequently after starting HAART because of the possibility of an inflammatory flare from immune reconstitution (see Section 6.1.3).

#### *Postpartum management of hepatitis B virus coinfection*

**6.1.12** Where the CD4 cell count is  $<500$  cells/ $\mu$ L, HAART should be continued postpartum if HBV coinfection exists because of the increased risk of HBV progressive disease. Grading: 1B

**6.1.13** Where the CD4 cell count is  $>500$  cells/ $\mu$ L and there is no other indication to treat HBV, consideration should be given to continuing anti-HBV treatment postpartum with HAART incorporating tenofovir and emtricitabine. Grading: 2C

**6.1.14** If a decision is taken to discontinue therapy, careful monitoring of liver function is imperative. Grading: 2D

**6.1.15** Where the CD4 cell count is  $>500$  cells/ $\mu$ L and there is HBV viraemia and evidence of liver inflamma-

tion or fibrosis, HAART containing tenofovir and emtricitabine should be continued. Grading: 2C

**6.1.16** Hepatitis flares that occur after HAART cessation should be treated by resumption of active anti-HBV treatment before significant liver dysfunction occurs. Grading: 2D

The decision to continue ART or not postpartum depends on whether HAART was indicated for maternal health and the level of HBV-related hepatic activity/fibrosis. There is consensus that all persons with active (HBsAg-positive and/or HBV DNA-positive) coinfection should receive ARVs if their CD4 cell count is  $<500$  cells/ $\mu$ L [154,170]. Hence, HAART incorporating agents active against HBV (tenofovir and emtricitabine) should be continued in this group. In those women with CD4 cell counts of  $>500$  cells/ $\mu$ L with a baseline HBV DNA  $>2000$  IU/mL and/or evidence of fibrosis on biopsy or Fibroscan, HBV treatment should be continued because of the risk of progressive liver disease if discontinued. In these patients, HAART incorporating tenofovir and emtricitabine should be continued. Adefovir is an option and has been evaluated against HBV in coinfecting patients. It does not select resistance against tenofovir but is less active than tenofovir. Neither entecavir (has antiviral activity to HIV and selects resistance) nor telbivudine (high resistance rates) are suitable in coinfection. In those with CD4 cell counts over 500 cells/ $\mu$ L who received HAART to prevent MTCT and who are not HBV viraemic ( $>2000$  IU/mL) or have evidence of established liver disease, strong consideration should be given to continuing anti-HBV therapy, in the form of tenofovir-based HAART because of the risk of progression of liver disease in coinfection.

Inflammatory flares, which may be severe, particularly in persons with cirrhosis can occur because of viral escape and HBV viraemia, if anti-HBV drugs are stopped. In an RCT comparing lamivudine with placebo for reducing HBV MTCT in patients with HBV mono-infection, an immediate increase in HBV DNA levels was observed on discontinuation of lamivudine postpartum [174]. Similarly, hepatitis flares among HIV/HBV coinfecting patients have been reported upon the discontinuation of lamivudine, emtricitabine and tenofovir. In the Swiss HIV observational cohort, liver enzyme elevation occurred in 29% of patients who discontinued lamivudine and in 5% this was severe, with three patients presenting with fulminant hepatitis [175] at a median time of 6 weeks after discontinuation. Hepatitis flares that occurred after ART cessation should be treated by resumption of active anti-HBV treatment before significant liver failure occurs.

**6.1.17** In the absence of obstetric complications, normal vaginal delivery can be recommended if

the mother has fully suppressed HIV VL on HAART. Grading: 2C

No data exist to support any benefit from PLCS in mothers with HBV/HIV coinfection and no robust RCT exists in HBV mono-infected women. In a meta-analysis of mono-infected HBV women (four randomized trials all from China involving 789 people were included) where routine HBV neonatal vaccine and HBIG were used, there was strong evidence that PLCS *vs.* vaginal delivery could effectively reduce the rate of MTCT of HBV (RR 0.41; 95% CI 0.28–0.60) [176]. However, methodological concerns, including lack of information on randomization procedure, lack of allocation concealment and lack of blinding make the role of PLCS for PMTCT of HBV uncertain. In addition, a meta-analysis of six RCTs where lamivudine was used from the third trimester has demonstrated that lamivudine is effective in reducing transmission (HR: 0.31; 95% CI 0.15–0.63) [177]. Similarly, a single RCT in women positive for HBsAg and with an HBV DNA > 10<sup>6</sup> IU/mL demonstrated that telbivudine was also effective in reducing MTCT for HBV (2.11% *vs.* 13.4%; *P* < 0.04) and lowering risk of postpartum ALT flare. Hence, the lack of a scientifically robust RCT evaluating the role of CS in preventing MTCT for mothers with HBV mono-infection and lack of any cohort or RCT data to support the use of CS in coinfection argue against advocating this in coinfecting mothers. Although HBV DNA levels are increased as a result of HIV, the efficacy of lamivudine as well as telbivudine in reducing the rate of intrapartum transmission in mono-infection, efficacy of lamivudine, tenofovir and emtricitabine as part of HAART in reducing HBV DNA in non-pregnant coinfecting patients, and use of tenofovir with either lamivudine or emtricitabine as standard practice in coinfecting patients, collectively provide further reason against recommending CS in those coinfecting.

**6.1.18 Neonatal immunization with or without HBIG should commence within 24 h of delivery. Grading: 1A**

Immunoprophylaxis with HBV vaccine with or without HBIG given to the neonate has been shown in separate meta-analyses of RCTs to significantly reduce MTCT from HBV mono-infected women. In the absence of neonatal immunization with HBV vaccine with or without HBIG, the rate of MTCT from a mono-infected mother who is HBsAg-positive and HBeAg-positive is 70–90% and for women who are HBsAg-positive but HBeAg-negative, 10–40%. By co-administering vaccination (effectiveness of vaccine *vs.* placebo RR: 0.28; 95% CI 0.2–0.4) and HBIG (effectiveness of HBIG/vaccine *vs.* vaccine alone RR: 0.54; 95% CI 0.41–0.73), transmission rates can be reduced to between 0% and 14%. However, 10% of the offspring of HBV carriers become chronic hepatitis B sufferers in early life despite this mainly being because of infection *in utero*. The most important

determinant of prophylaxis failure has been shown to be maternal serum HBV DNA levels. Transmission rates as high as 32%, despite active/passive immunization with vaccine and HBIG have been reported in infants born to mothers with HBV DNA concentrations >1.1 × 10<sup>7</sup> IU/mL. ART with HBV activity (lamivudine/emtricitabine, tenofovir) can reduce this risk to a negligible level [178].

## 6.2 Hepatitis C virus

Antenatal prevalence of HCV mono-infection ranges from <1 to about 2.5% increasing to 3–50% in coinfection with the wide range reflecting the proportion of women who are injecting drug users or come from high HCV prevalence areas in the cohorts studied [179,180]. Several meta-analyses and systematic reviews have shown the overall rate of MTCT for HCV approximates 5% (range 2–10%) if the mother is anti-HCV-positive only. Coinfection is associated with a significant increase in HCV transmission (OR up to 2.82) compared to HCV mono-infection [181–183]. In addition, a higher rate of MTCT is seen in mothers who are coinfecting and HCV viraemic compared to those who are coinfecting and non-viraemic (OR 2.82) as well as to HCV viraemic but HIV-negative (OR 1.97) [181,182]. Acquisition of infection of HCV is more likely in infants also becoming infected with HIV and vertical transmission of HIV occurs more often from women coinfecting with HIV and HCV than from those infected with HIV only (OR 1.82) where a modest association was found with HCV VL [184]. Numerous studies have shown that the height of the HCV VL correlates with the risk of HCV MTCT and it is likely there is a linear relationship between VL and transmission as for HIV [185,186]. Invasive obstetric procedures, internal fetal monitoring, prolonged ROMs and female infant sex have also been associated with transmission but breastfeeding and CS do not pose an additional risk in mono-infected mothers [187,188]. Effective HAART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia [188,189]. No correlation with HCV genotype or interleukin-28 polymorphisms and transmission has been identified [185,190,191]. Both intrauterine and intrapartum infection probably occur, but the relative contribution of each is uncertain. However, approximately one-third of neonates are HCV-viraemic at birth suggesting acquisition *in utero* [192].

**6.2.1 On diagnosis of new HCV infection, confirmation of HCV viraemia with quantitative VL and genotype, assessment of hepatic inflammation and function and concomitant liver disease should be performed. Grading: 1C**

**6.2.2 LFTs should be repeated at 2 weeks after commencing HAART to detect evidence of hepatotoxicity or**

**IRIS and then monitored throughout pregnancy and postpartum. Grading: 1C**

In a pregnant HIV-positive woman newly diagnosed with HCV, in addition to referral to the local designated specialist, baseline investigations including the presence (HCV RNA) and level of the virus (HCV VL), genotype and subtype, degree of inflammation and synthetic function (ALT, aspartate transaminase, albumin, INR), assessment of fibrosis, and exclusion of additional causes of liver disease (e.g. haemochromatosis, autoimmune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) and HBV (HBsAb) immunization, as well as for HBV coinfection (HBsAg). Fibroscan is contraindicated during pregnancy so that where there is suspicion of advanced liver disease, liver ultrasound scanning should be performed. It is important where cirrhosis is found to be present that there is close liaison with the hepatologist because of a significantly increased rate of complications [168]. However, in the absence of decompensated disease, most women with cirrhosis do not have obstetric complications from their HCV infection.

Because of the risk of ART-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat LFTs at 2 weeks post-initiation of HAART. Through pregnancy, it is routine to monitor LFT results at each antenatal clinic appointment as a marker for potential obstetric complications (HELLP, pre-eclampsia, acute fatty liver, etc.), particularly in the final trimester. Where there is a suspicion that acute hepatitis C may be presenting during pregnancy, it is important to monitor the HCV VL through pregnancy at 4-weekly intervals. In chronically infected patients there is unlikely to have been significant change in the HCV VL. However, the prenatal VL will give some idea as to the risk of MTCT and may be worth repeating near delivery. If pregnancy has occurred during treatment for HCV with pegylated interferon and ribavirin, in addition to immediate discontinuation of treatment, thyroid function test should be included in the routine bloods as thyroid dysfunction occurs in approximately 7% of patients.

Finally, it is recognized that a small number of coinfecting patients are HCV antibody negative but HCV viraemic. Where there is evidence of liver inflammation or fibrosis, profound immune deficiency, or risk factors, an HCV VL assay should be performed.

**6.2.3 Coinfecting mothers with HCV should not be treated for HCV with pegylated interferon with or without ribavirin and all women who discover they are pregnant while receiving treatment should discontinue both pegylated interferon and ribavirin immediately. Grading: 1B**

There is no evidence that HCV can be transmitted vertically in the absence of HCV viraemia so only viraemic

patients would be considered for therapy. The current standard of care in HCV therapy is the combination of pegylated interferon and ribavirin with the addition of either telaprevir or boceprevir for genotype 1. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy. However, pegylated interferons are abortifacient at high doses in monkeys and when given in the first trimester have been associated with an increased risk of fetal loss and low birthweight in humans. Ribavirin has been assigned to category X by the FDA and is not recommended for use in pregnancy. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. It is contraindicated in pregnancy and in male partners of women who are pregnant. Hence, active treatment during pregnancy can only be considered once directly acting antiviral agents have been shown to be safe and effective in combinations without pegylated interferon and ribavirin. In the Ribavirin Registry, 6.1% of women who received ribavirin at some point during their pregnancy had offspring with birth defects [193]. Given the evidence from animal data, women with coinfection should discontinue HCV therapy as soon as pregnancy is confirmed. Extreme care must be taken to avoid pregnancy during therapy and for the 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized. The outcome of an exposed pregnancy should be reported prospectively to the Ribavirin and Interferon Pregnancy Registries.

**6.2.4 In all non-immune HCV coinfecting women after the first trimester, vaccination against HBV is recommended. Grading: 2C**

Immunization for HBV uses an inactivated vaccine. Limited data are available on the use of hepatitis B vaccination in pregnancy and none in HIV-positive pregnant women. Moreover, no randomized trial has been performed on the optimum dosing schedule for use in pregnancy [194]. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HBV or HAV immunization, including in HCV coinfecting pregnant women [195,196]. In single-arm open studies in HIV uninfected persons, seroconversion rates for HBV are no different in the pregnant and non-pregnant woman and no fetal risks have been reported. In a prospective clinical trial in pregnant women, an accelerated schedule at 0, 1 and 4 months was found to be effective, well tolerated and had the advantage of potential completion before delivery [197]. Patients with higher CD4 cell counts and on HAART generally show improved responses to vaccination. Regardless of CD4 cell count, HBsAb level should be measured 6–8 weeks after completion of vaccination.



6.2.5 HAV vaccine is recommended as per the normal schedule (0 and 6–12 months) unless the CD4 cell count is <300 cells/ $\mu$ L when an additional dose may be indicated. Grading: 2C

Immunization for HAV also uses an inactivated vaccine and data for HAV vaccination in this setting are similarly limited. HIV-positive persons with CD4 cell counts <300 cells/ $\mu$ L should receive three doses of HAV vaccine over 6–12 months instead of the standard two [198].

6.2.6 In the absence of obstetric complications, normal vaginal delivery can be recommended if the mother is receiving HAART. Grading: 2C

As HCV antiviral therapy is contraindicated in pregnant women due to possible teratogenicity, mode of delivery remains the only possible risk factor amenable to intervention. No randomized studies of CS compared to normal vaginal delivery to prevent HCV MTCT have been performed. In mono-infection, two meta-analyses failed to show a significant decrease in HCV vertical transmission among mothers in the study who underwent CS compared with mothers who gave birth vaginally (OR 1.1 [199] to OR 1.19 [183]). In the first European Paediatric Hepatitis Network cohort, a subgroup analysis of women coinfecting with HIV ( $n = 503$ , 35.4%) demonstrated a reduced risk of vertical transmission of HCV with CS (OR 0.43; 95% CI 0.23–0.80) [183]. However, in a later analysis from the European Paediatric Hepatitis Network ( $n = 208$ , 15.0%) no such association was found (OR 0.76; 95% CI 0.23–2.53) [188]. In the later analysis, MTCT of HCV was less (8.7% *vs.* 13.9%) and more women probably received HAART (41%), which was associated with a significant HCV VL reduction compared to those who received monotherapy or no therapy (OR 0.26; 95% CI 0.07–1.01). There was also a trend to lower HCV VL in this group, which may go some way to explaining this. Also, in a small French cohort of coinfecting women (29% on HAART), rate of transmission did not differ significantly between children born by vaginal delivery or CS [200]. HAART should be given to all HCV/HIV coinfecting pregnant women, regardless of CD4 cell count or HIV VL because of the evidence of increased HIV transmission in coinfecting mothers.

#### *Postpartum management of hepatitis C virus coinfection*

6.2.7 Where the CD4 cell count is <500 cells/ $\mu$ L, HAART should be continued if active HCV coinfection exists

because of the increased risk of progressive HCV-related liver disease. Grading: 1B

6.2.8 Where the CD4 cell count is >500 cells/ $\mu$ L and there is no HCV viraemia or fibrosis, HAART should be discontinued. Grading: 2C

6.2.9 Where the CD4 cell count is >500 cells/ $\mu$ L and there is HCV viraemia and evidence of liver inflammation or fibrosis, continuing HAART is preferable because of a benefit on fibrosis progression. Grading: 2B

6.2.10 Where the CD4 cell count is between 350 and 500 cells/ $\mu$ L and there is no evidence of viraemia, inflammation or fibrosis, continuing HAART is preferable if the patient displays a preference to do so. Grading: 2C

The decision to continue ART or not postpartum depends on both HIV and HCV factors. There is consensus among guidelines that all persons with active (HCV-viraemic) coinfection should receive HAART if their CD4 cell count is <500 cells/ $\mu$ L [154,201,202]. In those women with CD4 cell counts of 350–500 cells/ $\mu$ L who have cleared infection either spontaneously (about 25%) or after treatment and with a sustained virological response (SVR) and who have normal liver histology as judged by biopsy or Fibrosan, consideration should be given to continuing cART where the patient expresses a preference to do so. This is because until completion of the randomized PROMISE trial, which addresses the question of whether to continue HAART postnatally in mothers with CD4 cell counts >400 cells/ $\mu$ L, there is equipoise as to correct management. In those with CD4 cell counts >500 cells/ $\mu$ L, who received HAART to prevent MTCT, and who are not HCV-viraemic and have no evidence of established liver disease, ARVs can be discontinued. Without additional risk factors (such as alcohol, steatosis) and assuming they are not reinfected, these women should have no further histological progression of their liver. In women with CD4 cell counts >500 cells/ $\mu$ L who have established liver disease (inflammation or fibrosis), therapy should be continued. Interruption of ART in the SMART study was shown to lead to a greater risk of non-opportunistic disease-related death, particularly among those with HIV/HCV coinfection. Furthermore, ART interruption has been associated with accelerated fibrosis in patients with active hepatitis C [203] and it has been shown that effective HIV suppression improves liver histology even in the absence of effective HCV treatment [204,205].

## 7.0 Obstetric management

### 7.1 Antenatal management

**7.1.1 Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status. Grading: 1D**

The National Screening Committee [206] and the NICE antenatal guidelines [207] recommend that ultrasound screening for fetal anomaly should be offered to all pregnant women between 18 + 0 and 20 + 6 weeks' gestation. There is no evidence to alter this for women infected with HIV.

In the past, because of a theoretical increased risk of anomaly due to first trimester ART exposure, more detailed ultrasound scanning (i.e. in a fetal medicine unit) has been considered. The evidence from prospective reports of first trimester ART exposure to the APR [49] does not support the need for increased surveillance with the most commonly prescribed therapies (listed in Appendix 4), although with newer medication the knowledge base is inevitably limited. APR reports on the frequency and nature of birth defects and ART are updated every 6 months (<http://www.apregistry.com/>).

**7.1.2 The combined screening test for trisomy 21 is recommended as this has the best sensitivity and specificity and will minimize the number of women who may need invasive testing. Grading: 2C**

Clinical Guidance 62 (CG62) [207] also recommends that all women should be offered screening for trisomy 21. The most effective screening is with the combined test at 11 + 0 to 13 + 6 weeks' gestation. This includes maternal age, nuchal translucency,  $\beta$ HCG and pregnancy-associated plasma protein A. In the general population this has a detection rate of 92.6% with a false positive rate of 5.2% [208].

For women who present too late for the combined test, the most clinically and cost-effective serum screening test (triple or quadruple test) should be offered between 15 + 0 and 20 + 0 weeks [207]. However, significantly increased levels of  $\beta$ HCG,  $\alpha$ -fetoprotein and lower levels of UE3 (the elements of the 'triple test') have been observed in the HIV-positive population [209–211] while a reduction in  $\beta$ HCG in patients treated with PI-based [212] or with NNRTI-based HAART has been reported. As Down's syndrome is associated with increased  $\beta$ HCG, theoretically, HIV infection *per se* may increase the false-positive rate in women and thus increase the number of invasive tests offered compared with the uninfected population.

Pregnancy-associated plasma protein A and nuchal translucency are unaltered by HIV infection or ART [213] and are thus the preferred screening modality.

**7.1.3 Invasive prenatal diagnostic testing should not be performed until after HIV status of the mother is known and should be ideally deferred until HIV VL has been adequately suppressed. Grading: 1C**

- Limited data suggest amniocentesis is safe in women on HAART. There are minimal data on other forms of prenatal invasive testing.
- All clinicians performing a prenatal invasive test should know the woman's HIV status, and if necessary delay the invasive test until the HIV result is available.
- Where possible, amniocentesis should be deferred until VL is <50 HIV RNA copies/mL.
- The fetal medicine team should discuss management with an HIV physician if the woman is HIV positive and has a detectable VL.

**7.1.4 If not on treatment and the invasive diagnostic test procedure cannot be delayed until viral suppression is complete, it is recommended that women should commence HAART to include raltegravir and be given a single dose of nevirapine 2–4 h before the procedure. Grading: 1D**

The French Pediatric HIV Infection Study Group observed a relative risk of HIV transmission of 1.9 (95% CI 1.3–2.7;  $P=0.003$ ) with 'antenatal procedures' that included amniocentesis, cerclage, laser therapy and amniocopy [214]. This study was conducted between 1985 and 1993 and, of the 1632 mother–infant pairs (overall transmission 19%), only 100 mothers had received zidovudine, mostly for advanced HIV infection.

There are few studies on the safety of invasive testing in the HAART era. A study of 9302 pregnancies in France in 2009 (of which 166 had an amniocentesis) showed that the risk of MTCT in the untreated rose from 16% to 25% in those who had an amniocentesis, in those on zidovudine alone the risk rose from 3.3% to 6.1% and in those on HAART there were no transmissions in 81 mothers who underwent amniocentesis [215]. VL data were not reported, but in other settings suppression of VL reduces transmission.

A further study of nine women in France on HAART in 2008 [216] and 17 women on HAART in Portugal (1996–2009) showed no transmissions, while transmission occurred in one of six women either not diagnosed with HIV prior to amniocentesis, or not treated before the pro-

cedure. There are no studies and few case reports in the HAART era reporting on chorionic villus sampling or cordocentesis [217]. For evidence relating to choice of ART to reduce transmission risk associated with amniocentesis, see Section 5.4 on late presentation.

#### 7.1.5 ECV can be performed in women with HIV. Grading: 2D

- ECV should be offered to women with a VL <50 copies/mL and breech presentation at >36 + 0 weeks in the absence of obstetric contraindications.

There is less obstetric risk to the baby and mother when the fetus is head-down at the time of birth. ECV is a procedure by which the fetus, which is lying bottom first, is manipulated through the mother's abdominal wall to the head-down position. If the fetus is not head down by about 36 weeks of pregnancy, ECV reduces the chance that the fetus will present as breech at the time of birth, and thus reduces the chance of CS. There is no published evidence that helps decision-making regarding ECV in the HIV-positive pregnant woman. For the general maternity population, ECV is recommended [207]. The question of whether ECV might increase the risk of MTCT of infections such as HIV is important and, in the absence of direct evidence, we have reviewed the relevant biological evidence and concluded that maternofetal transfusion, as a consequence of this procedure, is extremely rare, and unlikely to be precipitated by ECV [218]. It is also reassuring that in a randomized trial of fundal pressure to expel the baby during CS, no evidence of maternofetal transfusion was found [219].

## 7.2 Mode of delivery

### 7.2.1 Vaginal delivery is recommended for women on HAART with HIV VL <50 HIV RNA copies/mL plasma at gestational week 36. Grading: 1C

- For women taking HAART, a decision regarding recommended mode of delivery should be made after review of plasma VL results at 36 weeks.
- For women with a plasma VL <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, planned vaginal delivery is recommended.
- For women with a plasma VL of 50–399 HIV RNA copies/mL at 36 weeks, PLCS should be considered, taking into account the actual VL, trajectory of the VL, length of time on treatment, adherence issues, obstetric factors and the woman's views.
- Where the VL is  $\geq$ 400 HIV RNA copies/mL at 36 weeks, PLCS is recommended.

Published cohort data from the UK and other European countries have shown MTCT rates of <0.5% in women with plasma VL <50 HIV RNA copies/mL taking HAART, irre-

spective of mode of delivery [4,23,220,221]. These studies support the practice of recommending planned vaginal delivery for women on HAART with plasma VL <50 HIV RNA copies/mL.

Among HIV-positive women taking HAART in pregnancy and delivering between 2000 and 2006 in the UK and Ireland, there was no difference in MTCT rate whether they delivered by planned CS (0.7%; 17 of 2286) or planned vaginal delivery (0.7%; four of 559; adjusted odds ratio (AOR) 1.24; 95% CI 0.34–4.52]. Median VL on HAART was <50 HIV RNA copies/mL (IQR 50–184). MTCT was 0.1% (three transmissions) in 2117 women on HAART with a delivery VL <50 HIV RNA copies/mL. Two of the three infants were born by elective (pre-labour) CS (0.2%, two of 1135) and one by planned vaginal delivery (0.2%, one of 417); two of the three had evidence of *in utero* transmission (being HIV DNA PCR positive at birth). In this study there were no MTCT data for specific VL thresholds or strata >50 HIV RNA copies/mL plasma, but in the multivariate analysis, controlling for ART, mode of delivery, gestational age and sex, there was a 2.4-fold increased risk of transmission for every log<sub>10</sub> increase in VL, with lack of ART and mode of delivery strongly associated with transmission [4].

Data from the ANRS French Perinatal cohort reported on 5271 women delivering between 1997 and 2004 of whom 48% were on HAART. In women on HAART with a delivery VL of <400 copies/mL there was no significant difference in MTCT rates according to mode of delivery, with three of 747 (0.4%) transmission in the ECS group compared with three of 574 (0.5%) transmissions in the vaginal delivery group ( $P=0.35$ ). The effect of mode of delivery was also analysed for women delivering with a VL >10 000 HIV RNA copies/mL and no significant protective effect of elective CS was seen (OR 1.46; 0.37–5.80). MTCT was low at 0.4% in women delivering with a VL <50 HIV RNA copies/mL but mode of delivery data for this subset were not provided [23].

In contrast, data from the ECS of 5238 women delivering between 1985 and December 2007 showed that in 960 women delivering with a VL <400 HIV RNA copies/mL, elective CS was associated with an 80% decreased risk of MTCT (AOR 0.2; 95% CI 0.05–0.65) adjusting for HAART and prematurity. There were only two transmissions among 599 women delivering with VLs <50 HIV RNA copies/mL (MTCT 0.4%) with one delivering vaginally at <34 weeks and one by ECS at 37 weeks, but further analysis was not possible [221].

A potential explanation for the differing conclusions of the effect of mode of delivery on MTCT in women with delivery plasma VLs <400 HIV RNA copies/mL in these two studies is that the true value of the plasma VL in studies that use assays with a lower limit of detection of 400 copies/mL, is not known. It is conceivable that there may

exist a significant difference in the VL distribution <400 copies/mL between different cohorts, which could account for the contrasting findings. This highlights the fact that it is not possible to infer that MTCT rates from studies using a VL assay with cut-off <400 HIV RNA copies/mL can necessarily be applied to patients with plasma VLs of 50–399 HIV RNA copies/mL using current assays with lower limits of detection of 50 HIV RNA copies/mL or less.

There are no published data on the impact of mode of delivery on MTCT rates for women with plasma VLs between 50 and 399 HIV RNA copies/mL. Data from the NSHPC UK and Ireland cohort 2000–2011 (P Tookey and C French, unpublished data) and from the ECS 2000–2011 (C Thorne, unpublished data) have therefore been used to estimate the risk of MTCT and impact of mode of delivery for women on HAART with plasma VLs between 50 and 399 HIV RNA copies/mL. In the NSHPC, there were seven transmissions among 593 women with documented VL in this range: the transmission rate was 1% for those delivered by PLCS and 2.15% for those who delivered vaginally or by emergency Caesarean ( $P=0.19$ ). In the ECS cohort, of 405 women the transmission rates were 0.37% (95% CI 0.099–2.06) and 1.46% (95% CI 0.18–5.17), respectively. Although neither of these data sets show a significant difference in MTCT these findings suggest that for women with plasma VLs between 50 and 399 HIV RNA copies/mL, the risk of MTCT for women intending vaginal delivery is about 2%, and with PLCS it is 1% or less. We therefore recommend that PLCS should be considered in this group taking into account the actual VL, trajectory of the VL, length of time on treatment, adherence issues, obstetric factors and the woman's views.

Both sets of unpublished data again confirmed a lack of benefit for PLCS when the plasma VL is <50 HIV RNA copies/mL, MTCT being <0.5% irrespective of mode of delivery, supporting the recommendation of planned vaginal delivery for this group.

The UK, French and European cohorts described above all showed a protective effect of PLCS compared to vaginal delivery when applied to the entire cohort. The cohorts do not provide data to determine the viral threshold above which PLCS should definitely be recommended. However, given conflicting data regarding the effect of mode of delivery on MTCT in women with a VL <400 HIV RNA copies/mL, together with data from the UK study showing a 2.4-fold increased risk of transmission for every  $\log_{10}$  increase in VL associated with mode of delivery, the Writing Group felt that until further data are available, PLCS should be recommended for all women with a VL >400 HIV RNA copies/mL.

**7.2.2 In women for whom vaginal delivery has been recommended and labour has commenced, obstetric**

**management should follow the same principles as for the uninfected population. Grading: 1C**

Traditionally, amniotomy, fetal scalp electrodes and blood sampling, instrumental delivery and episiotomy have been avoided in HIV infection because of theoretical transmission risks. Data from the pre-HAART era have been reviewed. These show little or no risk for many of these procedures. Studies from the HAART era have not re-addressed these factors.

The French cohort (1985–1993) provides data on the risk of various obstetric factors in a predominantly untreated, non-breastfeeding population. Procedures, classified as amniocentesis, and other needling procedures, cerclage, laser therapy and amnioscopy were associated with an increased risk of transmission (RR 1.9; 95% CI 1.3–2.7). Fetal skin lesions (RR 1.2; 95% CI 0.7–1.8) and episiotomy tear (RR 1.0; 95% CI 0.7–1.3) were not associated with transmission [214]. In a retrospective study from Spain, in predominantly the pre-HAART era, HIV transmission occurred in 26.3% of infants exposed to fetal scalp monitoring (electrodes or pH sampling or both) compared with 13.6% who had neither (RR 1.94; 95% CI 1.12–3.37) [222]. However, prolonged ROMs was a significant contributor to the risk of transmission associated with this invasive monitoring. In the Swiss cohort neither fetal scalp electrodes (RR 2.0; 95% CI 0.58–6.91) nor pH blood sampling (RR 1.73; 95% CI 0.58–5.15) were confirmed as independent risk factors [223].

In the WITS cohort (1989–1994) artificial ROMs (RR 1.06; 95% CI 0.74–1.53) and exposure to blood during labour (RR 0.7; 95% CI 0.4–1.27) or delivery (RR 1.06; 95% CI 0.74–1.52) were not associated with transmission [37].

Induction has previously been avoided as there were concerns about the duration of ruptured membranes and risk of MTCT but recent evidence (see Section 7.3 Management of spontaneous rupture of membranes) would appear to be reassuring on this point.

Data from the predominantly untreated French cohort (1985–1993) showed no risk with instrumental vaginal delivery (RR 0.8; 95% CI 0.6–1.2) [214]. Data from the smaller Swiss cohort ( $n=494$ , 1986–1996, transmission rate 16.2%) also failed to identify instrumental delivery as a risk factor (RR 1.82; 95% CI 0.81–4.08) despite <20% of the cohort taking any ART for prophylaxis [223].

In the absence of trial data for women with HIV infection who undertake a vaginal operative delivery, evidence to support a benefit of any type of operative vaginal delivery over CS for them or their infants is limited to expert judgement and extrapolation from other data sets and is subject to inherent biases. There are theoretical reasons why low cavity traction forceps may be preferred to a vacuum-assisted delivery (i.e. as it is generally accepted

that they are associated with lower rates of fetal trauma than vacuum-assisted delivery).

In women with a VL <50 HIV RNA copies/mL it is unlikely that the type of instrument used will affect the MTCT and thus the one the operator feels is most appropriate should be used as in the non-HIV population (and following national guidance [224]).

The importance of the use of ART in the PMTCT of HIV is clear and undisputed. Good quality studies to determine the remaining contribution of obstetric events and interventions to MTCT in the setting of a fully suppressed HIV VL have not been performed and are unlikely to be performed in the near future. HIV DNA [225] and HIV RNA [18] in cervicovaginal lavage have been identified as independent transmission risk factors. Large cohort studies from the UK, Ireland and France have concluded there is no significant difference in MTCT in women with an undetectable VL when comparing those who have a planned vaginal delivery and those who have a PLCS. These studies provide some reassurance with regard to concerns raised about possible discordance between plasma and genital tract VL that have been reported in patients with an undetectable VL on HAART [21,226,227]. The clinical significance of this phenomenon is not clear and further research is warranted. Furthermore, there are reassuring results from the limited studies that have examined the effect on MTCT of amniocentesis and length of time of ROMs in women on HAART and in those with a VL <50 HIV RNA copies/mL. An association between MTCT and use of instrumental delivery, amniotomy and episiotomy is not supported by data from the pre-HAART era and there is a lack of data from the HAART era. Therefore, while acknowledging the potential for discordance between the plasma and genital tract VL, the Writing Group felt that there was no compelling evidence to support the continued avoidance of these procedures as well as induction of labour in women on HAART for whom a vaginal delivery had been recommended based on VL.

The data regarding fetal blood sampling and use of scalp electrodes also originate from the pre-HAART era and have yielded conflicting results. The Writing Group acknowledges a lack of data from the HAART era, but concluded that it is unlikely that use of fetal scalp electrodes or fetal blood sampling confers increased risk of transmission in a woman with an undetectable VL although this cannot be proven from the current evidence.

Electronic fetal monitoring should be performed according to national guidelines [224]. HIV infection *per se* is not an indication for continuous fetal monitoring, as there is no increased risk of intrapartum hypoxia or sepsis.

If the woman has no other risk factors, she can be managed by midwives either in a midwifery-led unit or at

home. She will need to continue with her HAART through labour and adequate provision needs to be made for examination and testing of the newborn and dispensing of medication to the newborn in a timely fashion.

### 7.2.3 VBAC should be offered to women with a VL <50 HIV RNA copies/mL. Grading: 1D

In the absence of randomized trial data for women with HIV infection who undertake VBAC, evidence to support benefit of VBAC and vaginal birth over elective CS is limited to expert judgement that is subject to inherent biases.

The probability of a successful vaginal delivery remains dependent on current and past obstetric factors. In general, provided that the woman is being cared for in a consultant-led maternity unit and the labour properly monitored with rapid recourse to CS in the face of any difficulty, the outcome of trial of labour for mother and neonate is good, even if scar dehiscence occurs [228]. In the non-HIV population, 70% of VBACs manage a vaginal delivery with a uterine rupture rate of about 0.3%.

Therefore, where a vaginal birth has been recommended based on ART and VL, maternal management of the delivery, including a decision regarding VBAC, should be as for an uninfected woman.

### 7.2.4 Delivery by PLCS is recommended for women taking zidovudine monotherapy irrespective of plasma VL at the time of delivery (Grading: 1A) and for women with VL >400 HIV RNA copies/mL regardless of ART (see Recommendation 7.2.1) with the exception of elite controllers (see Section 5.5: Elite controllers). Grading: 1D

Zidovudine monotherapy with a planned pre-labour pre-ROMs CS is a proven option for women not requiring treatment for themselves, with a pretreatment VL <10 000 HIV RNA copies/mL plasma.

Observational studies conducted in the early 1990s, before the use of HAART, found a reduction in MTCT with PLCS. In 1999, a large international meta-analysis ( $n=8533$ ) [229] and an RCT of mode of delivery in Europe ( $n=436$ ) [131] both demonstrated a protective effect of PLCS, with reductions in MTCT of 50% and 70% respectively. In the latter study, the risk of transmission in women who were taking zidovudine monotherapy and who were delivered by PLCS was <1%. Cohort data from the UK and Ireland between 2000 and 2006 have shown that the MTCT rate in women on zidovudine monotherapy combined with PLCS was 0% (0 of 467 patients; 95% upper CI 0.8%) [4]. This was not significantly different from the 0.7% transmission rate with HAART plus PLCS (17 of 2337 patients; 95% CI 0.4–1.2%) or the 0.7% rate with HAART plus planned vaginal delivery (four of 565 patients; 95% CI 0.2–1.8%). These findings support the option of zidovudine monotherapy in women not

requiring treatment for themselves with low VLs who either have an obstetric indication for, or are prepared to be delivered by, PLCS.

There is no evidence that women on HAART with a low VL have increased surgical morbidity compared with the HIV-negative population

A Cochrane review evaluating the risk of postpartum morbidity according to mode of delivery included five studies: the European randomized mode of delivery trial and five observational studies from North America and Europe [230]. This review found a higher incidence of minor postpartum morbidity, including fever and anaemia requiring transfusion, among HIV-positive women delivered by CS compared with those who delivered vaginally. Low CD4 cell count and co-morbidities such as diabetes were independent risk factors for postpartum morbidity. This review included women who were not on HAART.

More recent cohort data from Europe [220,231] and from case-controlled studies in the USA [232] and UK [233] involving women on HAART with undetectable VLs have demonstrated very low rates of maternal morbidity, irrespective of mode of delivery.

**7.2.5 Where the indication for PLCS is the prevention of MTCT, PLCS should be undertaken at between 38 and 39 weeks' gestation. Grading: 1C**

Where PLCS is undertaken only for obstetric indications and plasma VL is <50 copies/mL, the usual obstetric considerations apply and timing will usually be at between 39 and 40 weeks.

The timing of PLCS is a balance between the risks of transient tachypnoea of the newborn (TTN) and the likelihood of labour supervening before the scheduled CS [234]. Where the indication for PLCS is PMTCT, the earlier timing reflects the importance of avoiding the onset of labour. In these cases, the risk of MTCT associated with labour and ROMs is considered to outweigh the risk of TTN. Where PLCS is undertaken only for obstetric indications, the optimal timing of PLCS is between 39 and 40 weeks [228]. The risk of TTN at this gestation is approximately 1 in 300 and this risk doubles for every week earlier that delivery occurs. The administration of steroids to the mother to reduce the risk of TTN should be considered for PLCS prior to 38 completed weeks.

### 7.3 Management of spontaneous rupture of membranes

**7.3.1 In all cases of term pre-labour spontaneous ROM, delivery should be expedited. Grading: 1C**

**7.3.2 If maternal HIV VL is <50 HIV RNA copies/mL immediate induction of labour is recommended, with a**

**low threshold for treatment of intrapartum pyrexia. Grading: 1C**

**7.3.3 For women with a last measured plasma VL 50–999 HIV RNA copies/mL, immediate CS should be considered, taking into account the actual VL, the trajectory of the VL, length of time on treatment, adherence issues, obstetric factors and the woman's views. Grading: 1C**

**7.3.4 If maternal HIV VL is  $\geq 1000$  RNA copies/mL plasma, immediate CS is recommended. Grading: 1C**

In the pre-HAART era, several studies [37,39,235] suggested that prolonged duration of ruptured membranes, usually analysed as >4 h, in women who were either untreated or if treated were largely receiving zidovudine monotherapy, resulted in a significantly increased risk of MTCT. A widely quoted meta-analysis (not reporting VL data) subsequently showed a 2% increase in relative risk of transmission per hour of membrane rupture (AOR 1.02). Transmission increased from 12% with <1 h membrane rupture to 19% with >12 h of membrane rupture [236].

There are few published studies from the HAART era. A study from Spain of 500 HIV-positive women examined the effect of various obstetric risk factors on MTCT rates in women on no treatment, monotherapy or dual therapy, and finally in those on HAART. ROMs >6 h compared to <6 h was only significantly associated with MTCT in the group of women on no treatment (26.6% vs. 11.9%;  $P \leq 0.01$ ). Corresponding transmission rates for the mono-dual therapy group were 14.3% vs. 7.1% ( $P = \text{NS}$ ) and in the women on HAART (0.8% vs. 0.0%;  $P = \text{NS}$ ) [237].

The NSHPC study of HIV-positive women in the UK and Ireland reported on 1050 women where length of time of ROM was recorded from 2007. In 618 women delivering with a VL <50 HIV RNA copies/mL when comparing those with ROM  $\leq 4$  h to >4 h the MTCT rate was 0.3% (one of 326) and 0.0% (none of 292), respectively ( $P = 0.34$ ). Restricting the analysis to the 386 women with a VL <50 copies/mL who delivered vaginally did not alter this conclusion [238]. Therefore, for women on HAART who rupture their membranes at term with a VL <50 HIV RNA copies/mL and who do not have an obstetric contraindication to vaginal delivery, a CS is not recommended.

As both acute and chronic chorioamnionitis have been associated with perinatal transmission [39,239–241], albeit from studies largely performed in the pre-HAART era, it is recommended that labour should be expedited for all women with ROM at term. Hence, women with ROM at term with a VL <50 HIV RNA copies/mL should have immediate induction with a low threshold for the treatment of intrapartum pyrexia. The NICE induction of labour

guidelines [242] and NICE intrapartum guidelines [224] should be followed with regard to use of antibiotics and mode of induction.

NSHPC data for the effect of ROM greater or less than 4 h for women with a VL > 50 HIV RNA copies/mL are more difficult to interpret as the numbers are currently small. In women with VL 50–999 HIV RNA copies/mL there were two transmissions with ROM > 4 h (two of 51) and none in the women with ROM ≤ 4 h (none of 43). The two transmitters both had emergency CSs but the timing of this is not known. Although not statistically significant ( $P = 0.19$ ), these limited unpublished data suggest a possible trend towards greater transmission risk with ROMs > 4 h for those with VL ≥ 50 HIV RNA copies/mL, and until further data are available, it is the recommendation of the Writing Group that CS should be considered for women with a VL of 50–999 HIV RNA copies/mL at term. Again, if CS is not undertaken, delivery should be expedited, as above.

Data from the NSHPC for women with a VL > 1000 HIV RNA copies/mL are sparse at present, with one of 14 (7.1%) transmitting with ROM ≤ 4 h compared to three of 15 (20%) with ROM > 4 h. A single-centre study from Miami of 707 women on ART showed ROM > 4 h to be associated with an increased risk of MTCT if the VL was > 1000 HIV RNA copies/mL. There was no association at < 1000 HIV RNA copies/mL but it is not possible to determine the number of women with a VL > 50 and < 1000 HIV RNA copies/mL in this group. Until further data are available, an urgent (category 2) CS is recommended where the VL is > 1000 HIV RNA copies/mL regardless of treatment [243].

In women who have a detectable VL it may be possible to optimize their HAART regimen to reduce the risk of MTCT (See Recommendation 4.2.6).

**7.3.5 The management of PPRoMs at ≥ 34 weeks is the same as term ROM (see Section 7.3 Management of spontaneous rupture of membranes) except women who are 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines. Grading: 1C**

**7.3.6 When PPRoM occurs at < 34 weeks: Grading: 1C**

- Intramuscular steroids should be administered in accordance with national guidelines.
- Virological control should be optimized.
- There should be multidisciplinary discussion about the timing of delivery.

There are no data to inform the optimum management of preterm labour or early preterm pre-labour ROMs. Decisions regarding the optimum management of early preterm ROM require the assessment of a number of factors, including the exact gestation, facilities available, maternal VL and presence of other co-morbidities such as infection

and pre-eclampsia. Corticosteroids to improve fetal lung maturation should be given as per the Royal College of Obstetricians and Gynaecologists guidelines [244] and (if delivery is to be delayed) oral erythromycin [245]. Decisions regarding timing of delivery should be made in consultation with the full MDT, including the neonatal unit.

There is no evidence that steroids for fetal lung maturation (with the associated 24-h delay in induction) are of overall benefit at 34–37 weeks' gestation in women with ROMs, thus delay for the optimization of fetal lung maturity is not recommended. For this reason, and to minimize the risk of developing chorioamnionitis, induction is recommended from 34 weeks' gestation in women with ROMs who are not in labour.

If the maternal VL is not fully suppressed, consideration should be given to the options available to optimize therapy. An additional concern is that the early preterm infant may be unable to tolerate oral therapy and therefore loading the infant through the transplacental route with maternal therapy is recommended (see Section 5: Use of antiretroviral therapy in pregnancy). There is most experience with maternal oral nevirapine 200 mg stat > 2 h before delivery, but double-dose tenofovir and standard-dose raltegravir can also be considered.

#### 7.4 Use of intrapartum intravenous infusion of zidovudine

**7.4.1 Intrapartum intravenous zidovudine infusion is recommended in the following circumstances:**

- For women with a VL > 10 000 HIV RNA copies/mL plasma who present in labour, or with ROMs or who are admitted for planned CS. Grading: 1C
- For untreated women presenting in labour or with ROMs in whom the current VL is not known. Grading: 1C
- In women on zidovudine monotherapy undergoing a PLCS intravenous zidovudine can be considered. Continued oral dosing is a reasonable alternative. Grading: 1B

There are no data to support the use of intrapartum intravenous zidovudine infusion in women on HAART with a VL < 10 000 HIV RNA copies/mL plasma.

The use of intravenous zidovudine is suggested for women taking zidovudine monotherapy as per Recommendation 5.3.4. The use of intravenous zidovudine for women on HAART with a VL between 50 and 10 000 HIV RNA copies/mL can be considered regardless of mode of delivery. However, continued oral dosing of their current regimen is a reasonable alternative.

The effectiveness of zidovudine monotherapy in preventing MTCT was first demonstrated in the ACTG 076 RCT of non-breastfeeding women in which zidovudine was initiated orally before the third trimester, given intravenously during labour and delivery, and orally to the neonate for the first 6 weeks of life, reducing MTCT by 67% [61]. Intravenous zidovudine has therefore been included in the management of all women treated with zidovudine monotherapy. However, the data on the contribution of intravenous zidovudine are poor. In a prospective study of all women prescribed zidovudine monotherapy during pregnancy before the publication of the ACTG 076 findings (1988–1994) in which the 8.8% transmission rate among women with CD4 cell counts  $>200$  cells/ $\mu\text{L}$  is similar to that of the zidovudine monotherapy arm of ACTG 076 (8.3%), intrapartum intravenous zidovudine was not associated with lower rates of transmission [246]. One rationale for intrapartum intravenous zidovudine in ACTG 076 was that labour would be associated with poor absorption of oral therapy. While not strictly comparable, the well-recognized rapid absorption of single-dose nevirapine during labour suggests that the impact of labour on absorption may be overestimated. Pharmacokinetic data from an RCT of oral zidovudine monotherapy *vs.* placebo indicate that adequate (therapeutic) zidovudine concentrations are achieved in cord blood with oral dosing. Although the concentrations are lower than have been reported with intravenous infusion, transmission was not associated with zidovudine cord blood concentration [247].

Intravenous zidovudine has historically been considered for women whose plasma VL has not been completely suppressed at the time of delivery. There is no evidence that the intravenous administration of zidovudine alters the rate of placental transfer but higher maternal plasma levels will be reflected in the cord blood concentrations.

Intravenous zidovudine (as part of an intervention package; see Section 5: Use of antiretroviral therapy in

pregnancy) has also been recommended for women who present in labour, having not received ART. However, data from the New York State HIV diagnostic service (1995–1997) suggest that intrapartum intravenous zidovudine alone does not significantly reduce transmission (10%; 95% CI 3.3–21.8%), as, provided neonatal prophylaxis is commenced within 48 h of delivery (this being the only intervention accessed), the latter has similar efficacy (9.3%; 95% CI 4.1–17.5%) [138].

From the French data there is no evidence that intrapartum intravenous zidovudine further reduces the risk of MTCT in women on HAART unless maternal HIV VL is  $>10\,000$  copies/mL [23]. However, individual circumstances vary, and intravenous intrapartum zidovudine may be considered as one of a number of maternal intrapartum ART options for women with VLs  $>50$  HIV RNA copies/mL who present in labour, or with ROMs or who are admitted for planned CS provided this does not delay other interventions.

The evidence for the efficacy of intravenous zidovudine in the HAART era is generally poor. However, data from the French cohort support this practice for women on HAART with a VL  $>10\,000$  HIV RNA copies/mL. One could extrapolate that it may be of potential benefit in women presenting untreated in labour with an unknown current VL although this is not supported by the New York State data. Therefore in this setting, the Writing Group recommends the immediate administration of oral agents (see Section 5: Use of antiretroviral therapy in pregnancy) with intravenous zidovudine as an option.

In women on HAART with a VL between 50 and  $<10\,000$  HIV RNA copies/mL, intravenous zidovudine can be considered. Continued oral dosing is a reasonable alternative.

Intravenous zidovudine is not recommended for women taking HAART who have an undetectable VL at the time of labour or CS. Oral HAART should be taken at the normal dosing interval.



## 8.0 Neonatal management

### 8.1 Infant post-exposure prophylaxis

(See Table 1 for quick reference guides to infant ARV regimens and infant dosing.)

**8.1.1 Zidovudine monotherapy is recommended if maternal VL is <50 HIV RNA copies/mL at 36 weeks' gestation or thereafter before delivery (or mother delivered by PLCS while on zidovudine monotherapy). Grading: 1C**

For women with fully suppressed HIV and a history of zidovudine resistance see discussion below.

Zidovudine monotherapy for the infant has been part of the PMTCT strategy since publication of the ACTG 076 results [61]. The relative contributions of the antenatal, peripartum and infant components have been difficult to quantify. In ACTG 076 neonatal zidovudine 2 mg/kg every 4 h (five doses) was given for 6 weeks.

Monotherapy for the infant is appropriate when there is a very low risk of HIV transmission. This occurs when a mother on combination therapy delivers with a VL <50 HIV RNA copies/mL. The neonate should receive single-drug therapy for 4 weeks; this is practically easier for the family and reduces the risk of adverse events. With many years of experience, twice-daily zidovudine monotherapy is the neonatal treatment of choice, whatever the maternal ART combination.

For infants born to mothers on fully suppressive ART, zidovudine monotherapy PEP remains reasonable even where the mother has a previous history of zidovudine exposure with resistance (thymidine-associated mutations). On HAART, the risk of transmission in the mother with fully suppressed viral replication is extremely low (about 0.1%), and although history of zidovudine resistance in maternal virus and infant PEP regimen has not been dissected, the frequency of transmission of zidovudine-resistant virus is concomitantly very low. Data from the era when only maternal zidovudine monotherapy was available indicate preferential transmission of wild-type over zidovudine-resistant virus when a mixed population of virions are present [248]. In the Swiss cohort, none of six infants born to mothers harbouring zidovudine-resistant HIV (based on codon 215 analysis only) became infected [249]. In a subset of participants of the ACTG 076 study, the prevalence of low-level zidovudine resistance was 4.3% (mutation at codon 70) and no significant increase in the risk of transmission was observed after adjusting for VL at delivery (OR 4.8; with wide 95% CI 0.2–131;  $P = 0.35$ ) [250]. High-level resistance was not reported and the

median CD4 cell count in the women was 540 cells/ $\mu$ L. In retrospective cohort studies from France [251] and the USA [252], 20% and 8.3%, respectively, of HIV-positive newborns had zidovudine-resistance mutations after maternal zidovudine prophylaxis. In the WITS, lower CD4 cell count and higher HIV VL at delivery were associated with increased risk of transmission while in the multivariate analysis, the presence of at least one mutation associated with zidovudine resistance was also associated with an increased risk of transmission (OR 5.15; 95% CI 1.4–18.97) [253]. With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred, an advantage of zidovudine. Important in this age group, where therapeutic options are more limited than in older children and adults, should transmission occur multidrug resistance is avoided. However, some clinicians prefer to choose another ARV, with no history of maternal resistance, for infant post-exposure monotherapy. The established alternatives, nevirapine and lamivudine, have potent ARV effect but a low (single-point mutation) barrier to resistance. The dosing and safety issues with newer therapies, such as lopinavir/ritonavir, are outlined below. It is therefore suggested that neonatal zidovudine monotherapy remains a reasonable approach for infants born to mothers with a HIV VL <50 HIV RNA copies/mL plasma, even if there is a history of zidovudine resistance. Further investigation of the national cohort data to address this question is under way.

Where a low transmission-risk mother (see Section 5: Use of antiretroviral therapy in pregnancy) chooses zidovudine monotherapy plus PLCS, the infant should receive zidovudine monotherapy [4].

There are two situations where triple combination PEP for neonates is advised:

- (i) Post-delivery infant-only prophylaxis: mother found to be HIV positive after delivery, which is only effective if given within 48–72 h of birth.
- (ii) Detectable maternal viraemia (>50 HIV RNA copies/mL) at delivery, mother may be on HAART or not:
  - delivery before complete viral suppression is achieved (e.g. starting HAART late or delivery premature);
  - viral rebound with or without resistance, with or without poor adherence;
  - unplanned delivery (e.g. premature delivery before starting ART or late presentation when maternal HIV parameters may be unknown).

Table 1 Infant doses of ARV therapy (all treatment for 4 weeks except nevirapine)

Drug	Dose	Mono/combo	Study	Comments/side effects
Zidovudine (ZDV, AZT)	<b>Oral</b>	Combo (+ lamivudine)	Moodley 2001 [330] Boucher 1993 [260]	Anaemia, neutropenia – more common with combination therapy in mother and infant. In French study of ZDV + lamivudine a small proportion of infants required either blood transfusions or early stop of therapy. Transient lactic acidemia has been observed in HIV-uninfected infants exposed to HAART <i>in utero</i> and/or ZDV neonatally [332]
	<i>Term</i> (>34 weeks): 4 mg/kg twice daily	Mono	Capparelli 2003 [275]	
	<i>Premature</i> (30–34 weeks): 2 mg/kg twice daily for 2 weeks then 2 mg/kg three times a day for 2 weeks	Mono Mono	Boucher 1993 [260] Frasca 2009 [331]	
	<i>Premature</i> (<30 weeks): 2 mg/kg twice daily for 4 weeks	Mono		
	<b>Intravenous</b>			
	<i>Term</i> : 1.5 mg/kg four times a day <i>Prem</i> : 1.5 mg/kg twice daily			
Lamivudine (3TC)	2 mg/kg twice daily	Combo (all with ZDV)	Mandelbrot 2001 [259] Moodley 2003 [256]	Anaemia, neutropenia (but less common than with ZDV). More common with combination therapy in mother and infant.
		Combo (+ nelfinavir)	Durand-Gasselín 2008 [333] Hirt 2011 [139] Mirochnick 2011 [261] Jullien 2005 [264]	
Abacavir (ABC)	2 mg/kg twice daily	Mono		Hypersensitivity reaction has not been noted in infants (only small numbers treated)
Didanosine (ddl)	60 mg/m <sup>2</sup> twice daily	Mono	Wang 1999 [108]	Much better absorbed on an empty stomach. Difficult to separate dosing from feeding. May cause gastrointestinal symptoms. Variable absorption in neonates
Emtricitabine (FTC)	2 mg/kg as a single dose (with 13 mg/kg of TDF) within 12 h after birth	Combo (with TDF)	Hirt 2011 [334]	Mothers received two tablets of TDF/FTC at onset of labour and then one tablet daily for 7 days postpartum. This dose resulted in high FTC levels in neonates. Can cause neutropenia, anaemia
	1 mg/kg as a single dose immediately after birth.	Combo (with ZDV and NVP)	Hirt 2009 [263]	Dose based on pharmacokinetic modelling study
Tenofovir (TDF)	13 mg/kg as a single dose within 12 h of life.	Combo (with NVP, FTC and ZDV)	Hirt 2011 [139]	Single dose administered to neonate after the mothers had received two tablets of TDF/FTC at delivery. Associated with renal dysfunction: monitor renal function in neonates.
	On the first day of life, neonates received a single dose of NVP syrup (2 mg/kg), within the 12 h after birth a single dose of TDF oral solution (13 mg/kg) and a single dose of FTC oral solution (2 mg/kg), and for 7 days ZDV syrup (4 mg/kg every 12 h).			
Nevirapine (NVP, NEV)	Daily dosing regimen: 2 mg/kg once a day for 1st week then 4 mg/kg once a day for 2nd week then stop. Use 4 mg/kg once a day for 2 weeks if mother has received more than 3 days NVP.	Mono Mono	Shetty 2004 [335]	Daily dosing regimen from HIVNET 023 (breastfeeding prophylaxis study)
	Single-dose regimen: one 2 mg/kg dose 48–72 h from birth 2 mg/kg as a single dose on the first day of life plus ZDV 4 mg/kg every 12 h for 7 days.	Combo (with ZDV)	Hirt 2009 [263]	Mothers received ZDV 300 mg twice a day to the delivery date, one tablet of NVP (200 mg) and two tablets of TDF/FTC at start of labour, and one tablet of TDF/FTC daily for 7 days postpartum.
Nelfinavir (NEL/NFV)	50–75 mg/kg twice daily	Combo (with ZDV+ 3TC)	NICHD/HPTN 040/P1043 Mirochnick 2011 [261]	Nelfinavir 250 mg tablets can be dispersed in water.

Table 1 (Contd.)

Drug	Dose	Mono/combo	Study	Comments/side effects
Lopinavir/ ritonavir	300 mg/m <sup>2</sup> twice daily 1–2 kg: 40 mg every 12 h 2–6 kg: 80 mg every 12 h	Combo	Jullien 2006 [336] Verweel 2007 [337] Chadwick 2008 [268] Chadwick 2011 [269] Urien 2011 [271]	Some pharmacokinetic studies have suggested that a twice-daily dose may give low levels in neonates. Frequent dose adjustment for weight gain is advisable. Adrenal dysfunction reported in newborns. Monitor electrolytes. Avoid in premature babies [272]. FDA recommendation (August 2011): the use of Kaletra oral solution should be avoided in premature babies until 14 days after their due date, or in full-term babies <14 days of age unless a healthcare professional believes that the benefit of using Kaletra oral solution to treat HIV infection immediately after birth outweighs the potential risks. In such cases, FDA strongly recommends monitoring for increases in serum osmolality, serum creatinine and other signs of toxicity.
Co-trimoxazole	900 mg/m <sup>2</sup> once daily Mon/Wed/Fri <6 months: 120 mg once daily Mon/Wed/Fri 6–12 months: 240 mg once daily Mon/Wed/Fri	PCP prophylaxis	Simmonds 1995 [338]	May cause rash, bone marrow suppression. Give to infants aged over 4 weeks born to mothers with a higher risk of transmission

### 8.1.2 Infants <72 h old, born to untreated HIV-positive mothers, should immediately initiate three-drug ART for 4 weeks. Grading: 1C

There is one large RCT of combination therapy in neonates born to mothers who did not receive any ART before delivery ( $n = 1684$ , in Brazil, Argentina, South Africa and the USA) [254]. Infants were randomly allocated at <48 h of age to: 6 weeks of zidovudine monotherapy; or 6 weeks of zidovudine with three doses of nevirapine in the first week of life; or 6 weeks of zidovudine, with nelfinavir and lamivudine for 2 weeks. Overall, in this high-risk group, the HIV transmission rate was 8.5%, and in multivariate analysis, only ART arm and maternal VL were significantly associated with transmission. For infants uninfected at birth, transmission was twofold higher in the zidovudine-alone arm compared to the multiple ART arms ( $P = 0.034$ ). There was no significant difference in transmission rates between the two multiple ARV arms and neonatal neutropenia was significantly higher in the three-drug arm.

In a randomized African study, babies born to mothers presenting at delivery received single-dose nevirapine or single-dose nevirapine and 1 week of zidovudine. Of those HIV negative at birth, 34 (7.7%) who received nevirapine plus zidovudine and 51 (12.1%) who received nevirapine alone were infected ( $P = 0.03$ ): a protective efficacy of 36% for the dual combination [255]. However, in two other

randomized African studies where the mothers received short-course ART, for infants uninfected at birth there was no significant difference in transmission rate at 6 weeks for dual *vs.* monotherapy short-course regimens to the infant: zidovudine plus lamivudine *vs.* nevirapine [256]; or zidovudine plus nevirapine *vs.* nevirapine [257].

PEP for the infant of an untreated mother should be given as soon as possible after delivery. There are no studies of time of initiation of combination PEP, but in a US cohort study a significantly reduced risk of transmission was only observed in infants commenced on zidovudine when this was started within 48 h of birth [138]. For this reason, infant PEP should only be started where a mother is found to be HIV positive after delivery if it is within 48–72 h of birth.

NSHPC data from the UK and Ireland 2001–2008 demonstrate how the clinical practice of combination PEP in neonates has increased over time [258]. In total, 99% of 8205 infants received any PEP, and for the 86% with data on type of PEP, 3% received dual and 11% triple. The use of triple PEP increased significantly over this period, from 43% to 71% for infants born to untreated women, and from 13% to 32% where mothers were viraemic despite HAART. HIV infection status was known for 89% of infants with information on PEP; 14.7% of infants who received no PEP were infected (five of 34, all born vaginally to untreated

mothers), compared to 1% of those who received any PEP (72 of 7286). Among infants born vaginally to untreated mothers, those who received PEP were significantly less likely to be infected than those who did not [8.5% (four of 47) *vs.* 45.5% (five of 11),  $P=0.002$ ]. However, in this cohort study, because of the overall low rate of transmission and selective use of triple PEP for infants at higher risk of HIV, it was not possible to explore the association between type of PEP and infection status.

**8.1.3. Three-drug infant therapy is recommended for all circumstances other than Recommendation 8.1.1 where maternal VL at 36 weeks' gestation/delivery is not <50 HIV RNA copies/mL. Grading: 2C**

Delivery with a detectable maternal VL (>50 HIV RNA copies/mL) is not uncommon. The virus may never have been suppressed due to: premature delivery; poor adherence; very high starting maternal VL (>100 000 HIV RNA copies/mL); or late commencement of HAART; or there may have been viral rebound during gestation due to poor adherence or development of resistance.

There are no randomized trials of combination therapy PEP for infants where mothers are receiving HAART. In a French study, transmission rates with dual therapy (zidovudine and lamivudine) to both the neonate and mother (1.6%) were lower than zidovudine monotherapy reported in historical controls (6.8%; OR 0.22; 95% CI 0.2–0.5) [259].

The strength of recommendation is proportionate to the estimated risk of transmission. Thus, benefit of additional neonatal therapy is anticipated at higher VLs, in circumstances where resistance is suspected or confirmed and where VL is increasing despite treatment. As with the recommendations regarding PLCS at VLs <400 HIV RNA copies/mL, favourable trends can be considered in the risk assessment. Despite the lack of evidence for its use, NSHPC data indicate a trend towards increasing use of triple-neonatal PEP.

When an infant has been started on triple-combination PEP because the maternal VL is >50 HIV RNA copies/mL at 36 weeks and subsequently a delivery maternal VL is <50 HIV RNA copies/mL, then it is reasonable to simplify the infant PEP to monotherapy.

#### *Choice of triple combination post-exposure prophylaxis for neonates*

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 cARTs to which neonates are being exposed *in utero* continues to increase. Neonatal drug metabolism is generally slower than that of older infants or children and premature neonates have even less efficient metabolism. Owing to a lack of neonatal pharmacokinetic and efficacy studies and

suitable formulations, ART dosing regimens remain restricted to a small proportion of the ARV drugs currently manufactured (Table 1). Small pharmacokinetic studies have been performed (zidovudine [260], lamivudine [261,262], tenofovir [139], emtricitabine [263]) and dosing regimens are available for most of the nucleoside analogues and for abacavir from age 1 month [264], while limited study of didanosine in neonates suggests that the pharmacokinetics are highly variable [108]. The pharmacokinetics of nevirapine in neonates has been described in more detail [72,74,265–267]. Pharmacokinetic-supported dosing is available for the PIs nelfinavir [261] and ritonavir-boosted lopinavir (based on HIV-1 infected infants initiating therapy in the first 6 weeks of life) [268–270] and a study that included some infants treated from birth [271]. However, evidence of adrenal suppression has been documented in some neonates treated with lopinavir/ritonavir, particularly when preterm [272], in addition to case reports of cardiac, renal and neurological toxicity, especially in, but not restricted to, premature infants, and including one death during PEP with lopinavir/ritonavir [273]. No effects have been observed with maternal lopinavir/ritonavir in the absence of neonatal dosing. It remains unclear whether these effects are related to lopinavir/ritonavir specifically or could be seen with other ritonavir-boosted PIs. The Writing Group therefore recommends that this PI should be avoided in routine infant PEP and should only be prescribed to preterm neonates in exceptional circumstances. Its use should only be considered after seeking expert advice and where there is multi-drug resistance. Close metabolic monitoring in hospital should be undertaken. Nelfinavir, the only other PI with an infant-dosing regimen, will be withdrawn in the near future and will no longer be available for prescription in the UK or elsewhere in Europe. See the CHIVA website for dosing updates (<http://www.chiva.org.uk>).

In contrast to the PIs, nevirapine efficiently crosses the placenta (see below) and is well absorbed by the neonate [274]. Neonatal metabolism of nevirapine is induced where there has been antenatal *in utero* exposure [72,74]; if this drug is given to the neonate when the mother has taken it for 3 or more days, the full dose of 4 mg/kg per day should be started at birth, rather than the induction dose of 2 mg/kg per day (Table 1). Owing to its long half-life, nevirapine should be stopped 2 weeks before co-prescribed ARV drugs with shorter half-lives to reduce the risk of nevirapine monotherapy exposure and the development of NNRTI resistance should transmission have occurred.

The only licensed ART available for intravenous use in sick and/or premature neonates, unable to take oral medication, is zidovudine [260,275]. Reduced oral and intravenous dosing schedules for premature infants are available

(Table 1). The fusion inhibitor, enfuvirtide does not cross the placenta. Although intravenous enfuvirtide (T20) has been given to a small number of infants born to mothers with multidrug resistant HIV, no formal neonatal pharmacokinetic studies for enfuvirtide have been conducted to date. The dose used has been adapted from a paediatric subcutaneous treatment study [276] and an adult intravenous dosing study [277].

For infants born to ART-naïve women or where drug resistance is unlikely, zidovudine, lamivudine and nevirapine is the well-tolerated combination therapy regimen with most experience (see Table 1 for dosing). Infants born to non-naïve mothers, or mothers known to have ART resistance, may require other combinations (seek expert advice).

Resistance testing should be carried out in the mother. Where this is not available, choice of treatment has to be made based on history of drug exposure and any previous resistance data in the mother. If the infant is infected, then the first HIV-positive sample should also be tested for the resistance pattern of the transmitted virus.

#### *Intravenous antiretroviral therapy in the neonate.*

The very premature neonate is at risk of necrotizing enterocolitis if enteral feeding is commenced too soon or increased too rapidly. It is not known whether very early enteral administration of ART can exacerbate this risk. In a large French case-controlled study of cases of necrotizing enterocolitis, being an infant of a mother with HIV was associated with an increased risk of necrotizing enterocolitis (OR 6.63; 95% CI 1.26–34.8;  $P=0.025$ ), although the numbers were too small to ascertain the effect of maternal and/or infant ART [278]. Premature infants should be commenced on intravenous zidovudine, but once enteral feeding is established, zidovudine may be given enterally and the premature dosing regimen should be used (Table 1). Enfuvirtide is the only other ARV administered parenterally, usually subcutaneously, in adults and children. An unlicensed intravenous dosing regimen has been adapted for use as part of cART in neonates at risk of multidrug resistant HIV (seek expert advice) [277].

**8.1.4 Neonatal PEP should be commenced very soon after birth, certainly within 4 h. Grading: 1C**

There are no clear data on how late infant PEP can be initiated and still have an effect, but all effective studies of infant PEP have started treatment early and animal data show a clear relationship between time of initiation and effectiveness [279–281]. Immediate administration of PEP is especially important where the mother has not received any ART.

**8.1.5 Neonatal PEP should be given for 4 weeks. Grading: 1C**

In the original ACTG 076 study, zidovudine was administered for 6 weeks after birth and this subsequently became standard of care [61]. Simplification to zidovudine twice daily for 4 weeks has become common practice in the UK and data from the NSHPC suggest that regimens adopting this strategy remain highly effective [4]. Recent cohort studies from Ireland [282] and Spain [283] have demonstrated efficacy and reduced haematological side effects with 4 vs. 6 weeks of neonatal zidovudine. In a Thai study, where a short course of 3 days of neonatal monotherapy zidovudine PEP was compared with 6 weeks, there was no significantly increased HIV transmission where the mother received zidovudine monotherapy from 28 weeks' gestation [284]. Whether 4 weeks of zidovudine is necessary for infants born to mothers on HAART with fully suppressed HIV is not known, shorter courses may be considered in the future.

### 8.2 *Pneumocystis pneumonia prophylaxis*

**8.2.1 PCP prophylaxis, with co-trimoxazole, should be initiated from age 4 weeks in:**

- All HIV-positive infants. Grading: 1C
- In infants with an initial positive HIV DNA/RNA test result (and continued until HIV infection has been excluded). Grading: 1C
- Infants whose mother's VL at 36 weeks' gestational age or at delivery is >1000 HIV RNA copies/mL despite HAART or unknown (and continued until HIV infection has been excluded). Grading: 2D

Primary PCP in infants with HIV remains a disease with a high mortality and morbidity. 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 viraemic mothers at high risk of transmission. The infant's birth HIV molecular diagnostic test (see below) and maternal delivery VL should be reviewed before the infant is aged 3 weeks. If the HIV molecular diagnostic test taken in the first 24 h is positive, the infant should be reviewed before 4 weeks for an early repeat test and to be started on co-trimoxazole prophylaxis, which should be continued if the HIV infection is confirmed, and stopped if infection is excluded (see section on diagnosis below). Infants with a first positive HIV molecular diagnostic test at age 6 or 12 weeks should be started on co-trimoxazole prophylaxis until HIV infection is confirmed or excluded (see Table 1 for dose).

If the birth HIV diagnostic test is negative, and the maternal delivery VL is <1000 HIV RNA copies/mL, there is

no need to start co-trimoxazole prophylaxis and the baby can be seen routinely for a second HIV diagnostic test at age 6 weeks.

Co-trimoxazole prophylaxis against PCP is effective, but there are no data on when to initiate it in infants of indeterminate HIV status being followed up after *in utero* exposure to HIV. A maternal VL of 1000 HIV RNA copies/mL is an arbitrary cut-off to define infants at higher risk of transmission, in whom it is recommended to start prophylaxis until lack of transmission has been established.

### 8.3 Immunization

**8.3.1 Infants born to HIV-positive mothers should follow the routine national primary immunization schedule. Grading: 1D**

Generally, BCG vaccine should only be given when the exclusively formula-fed infant is confirmed HIV uninfected at 12–14 weeks. However, infants considered at low risk of HIV transmission (maternal VL <50 HIV RNA copies/mL at or after 36 weeks' gestation) but with a high risk of tuberculosis exposure may be given BCG at birth.

Where the mother is coinfecting with HBV, immunization against HBV infection should be as per the Green Book and does not differ from management of the HIV-unexposed infant [285].

With sensitivity to concerns about confidentiality, 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.

### 8.4 Infant feeding

**8.4.1 All mothers known to be HIV positive, regardless of ART, and infant PEP, should be advised to exclusively formula feed from birth. Grading: 1A**

It is well established that HIV can be transmitted from mother to child by breastfeeding [286–288]. RCT evidence from Kenya puts the transmission rate at 16% over 2 years, accounting for almost half the total MTCTs [288]. Complete avoidance of breastfeeding removes this risk altogether [288–290] and is the current standard of care in the UK [50,291]. This is in line with previous World Health Organization (WHO) guidance, that exclusive feeding with infant formula milk should be recommended for women with HIV where it is affordable, feasible, acceptable, sustainable and safe [292].

Recently, cohort [293–296] and RCT [66,78,297] data from Africa have shown that ART can significantly reduce

the risk of HIV transmission from breastfeeding. This is in settings where breastfeeding is not affordable, feasible, acceptable, sustainable and safe, and mortality from formula feeding outweighs additional mortality from HIV transmission by breastfeeding [298,299]. WHO guidance remains that in countries where formula feeding is safe, a national or regional policy decision should be made on feeding policy [300]. Although breastfeeding transmission is reduced by ART, it is not abolished [78,293,295–297,301,302]. There is laboratory evidence that the breast milk of HIV-positive women on ART contains cells that may shed virus [303]. As avoidance of breastfeeding can completely abolish the risk of postnatal transmission, this remains the recommended course of action.

There may be social or financial pressures on women to breastfeed, and support of formula feeding is important. The NSHPC report on perinatal HIV transmission in the UK [14] noted adverse social factors as a frequent factor in HIV transmission. A recent House of Lords report recommends the provision of free infant formula milk to HIV-positive mothers who have no recourse to public funds [304].

**8.4.2 In very rare instances where a mother who is on effective HAART with a repeatedly undetectable VL chooses to breastfeed, this should not constitute grounds for automatic referral to child protection teams. Maternal HAART should be carefully monitored and continued until 1 week after all breastfeeding has ceased. Breastfeeding, except during the weaning period, should be exclusive and all breastfeeding, including the weaning period, should have been completed by the end of 6 months. Grading: 1B**

Breastfeeding while not on HAART, or with detectable viraemia on HAART does constitute a potential child protection concern.

Because the risk of HIV transmission by breastfeeding is entirely avoidable, maternal breastfeeding against medical advice has previously been considered a child protection concern warranting referral to social services and, where necessary, legal intervention. The efficacy of ART in reducing HIV transmission by breastfeeding in the UK has not been measured. However, while the African data do not warrant a change in the recommendation not to breastfeed in these UK guidelines, they do make it likely that the risk of transmission is low enough that breastfeeding by a woman with HIV and fully suppressed virus on ART should no longer automatically constitute grounds for a child safeguarding referral. It is considered safer for women to be engaging with medical services while breastfeeding than for them to be breastfeeding without disclosing this. Data from Africa, in women not on HAART, show that mixed feeding carries a higher risk of HIV transmission than exclusive breastfeeding [305]. It is recommended that breastfeeding

be stopped as soon as is acceptable to the mother, but in any case by 6 months. A short period of mixed feeding may be necessary while ending breastfeeding.

**8.4.3 Prolonged infant prophylaxis during the breastfeeding period, as opposed to maternal HAART, is not recommended. Grading: 1D**

Studies in Africa have included both ART given to the mother and ART given as prophylaxis to the infant during breastfeeding. While serious adverse events were not reported in the infants given nevirapine for up to 6 months [297], there are currently insufficient safety data to advocate this approach given the particular safety concerns regarding the use of nevirapine in adults uninfected by HIV. The use of nevirapine for longer than the 2–4 weeks currently recommended for PEP is not advised [306].

**8.4.4 Intensive support and monitoring of the mother and infant are recommended during any breastfeeding period, including monthly measurement of maternal HIV plasma VL, and monthly testing of the infant for HIV by PCR for HIV DNA or RNA (VL). Grading: 1D**

Where a woman chooses to breastfeed against the medical advice in Recommendation 8.4.2, she and the baby should be monitored regularly for maternal adherence to ART; VL monitoring of the mother and diagnostic testing of the baby should be performed regularly (monthly). If the mother's adherence is suboptimal or she has detectable viraemia or an intercurrent illness that affects her ability to take or absorb ART, or she develops mastitis, she should be advised again to stop breastfeeding.

**8.4.5 All infants born to mothers infected with HIV should have an antibody test at age 18 months. Grading: 1C**

The potential for breastfeeding emphasizes the possibility of late transmission of HIV after the standard 3-month PCR test. Babies known to be breastfed should be tested monthly by PCR as above, but not all breastfeeding will be disclosed, and all babies born to HIV-positive women should have a negative HIV antibody test documented at age 18 months (see Section 8.5: Infant testing below).

## 8.5 Infant testing

**8.5.1 HIV DNA PCR (or HIV RNA testing) should be performed on the following occasions (Grading: 1C):**

- During the first 48 h and before hospital discharge.
- 2 weeks post infant prophylaxis (6 weeks of age).
- 2 months post infant prophylaxis (12 weeks of age).
- On other occasions if additional risk (e.g. breastfeeding).

**HIV antibody testing for seroreversion should be checked at age 18 months.**

## 8.6 Laboratory diagnosis of HIV infection in non-breastfed infants

The gold standard test for HIV infection in infancy was HIV DNA PCR on peripheral blood lymphocytes, although a number of studies, including the large French perinatal cohort have now demonstrated equal or increased early sensitivity with amplification of viral RNA with no false positives [307]. Infants infected intrapartum may have low peripheral blood HIV levels, so HIV DNA/RNA may not be amplified from all infected infants at birth. Indeed a positive HIV DNA PCR result within 72 h of birth is taken as presumptive evidence of intrauterine transmission. Within the first few weeks of life, sensitivity of the viral diagnostic tests increases dramatically and by 3 months of age, 100% of non-breastfed HIV-positive infants are likely to be detected [308]. In view of the genomic diversity of HIV where infant diagnosis will rely on HIV DNA amplification, a maternal sample should always be obtained for HIV DNA amplification with, or prior to, the first infant sample to confirm that the primers used detect the maternal virus. If the maternal virus cannot be detected then a different primer set and/or test should be used.

Infant HIV diagnostic testing should be undertaken at birth, 6 weeks and 12 weeks of age. 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 [309]. For this reason, the second and third HIV molecular tests are performed at 2 weeks and 2 months after stopping PEP (i.e. usually at 6 weeks and 12 weeks of age). If all tests are negative and the baby is not being/has not been breastfed, then parents can be informed that the child is not HIV infected. For infants at high risk of infection an additional early HIV test maybe undertaken at 2–3 weeks of age. For infants breastfeeding from mothers on HAART (see above), HIV viral diagnostic tests should be undertaken at least monthly on mother and infant while breastfeeding, and then twice on the infant, ideally between 2 and 8 weeks after weaning.

Loss of maternal HIV antibodies should be confirmed at 18–24 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 latest tests are highly sensitive and may give a positive HIV result until up to 2 years of age [310]. Testing for loss of maternal HIV antibody remains important as rarely, late postnatal infection may occur, even when all early HIV viral genome diagnostic tests were negative (French Perinatal cohort: five of 4539 cases) [311]. This may be due to covert breastfeeding, premastication of infant food or unknown intra-familial exposure.

If any of the infant HIV tests are found to be positive, an immediate repeat on a new sample should be requested to confirm infection. When an infant is found to be HIV positive, PCP prophylaxis should be started immediately, if the baby is not already on it, and an urgent referral to the local specialist HIV clinic should be made to initiate infant HAART. Maternal and infant HIV resistance testing should be undertaken to help delineate reasons for treatment failure and guide treatment. HIV services for children in the UK are organized in managed networks, details of the Children's HIV Network (CHIN) and contacts for local paediatricians can be found on the CHIVA website (<http://www.chiva.org.uk>) [312].

### 8.7 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 MDT is crucial to support these women, as they are often the most isolated and unsupported.

Where, despite all efforts, the MDT is unable to influence a mother's views antenatally, 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 PEP and prevent breastfeeding. Preparation of the legal case may be lengthy and time consuming; useful documentation can be obtained from colleagues who have already undertaken this.



## 9.0 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 informed decisions that will affect the long-term health of herself, her fetus and her male partner.

PMCT can only be achieved if the pregnant woman embraces medical interventions appropriately. To maximize the effectiveness of interventions for pregnant women in reducing MTCT the psychosocial context of their HIV infection must not be overlooked. Clinical experience indicates that the management of issues, including dealing with the diagnosis and uncertainty during pregnancy and robust confidentiality processes have an impact on adherence to ART and acceptance of recommended interventions and all clinicians must be mindful of this.

### 9.1. Antenatal HIV care should be delivered by MDT, the precise composition of which will vary. Grading: 1D

The minimum team would comprise an HIV specialist, obstetrician, specialist midwife and paediatrician, with 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, Citizens Advice Bureau workers, interpreters, community midwives, clinical nurse specialists and health visitors [313].

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, can 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 follow-up need to be identified and actively followed-up.

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 [314].

The importance of informing appropriate healthcare workers should be emphasized. This includes midwives, general practitioners, 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.

Depending on the setting, levels of disclosure of newly diagnosed pregnant women about their HIV status vary, and there are cultural factors that influence the patterns of self-disclosure to partners and other social network members [313,315]. Disclosure should be encouraged in all cases but may be viewed as a process that may take some time [316,317]. 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 to inform a sexual partner of the index patient's positive HIV status is sanctioned as a 'last resort' by the WHO [318] and General Medical Council [319]. However, it is not to be taken lightly as it could have the negative impact of deterring others from testing because of the 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 CS, 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 [320].

Between 20% and 80% of newly diagnosed HIV-positive pregnant women may have partners who are HIV negative, depending on the setting [315,321]. Such couples require advice regarding condom use and PEP following sexual exposure [322].

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. Women with very limited funds should have access to supplementary formula feed [291,323].

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 [324–326].

The testing of existing children should be raised with all newly diagnosed pregnant women. In practice, if the children are asymptomatic the testing is often most easily done when the newborn is attending paediatric follow-up for HIV diagnostic tests [327].

Adherence to medication 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 [328].

Legislation concerning eligibility to free NHS healthcare in the UK changed in 2004. Patients who have been resident in the UK for 12 months do not have an automatic entitlement to free care in the NHS. There is an exclusion for 'immediately necessary care' and it has been 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 General Medical Council, British Medical Association and Medical Defence Organizations in difficult cases. Legal advice can also be sought from organizations such as the Terrence Higgins Trust (<http://www.tht.org.uk>), or the National AIDS Trust (<http://www.nat.org.uk>).

Postnatal depression is relatively common in the general population, tends to be underdiagnosed and is a risk in HIV-positive women. Women with, or at risk of, antenatal depression should be assessed early and referred onward appropriately [329].

## 10.0 Acknowledgements and conflicts of interest

The Writing Group thanks Dr David Hawkins, Dr Fiona Lyons and Dr Danielle Mercey for their peer-review of the Guidelines.

### Conflicts of interest

Dr A de Ruiter has received lecture and consultancy fees from Bristol-Myers Squibb and Gilead.

Dr GP Taylor's department has received research grants from Abbott.

Dr A Palfreeman has received conference support from Bristol-Myers Squibb and Gilead.

Miss P Clayden has no conflicts of interest to declare.

Dr J Dhar has received conference support from ViiV.

Mrs K Gandhi has no conflicts of interest to declare.

Dr Y Gilleece has received lecture and consultancy fees from ViiV.

Dr K Harding has no conflicts of interest to declare.

Dr D Hawkins has received lecture fees from Janssen, consultancy fees from Bristol-Myers Squibb, and his

department has received research grant support from Bristol-Myers Squibb.

Dr P Hay has received lecture and consultancy fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Johnson and Johnson (Tibotec) and ViiV. He has received conference support from Bristol-Myers Squibb, Gilead and Janssen and his department has received research grant support from Abbott, Boehringer Ingelheim, Gilead, Janssen and ViiV.

Ms J Kennedy has no conflicts of interest to declare.

Dr N Low-Beer has no conflicts of interest to declare.

Dr H Lyall has received lecture fees from Danone and ViiV.

Dr F Lyons has no conflicts of interest to declare.

Dr D Mercey has no conflicts of interest to declare.

Dr P Tookey has no conflicts of interest to declare.

Dr S Welch has no conflicts of interest to declare.

Dr E Wilkins has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme and Pfizer.

## 11.0 References

- 1 Health Protection Agency. HIV in the United Kingdom: 2010 report. *Health Protection Report* 2010; 4(Number 47): 8–9. Available at [http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1287145367237](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287145367237) (accessed April 2012).
- 2 Data tables of the unlinked anonymous dried blood spot survey of newborn infants- prevalence of HIV in women giving birth. Surveillance update. *Health Protection Agency* 2010; Available at [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1287144874352](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1287144874352) (accessed April 2012).
- 3 Duong T, Ades AE, Gibb D, Tookey P, Masters J. Vertical transmission rates for HIV on the British Isles: estimates based on surveillance data. *BMJ* 1999; 319: 1227–1229.
- 4 Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS* 2008; 22: 973–981.
- 5 National Study of HIV in Pregnancy and Childhood. National surveillance data. 2012. Available at <http://www.nshpc.ucl.ac.uk> (accessed April 2012).
- 6 Health Protection Agency. United Kingdom: new HIV diagnoses data to end June 2011. Health Protection Agency 2011. Available at [http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1237970242135](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1237970242135) (accessed April 2012).
- 7 Judd A, Doerholt K, Tookey PA *et al.* Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996–2006: planning for teenage and adult care. *Clin Infect Dis* 2007; 45: 918–924.
- 8 Collaborative HIV Paediatric Study. 2011. Available at <http://www.chipscohort.ac.uk/default.asp> (accessed April 2012).
- 9 Kenny J, Williams B, Prime K, Tookey P, Foster C. Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV. *HIV Med* 2012; 13: 304–308.
- 10 Intercollegiate Working Party. Reducing Mother to Child Transmission of HIV Infection in the United Kingdom. 2006. Available at [http://www.rcpch.ac.uk/sites/default/files/asset\\_library/Publications/R/HIVreport.pdf](http://www.rcpch.ac.uk/sites/default/files/asset_library/Publications/R/HIVreport.pdf) (accessed April 2012).
- 11 Townsend CL, Cliffe S, Tookey PA. Uptake of antenatal HIV testing in the United Kingdom: 2000–2003. *J Public Health* 2006; 28: 248–252.
- 12 UK National Screening Committee. Infectious diseases in pregnancy screening programme: programme standards. NHS Screening programmes. 2010. Available at <http://infectiousdiseases.screening.nhs.uk/standards> (accessed April 2012).
- 13 UK National Screening Committee. Infectious diseases in pregnancy screening programme: 2008–2009 annual report. NHS Screening Programmes. 2010. Available at <http://infectiousdiseases.screening.nhs.uk/publications> (accessed April 2012).
- 14 AIAU, NSHPC, CHIVA. Perinatal Transmission of HIV in England 2002–2005. Audit, Information and Analysis Unit. 2007. Available at [http://www.nshpc.ucl.ac.uk/Audit/Vertical\\_Transmission\\_Executive\\_SummaryOctober\\_2007.pdf](http://www.nshpc.ucl.ac.uk/Audit/Vertical_Transmission_Executive_SummaryOctober_2007.pdf) (accessed April 2012).
- 15 Madge S, Phillips AN, Griffioen A, Olaitan A, Johnson MA. Demographic, clinical and social factors associated with human immunodeficiency virus infection and other sexually transmitted diseases in a cohort of women from the United Kingdom and Ireland. MRC Collaborative Study of women with HIV. *Int J Epidemiol* 1998; 27: 1068–1071.
- 16 Leroy V, De Clerq A, Ladner J, Bogaerts J, Van der Perre P, Dabis F. Should screening of genital infections be part of antenatal care in areas of high HIV prevalence? A prospective cohort study from Kigali, Rwanda, 1992–1993. The pregnancy and HIV (EGE) Group. *Genitourin Med* 1995; 71: 207–211.
- 17 Low N, Sterne JAC, Barlow D. Inequalities in rates of gonorrhoea and chlamydia between black ethnic groups in south east London: cross sectional study. *Sex Transm Infect* 2001; 77: 15–20.
- 18 Chuachoowong R, Shaffer N, Siriwasin W *et al.* Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. Bangkok Collaborative Perinatal HIV Transmission Study Group. *J Infect Dis* 2000; 181: 99–106.
- 19 Hart CE, Lennox JL, Pratt-Palmore M *et al.* Correlation of human immunodeficiency virus type 1 RNA levels in blood and female genital tract. *J Infect Dis* 2000; 179: 871–882.
- 20 Fiore JR, Suligoi B, Saracino A *et al.* Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. *AIDS* 2003; 17: 169–176.
- 21 Kovacs A, Wasserman SS, Burns D *et al.* Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001; 358: 1593–1601.
- 22 de Pasquale MP, Leigh-Brown AJ, Cu-Uvin S *et al.* Differences in HIV-1 pol sequences from female genital

- tract and blood during antiretroviral therapy. *J Acquir Immune Defic Syndr* 2003; **34**: 37–44.
- 23 Warszawski J, Tubiana R, Le Chenadec J *et al*. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* 2008; **22**: 289–299.
- 24 Cameron DW, Simonsen JN, D'Costa LJ *et al*. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989; **ii**: 403–407.
- 25 Dickerson MC, Johnston J, Delea TE, White A, Andrews E. The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. An application of the Bradford Hill criteria. *Sex Transm Dis* 1996; **23**: 429–440.
- 26 Ghys PD, Franssen K, Diallo MO *et al*. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS* 1997; **11**: F85–F93.
- 27 Lawn SD, Subbarao S, Wright JTC *et al*. Correlation between human immunodeficiency virus type 1 RNA levels in the female genital tract and immune activation associated with ulceration of the cervix. *J Infect Dis* 2000; **181**: 1950–1956.
- 28 Hashemi FB, Ghassemi M, Roebuck KA, Spear GT. Activation of human immunodeficiency virus type 1 expression by *Gardnerella vaginalis*. *J Infect Dis* 1999; **179**: 924–930.
- 29 Hashemi FB, Ghassemi M, Faro S, Aroutcheva A, Spear GT. Induction of human immunodeficiency virus type 1 expression by anaerobes associated with bacterial vaginosis. *J Infect Dis* 2000; **181**: 1574–1580.
- 30 McClelland RS, Wang CC, Mandaliya K *et al*. Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. *AIDS* 2001; **15**: 105–110.
- 31 Cowan FM, Humphrey JH, Ntozini R, Mutasa K, Morrow R, Iliff P. Maternal herpes simplex virus type 2 infection, syphilis and risk of intra-partum transmission of HIV-1: results of a case control study. *AIDS* 2008; **22**: 193–201.
- 32 Bollen LJ, Whitehead SJ, Mock PA *et al*. Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission? *AIDS* 2008; **22**: 1169–1176.
- 33 Ouedraogo A, Nagot N, Vergne L *et al*. Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: a randomized controlled trial. *AIDS* 2006; **20**: 2305–2313.
- 34 Patterson J, Hitti J, Selke S *et al*. Genital HSV detection among HIV-1-infected pregnant women in labor. *Infect Dis Obstet Gynecol* 2011; **2011**: 157680.
- 35 Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med* 2000; **342**: 1500–1507.
- 36 Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *N Engl J Med* 1988; **319**: 972–978.
- 37 Landesman SH, Kalish LA, Burns DN *et al*. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study. *N Engl J Med* 1996; **334**: 1617–1623.
- 38 Newell ML, Dunn DT, Peckham CS, Semprini AE, Pardi G. Vertical transmission of HIV-1: maternal immune status and obstetric factors: the European Collaborative Study. *AIDS* 1996; **10**: 1675–1681.
- 39 Van Dyke RB, Korber BT, Popek E *et al*. The Ariel Project: a prospective cohort study of maternal-child transmission of human immunodeficiency virus type 1 in the era of maternal antiretroviral therapy. *J Infect Dis* 1999; **179**: 319–328.
- 40 Taha TE, Brown ER, Hoffman IF *et al*. A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission. *AIDS* 2006; **20**: 1313–1321.
- 41 Hillier SL, Nugent RP, Eschenbach DA *et al*. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. *N Engl J Med* 1995; **333**: 1737–1742.
- 42 Taha TE, Gray RH. Genital tract infections and perinatal transmission of HIV. *Ann N Y Acad Sci* 2000; **918**: 84–98.
- 43 McDonald H, Brocklehurst P, Parsons J, Vigneswaran R. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2003; (2)CD000262.
- 44 Varma R, Gupta JK, James DK, Kilby MD. Do screening-preventative interventions in asymptomatic pregnancies reduce the risk of preterm delivery. A critical appraisal of the literature. *Eur J Obstet Gynecol Reprod Biol* 2006; **127**: 145–159.
- 45 Farquhar C, Mbori-Ngacha D, Overbaugh J *et al*. Illness during pregnancy and bacterial vaginosis are associated with in-utero HIV-1 transmission. [Letter]. *AIDS* 2010; **24**: 153–155.
- 46 McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2007; (1)CD000262.
- 47 Fakoya A, Lamba H, Mackie N *et al*. 2007 UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection. *HIV Med* 2008; **9**: 681–720.
- 48 Luesley D, Leeson S. Colposcopy and programme management. In: Sheffield, NHS Cancer Screening Programmes, 2010: 1–59. *Guidelines for the NHS Cervical Screening Programme*, 2nd edn. NHCSP Publication No.

- 20 May 2010. Available at <http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf> (accessed April 2012).
- 49 Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2011*. Wilmington, NC, Registry Coordinating Center, 2011: Available at <http://www.APRRegistry.com> (accessed April 2012).
  - 50 de Ruiter A, Mercey D, Anderson J *et al*. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med* 2008; **9**: 452–502.
  - 51 Nightingale SL. From the food and drug administration. *JAMA* 1998; **280**: 1472.
  - 52 Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002; **16**: 299–300.
  - 53 Saitoh A, Hull AD, Franklin P, Spector SA. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol* 2005; **25**: 555–556.
  - 54 Ekouevi DK, Coffie PA, Ouattara E *et al*. Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS Databases, Abidjan, Cote d'Ivoire. *J Acquir Immune Defic Syndr* 2011; **56**: 183–187.
  - 55 Ford N, Mofenson L, Kranzer K *et al*. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS* 2010; **24**: 1461–1470.
  - 56 Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2011; **25**: 2301–2304.
  - 57 Brogly SB, Abzug MJ, Watts DH *et al*. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J* 2010; **29**: 721–727.
  - 58 Knapp KM, Brogly SB, Muenz DG *et al*. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J* 2012; **31**: 164–170.
  - 59 Joao EC, Calvet GA, Krauss MR *et al*. Maternal antiretroviral use during pregnancy and infant congenital anomalies: the NISDI perinatal study. *J Acquir Immune Defic Syndr* 2010; **53**: 176–185.
  - 60 Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007. *AIDS* 2009; **23**: 519–524.
  - 61 Connor EM, Sperling RS, Gelber R *et al*. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994; **331**: 1173–1180.
  - 62 Tariq S, Townsend CL, Cortina-Borja M *et al*. Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000–2009. *J Acquir Immune Defic Syndr* 2011; **57**: 326–333.
  - 63 Tubiana R, Matheron S, Le Chenadec J *et al*. Extremely low risk of MTCT of HIV in women starting HAART before pregnancy: French Perinatal Cohort, ANRS EPF C01/11. *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA, February 2011 [Abstract 735].
  - 64 Lallemand M, Jourdain G, Ngo-Giang-Huong N *et al*. A phase III randomized, partially double-blind and placebo-controlled trial comparing the efficacy and safety of maternal and infant NVP vs infant only NVP, or maternal LPV/r, in addition to standard ZDV prophylaxis to prevent perinatal HIV transmission: Thailand, PHPT-5. *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA, February 2011 [Abstract 741].
  - 65 US Food and Drug Administration. Important drug warning. Videx (didanosine) and Zerit (stavudine) Dear Healthcare Professional Letter Jan 2001. [Retyped letter from Bristol-Myers Squibb Company, dated 5 January 2001]. 2001 Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172676.htm> (accessed April 2012).
  - 66 Shapiro RL, Hughes MD, Ogwu A *et al*. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010; **362**: 2282–2294.
  - 67 European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005; **40**: 458–465.
  - 68 Edwards S, Larbalestier N, Hay P *et al*. Experience of nevirapine use in a London cohort of HIV infected pregnant women. *HIV Med* 2001; **2**: 89–91.
  - 69 Natarajan U, Pym A, McDonald C *et al*. The safety of nevirapine in pregnancy. *HIV Med* 2007; **8**: 64–69.
  - 70 Ouyang DW, Brogly SB, Lu M *et al*. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS* 2010; **24**: 109–114.
  - 71 Phanuphak N, Apornpong T, Intarasuk S, Teeratakulpisarn S, Phanuphak P. Toxicities from nevirapine in HIV-infected males and females, including pregnant females with various CD4 cell counts. *12th Conference on Retroviruses and Opportunistic Infections*. Boston MA, February 2005 [Abstract 22].
  - 72 Mirochnick M, Siminski S, Fenton T, Lugo M, Sullivan JL. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J* 2001; **20**: 803–805.
  - 73 Mirochnick M, Fenton T, Gagnier P *et al*. Pharmacokinetics of nevirapine in human immunodeficiency virus type-1

- infected pregnant women and their neonates. *J Infect Dis* 1998; 178: 368–374.
- 74 Taylor GP, Lyall E, Back D, Ward C, Tudor-Williams G. Pharmacological implications of prolonged in utero exposure to nevirapine. *Lancet* 2000; 355: 2134–2135.
- 75 Brooks Jackson J, Musoke P, Fleming T *et al*. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18 month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003; 362: 859–868.
- 76 Dabis F, Bequent L, Ekouevi DK *et al*. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS* 2005; 19: 309–318.
- 77 Lallemand M, Jourdain G, Le Couer S *et al*. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; 351: 217–228.
- 78 de Vincenzi I, Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis* 2011; 11: 171–180.
- 79 Samuel M, Bradshaw D, Perry M *et al*. Atazanavir in pregnancy: a report of 155 cases. *HIV Med* 2011; 12 (Suppl 1): 9. [Abstract 025].
- 80 van der Lugt J, Colbers A, Molto J *et al*. The pharmacokinetics, safety and efficacy of boosted saquinavir tablets in HIV type-1-infected pregnant women. *Antivir Ther* 2009; 14: 443–450.
- 81 Vithayasai V, Moyle GJ, Supajatura V *et al*. Safety and efficacy of saquinavir soft-gelatin capsules plus zidovudine plus optional lamivudine in pregnancy and prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr* 2002; 30: 410–412.
- 82 Patel D, Cortina-Borja M, Thorne C, Newell ML. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis* 2007; 44: 1647–1656.
- 83 Read PJ, Mandalia S, Khan P *et al*. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS* 2012; 26(9): 1095–1103.
- 84 Kay N, Fish R, Duncan S *et al*. The impact of HAART on HIV RNA decay during the first 2 weeks of therapy among HIV+ pregnant women. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. March 2012 [Abstract 1020].
- 85 Lorenzi P, Spicher VM, Laubereau B *et al*. Antiretroviral therapies in pregnancy: maternal, foetal and neonatal effects. *AIDS* 1998; 12: F241–F247.
- 86 European Collaborative Study, Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000; 14: 2913–2930.
- 87 European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr* 2003; 32: 380–387.
- 88 European Collaborative Study. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS* 2004; 18: 2337–2339.
- 89 Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS* 2007; 21: 1019–1026.
- 90 Tuomala RE, Shapiro DE, Mofenson LM *et al*. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med* 2002; 346: 1863–1870.
- 91 Tuomala RE, Watts DH, Li D *et al*. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr* 2005; 38: 449–473.
- 92 Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler M. G, for the Pediatric Spectrum of HIV Disease Consortium. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: pediatric Spectrum of HIV Disease, 1989–2004. *Pediatrics* 2007; 119: e900–e906.
- 93 Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis* 2006; 193: 1195–1201.
- 94 Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS* 2007; 21: 607–615.
- 95 Beckerman K, Albano J, Cohan D, Watts DH, Tilson H. Exposure to combination antiretroviral (cARV) regimens containing protease inhibitors (PI) during pregnancy and prevalence of low birth weight/preterm delivery (LBW/PTD) among women with low pre-existing risk for LBW/PTD: a stratified analysis of 10,082 pregnancies. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome. July 2011 [Abstract TULBPE018].
- 96 Machado ES, Hofer CB, Costa TT *et al*. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Ser Transm Infect* 2009; 85: 82–87.
- 97 Martin F, Taylor GP. Increased rates of pre-term delivery are associated with the initiation of highly active

- antiretroviral therapy during pregnancy: a single centre cohort study. *J Infect Dis* 2007; **196**: 558–561.
- 98 Patel K, Shapiro DE, Brogly S *et al*. Prenatal protease inhibitor use and risk of preterm birth among HIV-1 infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis* 2010; **201**: 1035–1044.
- 99 Sibiude J, Warszawski J, Tubiana R *et al*. Large increase in prematurity between 1990 and 2009 in HIV-infected women in the National ANRS French Perinatal Cohort: does ritonavir boost play a role? *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA. February 2011 [Abstract 743].
- 100 Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2010. *Natl Vital Stat Rep* 2011; **60**: 4–5 Available at [http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60\\_02.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_02.pdf) (accessed April 2012).
- 101 Powis KM, Kitch D, Ogwu A *et al*. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis* 2011; **204**: 506–514.
- 102 Kesho Bora Study Group, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis* 2011; **11**: 171–180.
- 103 Roberts SS, Martinez M, Covington DL, Rode RA, Pasley MV, Woodward WC. Lopinavir/ritonavir in pregnancy. *J Acquir Immune Defic Syndr* 2009; **51**: 456–461.
- 104 Rodman JH, Flynn PM, Robbins B *et al*. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type-1 infected women and newborn infants. *J Infect Dis* 1999; **180**: 1844–1850.
- 105 Odinecs A, Nusbich C, Keller RD, Baughman WL, Unadkat J. In vivo maternal-fetal pharmacokinetics of stavudine (2',3'-didehydro-3'-deoxythymidine) in pigtailed macaques (*Macaca nemestrina*). *Antimicrob Agents Chemother* 1996; **40**: 196–202.
- 106 Moodley J, Moodley D, Pillay K *et al*. Pharmacokinetics and antiretroviral activity of lamivudine alone or when co-administered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis* 1998; **178**: 1327–1333.
- 107 Best BM, Mirochnick M, Capparelli E *et al*. Impact of pregnancy on abacavir pharmacokinetics. *AIDS* 2006; **20**: 553–560.
- 108 Wang Y, Livingston E, Patil S *et al*. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected women and their neonates: an AIDS Clinical Trials Group study. *J Infect Dis* 1999; **180**: 1536–1541.
- 109 Burchett S, Best B, Mirochnick M *et al*. Tenofovir pharmacokinetics during pregnancy, at delivery and post partum. *14th Conference on Retroviruses and Opportunistic Infections*. Los Angeles, Ca. February 2007 [Abstract 738b].
- 110 Benaboud S, Hirt D, Launay O *et al*. Pregnancy-related effects on tenofovir pharmacokinetics: a population study with 186 women. *Antimicrob Agents Chemother* 2012; **56**: 857–862.
- 111 Hirt D, Urien S, Ekouevi DK *et al*. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther* 2009; **85**: 182–189.
- 112 Stek A, Best B, Luo W *et al*. Effect of pregnancy on emtricitabine pharmacokinetics. *HIV Med* 2012; **13**: 226–235.
- 113 Cressey TR, Stek A, Capparelli E *et al*. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA. February 2011 [Abstract 754].
- 114 Aweeka F, Stek A, Best BM *et al*. Lopinavir protein binding in HIV-1 infected pregnant women. *HIV Med* 2010; **11**: 232–238.
- 115 Best BM, Stek AM, Mirochnick M *et al*. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010; **54**: 381–388.
- 116 Else LJ, Douglas M, Dickinson L, Back DJ, Khoo SH, Taylor GP. Improved oral bioavailability of lopinavir in melt-extruded tablet formulation reduces impact of third trimester on lopinavir plasma concentrations. *Antimicrob Agents Chemother* 2012; **56**: 816–824.
- 117 Lyons F, Lechelt M, de Ruiter A. Steady-state lopinavir levels in third trimester of pregnancy. *AIDS* 2007; **21**: 1053–1054.
- 118 Acosta EP, Bardeguer A, Zorrilla CD *et al*. Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; **48**: 430–436.
- 119 Ripamonti D, Cattaneo D, Maggiolo F *et al*. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS* 2007; **21**: 2409–2415.
- 120 Mirochnick M, Best BM, Stek AM *et al*. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr* 2011; **56**: 412–419.
- 121 Colbers A, Molto J, Ivanovic J *et al*. A comparison of the pharmacokinetics of darunavir, atazanavir and ritonavir during pregnancy and post-partum. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. March 2012 [Abstract 1013].
- 122 Conradie F, Zorrilla C, Josipovic D *et al*. Safety and exposure of once-daily ritonavir-boosted atazanavir in HIV-infected pregnant women. *HIV Med* 2011; **12**: 570–579.



- 123 Capparelli E, Best BM, Stek A *et al.* Pharmacokinetics of darunavir once or twice daily during and after pregnancy. In: *3rd International Workshop on HIV Pediatrics*. Rome, 2011. [Abstract P\_72].
- 124 Cespedes M, Ford S, Pakes G, Vargas L, De Candia E, Aberg J. Pharmacokinetics, cord blood concentrations, and tolerability of boosted fosamprenavir in pregnancy. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract TUPE278].
- 125 Best BM, Capparelli EV, Stek A *et al.* Raltegravir pharmacokinetics during pregnancy. *50th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Boston, MA. September 2010 [Abstract H-1668a].
- 126 Colbers A, Molto J, Ivanovir J *et al.* A comparison of the pharmacokinetics of raltegravir during pregnancy and post-partum. *12th International Workshop on Clinical Pharmacology of HIV Therapy*. Miami, FL. April 2011 [Abstract P\_18].
- 127 Ceccaldi PF, Ferreira C, Gavard L, Gil S, Peytavin G, Mandelbrot L. Placental transfer of enfuvirtide in the ex vivo human placenta perfusion model. *Am J Obstet Gynecol* 2008; **198**: 433.e1–2.
- 128 Peytavin G, Tubiana R, Ferreira C *et al.* Genital tract diffusion of different HIV PI in HIV-1 infected pregnant women. *14th Conference on Retroviruses and Opportunistic Infections*. Los Angeles, CA. February 2007 [Abstract 744].
- 129 Dumond J, Yeh R, Patterson K *et al.* First dose and steady-state genital tract pharmacokinetics of ten antiretroviral drugs in HIV-infected women: implications for pre- and post- exposure prophylaxis. *13th Conference on Retroviruses and Opportunistic Infections*. Denver, CO. February 2006 [Abstract 129].
- 130 Shaffer N, Chuachoowong R, Mock PA *et al.* Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet* 1999; **353**: 773–780.
- 131 The European Mode of Delivery Collaboration. Elective caesarian-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; **353**: 1035–1039.
- 132 Lyall E, Blott M, de Ruyter A *et al.* Guidelines for the Management of HIV infection in pregnant women and the prevention of mother-to-child transmission. *British HIV Association. HIV Med* 2001; **2**: 314–334.
- 133 Read P, Khan P, Mandalia S *et al.* When should HAART be initiated in pregnancy to achieve an undetectable viral load? *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA. February 2010 [Abstract 896].
- 134 Markowitz M, Morales-Ramirez JO, Nguyen BY *et al.* Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naïve HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2006; **43**: 509–515.
- 135 Murray JM, Emery S, Kelleher AD *et al.* Antiretroviral therapy with the integrase inhibitor raltegravir alters decay kinetics of HIV, significantly reducing the second phase. *AIDS* 2007; **21**: 2315–2321.
- 136 Musoke P, Guay LA, Bagenda D *et al.* A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1 infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS* 1999; **13**: 479–486.
- 137 McKeown DA, Rosenvinge M, Donaghy S *et al.* High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. *AIDS* 2010; **24**: 2416–2418.
- 138 Wade NA, Birkhead GS, Warren BL *et al.* Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998; **339**: 1409–1414.
- 139 Hirt D, Ekouevi DK, Pruvost A *et al.* Plasma and intracellular tenofovir pharmacokinetics in the neonate (ANRS 12109 trial, step 2). *Antimicrob Agents Chemother* 2011; **55**: 2961–2967.
- 140 Walker BD. Elite control of HIV infection: implications for vaccines and treatment. *Top HIV Med* 2007; **15**: 134–136.
- 141 Ioannidis JP, Abrams EJ, Ammann AJ *et al.* Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis* 2001; **183**: 539–545.
- 142 Rutland E, Mani R. Management of pregnancy in an HIV elite controller. *Int J STD AIDS* 2010; **21**: 604–605.
- 143 Sperling RS, Shapiro DE, Coombs RW *et al.* Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med* 1996; **335**: 1621–1629.
- 144 Watts DH, Lambert J, Stiehm ER *et al.* Progression of HIV disease among women following delivery. *J Acquir Immune Defic Syndr* 2003; **33**: 585–593.
- 145 Melekhin VV, Shepherd BE, Jenkins CA *et al.* Postpartum discontinuation of antiretroviral therapy and risk of maternal AIDS-defining events, non-AIDS-defining events, and mortality among a cohort of HIV-1-infected women in the United States. *AIDS Patient Care STDS* 2010; **24**: 279–286.
- 146 Melo VH, Pinto JA, Freimanis-Hance L *et al.* Postpartum changes in plasma viral load and CD4 percentage among HIV-infected women from Latin American and Caribbean countries: the NISDI Perinatal Study. *Mem Inst Oswaldo Cruz* 2011; **106**: 97–104.
- 147 Onen NF, Nurutdinova D, Sungkanuparph S, Gase D, Mondy K, Overton ET. Effect of postpartum HIV treatment

- discontinuation on long-term maternal outcome. *J Int Assoc Physicians AIDS Care (Chic)* 2008; 7: 245–251.
- 148 Watts DH, Lu M, Thompson B *et al.* Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol* 2009; 2009: 456717.
- 149 El-Sadr WM, Lundgren JD, Neaton JD *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; 355: 2283–2296.
- 150 Danel C, Moh R, Minga A *et al.* CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet* 2006; 367: 1981–1989.
- 151 Kitahata MM, Gange SJ, Abraham AG *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009; 360: 1815–1826.
- 152 Sterne JA, May M, Costagliola D *et al.* Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; 373: 1352–1363.
- 153 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. 2012; 1–239. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (accessed April 2012).
- 154 Thompson MA, Aberg JA, Cahn P *et al.* Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA* 2010; 304: 321–333.
- 155 Bardeguez AD, Shapiro DE, Mofenson LM *et al.* Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *J Acquir Immune Defic Syndr* 2003; 32: 170–181.
- 156 Martin F, Navaratne L, Khan W *et al.* Pregnant women with HIV infection can expect healthy survival. *J Acquir Immune Defic Syndr* 2006; 43: 186–192.
- 157 Cohen MS, Chen YQ, McCauley M *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; 365: 493–505.
- 158 Pogany K, van Valkengoed IG, Prins JM *et al.* Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm<sup>3</sup>: 48-week Treatment Interruption in Early Starters Netherlands Study (TRISTAN). *J Acquir Immune Defic Syndr* 2007; 44: 395–400.
- 159 Ananworanich J, Gayet-Ageron A, Le BM *et al.* CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. *Lancet* 2006; 368: 459–465.
- 160 Steingrover R, Pogany K, Fernandez GE *et al.* HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of highly active antiretroviral therapy. *AIDS* 2008; 22: 1583–1588.
- 161 Palacios R, Senise J, Vaz M, Diaz R, Castelo A. Short-term antiretroviral therapy to prevent mother-to-child transmission is safe and results in a sustained increase in CD4 T-cell counts in HIV-1-infected mothers. *HIV Med* 2009; 10: 157–162.
- 162 Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis* 2003; 188: 571–577.
- 163 Rouet F, Chaix ML, Inwoley A *et al.* HBV and HCV prevalence and viraemia in HIV-positive and HIV-negative pregnant women in Abidjan, Cote d'Ivoire: the ANRS 1236 study. *J Med Virol* 2004; 74: 34–40.
- 164 Konopnicki D, Mocroft A, De WS *et al.* Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005; 19: 593–601.
- 165 Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. *Int J Infect Dis* 2010; 14: e1024–e1031.
- 166 Euler GL, Wooten KG, Baughman AL, Williams WW. Hepatitis B surface antigen prevalence among pregnant women in urban areas: implications for testing, reporting, and preventing perinatal transmission. *Pediatrics* 2003; 111 (5 Part 2): 1192–1197.
- 167 Lacombe K, Bottero J, Lemoine M, Boyd A, Girard PM. HIV/hepatitis B virus co-infection: current challenges and new strategies. *J Antimicrob Chemother* 2010; 65: 10–17.
- 168 Tiribelli C, Rigato I. Liver cirrhosis and pregnancy. *Ann Hepatol* 2006; 5: 201.
- 169 Brook G, Main J, Nelson M *et al.* British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. *HIV Med* 2010; 11: 1–30.
- 170 Panel for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2010. Department of Health and Human Services Available at <http://www.aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/> (accessed April 2012).
- 171 American Congress of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 86: viral hepatitis in pregnancy. *Obstet Gynecol* 2007; 110: 941–956.
- 172 Avihingsanon A, Lewin SR, Kerr S *et al.* Efficacy of tenofovir disoproxil fumarate/emtricitabine compared with

- emtricitabine alone in antiretroviral-naïve HIV-HBV coinfection in Thailand. *Antivir Ther* 2010; 15: 917–922.
- 173 Matthews GV, Avihingsanon A, Lewin SR *et al.* A randomized trial of combination hepatitis B therapy in HIV/HBV coinfecting antiretroviral naïve individuals in Thailand. *Hepatology* 2008; 48: 1062–1069.
- 174 Xu WM, Cui YT, Wang L *et al.* Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; 16: 94–103.
- 175 Bellini C, Keiser O, Chave JP *et al.* Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med* 2009; 10: 12–18.
- 176 Yang J, Zeng XM, Men YL, Zhao LS. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus – a systematic review. *Virol J* 2008; 5: 100.
- 177 Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. *Obstet Gynecol* 2010; 116: 147–159.
- 178 Han G, Jiang H, Zhao W, Ge C, Xu C, Pan C. Lamivudine use in the 2nd or 3rd trimester of pregnancy has similar efficacy in preventing vertical transmission (vt) of chronic hepatitis B (CHB) in highly viremic mothers. *The Liver Meeting*. San Francisco, CA. November 2011 [Abstract]. Available at <http://www.aasld.org/lm2011/abstracts/Pages/default.aspx> (accessed April 2012).
- 179 Landes M, Newell ML, Barlow P *et al.* Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe. *HIV Med* 2008; 9: 526–534.
- 180 Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. *Int J Epidemiol* 1998; 27: 108–117.
- 181 Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clin Infect Dis* 2007; 44: 1123–1131.
- 182 Pappalardo BL. Influence of maternal human immunodeficiency virus (HIV) co-infection on vertical transmission of hepatitis C virus (HCV): a meta-analysis. *Int J Epidemiol* 2003; 32: 727–734.
- 183 European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *Br J Obstet Gynaecol* 2001; 108: 371–377.
- 184 Hershov RC, Riester KA, Lew J *et al.* Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfecting mothers. Women and Infants Transmission Study. *J Infect Dis* 1997; 176: 414–420.
- 185 Zanetti AR, Tanzi E, Romano L *et al.* A prospective study on mother-to-infant transmission of hepatitis C virus. *Intervirology* 1998; 41: 208–212.
- 186 Ngo-Giang-Huong N, Jourdain G, Sirirungsi W *et al.* Human immunodeficiency virus-hepatitis C virus co-infection in pregnant women and perinatal transmission to infants in Thailand. *Int J Infect Dis* 2010; 14: e602–e607.
- 187 Mast EE, Hwang LY, Seto DS *et al.* Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005; 192: 1880–1889.
- 188 European Paediatric Hepatitis C Virus Network. A significant sex-but not elective cesarean section-effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis* 2005; 192: 1872–1879.
- 189 England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. *Lancet Infect Dis* 2006; 6: 83–90.
- 190 Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA *et al.* Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. *Hepatology* 2011; 53: 1830–1838.
- 191 Mok J, Pembrey L, Tovo PA, Newell ML. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F156–F160.
- 192 Resti M, Azzari C, Mannelli F *et al.* Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ* 1998; 317: 437–441.
- 193 Roberts SS, Miller RK, Jones JK *et al.* The ribavirin pregnancy registry: findings after 5 years of enrollment, 2003–2009. *Birth Defects Res A Clin Mol Teratol* 2010; 88: 551–559.
- 194 Sangkomkarn US, Lumbiganon P, Laopaiboon M. Hepatitis B vaccination during pregnancy for preventing infant infection. *Cochrane Database Syst Rev* 2011; (3)CD007879.
- 195 Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Department of Health and Human Services. 2011. 1–207. Available at <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf> (accessed April 2012).
- 196 American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 86: viral hepatitis in pregnancy. *Obstet Gynecol* 2007; 110: 941–955.

- 197 Sheffield JS, Hickman A, Tang J *et al.* Efficacy of an accelerated hepatitis B vaccination program during pregnancy. *Obstet Gynecol* 2011; **117**: 1130–1135.
- 198 Geretti AM, Brook G, Cameron C *et al.* British HIV Association guidelines for immunization of HIV-infected adults 2008. *HIV Med* 2008; **9**: 795–848.
- 199 Ghamar Chehreh ME, Tabatabaei SV, Khazanehdari S, Alavian SM. Effect of cesarean section on the risk of perinatal transmission of hepatitis C virus from HCV-RNA+/HIV- mothers: a meta-analysis. *Arch Gynecol Obstet* 2011; **283**: 255–260.
- 200 Marine-Barjoan E, Berrebi A, Giordanengo V, Favre SF *et al.* HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? *AIDS* 2007; **21**: 1811–1815.
- 201 European AIDS Clinical Society. European AIDS clinical society guidelines. Version 6. October 2011. Available at [http://www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6\\_english.pdf](http://www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf) (accessed April 2012).
- 202 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services 2011 [cited 2012 Jan. 14]; [1–167]. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (accessed April 2012).
- 203 Thorpe J, Saeed S, Moodie EE, Klein MB. Antiretroviral treatment interruption leads to progression of liver fibrosis in HIV-hepatitis C virus co-infection. *AIDS* 2011; **25**: 967–975.
- 204 Tural C, Fuster D, Tor J *et al.* Time on antiretroviral therapy is a protective factor for liver fibrosis in HIV and hepatitis C virus (HCV) co-infected patients. *J Viral Hepat* 2003; **10**: 118–125.
- 205 Qurishi N, Kreuzberg C, Luchters G *et al.* Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet* 2003; **362**: 1708–1713.
- 206 18+0 to 20+6 weeks fetal anomaly scan. National standards and guidance for England 2010. Available at <http://fetalanomaly.screening.nhs.uk/standardsandpolicies> (accessed April 2012).
- 207 National Institute for Health and Clinical Excellence. Antenatal care: routine care for the healthy pregnant woman. national institute of health and clinical excellence. 2008. CG62. Available at <http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf> (accessed 2012).
- 208 Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. *Ultrasound Obstet Gynecol* 2005; **25**: 221–226.
- 209 Gross S, Castillo W, Crane M, Espinosa B *et al.* Maternal serum alpha-fetoprotein and human chorionic gonadotropin levels in women with human immunodeficiency virus. *Am J Obstet Gynecol* 2003; **188**: 1052–1056.
- 210 Yudin MH, Prosen TL, Landers DV. Multiple-marker screening in human immunodeficiency virus-positive pregnant women: screen positivity rates with the triple and quad screens. *Am J Obstet Gynecol* 2003; **189**: 973–976.
- 211 Spencer K. First and second trimester markers of fetal aneuploidy in pregnant women with HIV infection. *Fetal Diagn Ther* 2011; **29**: 135–138.
- 212 Einstein FH, Wright RL, Trentacoste S, Gross S, Merkatz I, Bernstein PS. The impact of protease inhibitors on maternal serum screening analyte levels in pregnant women who are HIV positive. *Am J Obstet Gynecol* 2004; **191**: 1004–1008.
- 213 Savvidou MD, Samuel I, Syngelaki A, Poulton M, Nicolaides KH. First-trimester markers of aneuploidy in women positive for HIV. *Br J Obstet Gynaecol* 2011; **118**: 844–848.
- 214 Mandelbrot L, Mayaux MJ, Bongain A *et al.* Obstetric factors and mother to child transmission of human immunodeficiency virus type 1: the French perinatal cohort. *Am J Obstet Gynecol* 1996; **175**: 661–667.
- 215 Mandelbrot L, Jasseron C, Ekoukou DE *et al.* Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol* 2009; **200**: 160–169.
- 216 Ekoukou D, Khuong-Josses MA, Ghibaudo N, Mechali D, Rotten D. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. *Eur J Obstet Gynecol Reprod Biol* 2008; **140**: 212–217.
- 217 Lopez M, Coll O. Chronic viral infections and invasive procedures: risk of vertical transmission and current recommendations. *Fetal Diagn Ther* 2010; **28**: 1–8.
- 218 Holmes WR, Hofmeyr GJ. Management of breech presentation in areas with high prevalence of HIV infection. *Int J Gynaecol Obstet* 2004; **87**: 272–276.
- 219 Owens M, Bhullar A, Carlan SJ, O'Brien WF, Hirano K. Effect of fundal pressure on maternal to fetal microtransfusion at the time of cesarean delivery. *J Obstet Gynaecol Res* 2003; **29**: 152–156.
- 220 Boer K, Nellen JF, Patel D *et al.* The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *Br J Obstet Gynaecol* 2007; **114**: 148–155.
- 221 Boer K, England K, Godfried MH, Thorne C. Mode of delivery in HIV-infected pregnant women and prevention

- of mother-to-child transmission: changing practices in Western Europe. *HIV Med* 2010; 11: 368–378.
- 222 Maiques V, Garcia-Tejedor A, Perales A, Navarro C. Intrapartum fetal invasive procedures and perinatal transmission of HIV. *Eur J Obstet Gynecol Reprod Biol* 1999; 87: 63–67.
- 223 Kind C, Rudin C, Siegrist C-A *et al.* Prevention of vertical transmission: additive protective effect of elective caesarean section and zidovudine prophylaxis. *AIDS* 1998; 12: 205–210.
- 224 National Institute of Health and Clinical Excellence. Intrapartum care: care of healthy women and their babies during childbirth. 2007. CG55. Available at <http://www.nice.org.uk/guidance/CG55/NICEGuidance> (accessed April 2012).
- 225 Tuomala RE, O'Driscoll PT, Bremer JW *et al.* Cell-associated genital tract virus and vertical transmission of human immunodeficiency virus type 1 in antiretroviral-experienced women. *J Infect Dis* 2003; 187: 375–384.
- 226 Cu-Uvin S, DeLong AK, Venkatesh KK *et al.* Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS* 2010; 24: 2489–2497.
- 227 Neely MN, Benning L, Xu J *et al.* Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007; 44: 38–42.
- 228 National Institute of Health and Clinical Excellence. Caesarean section. 2011. CG132 Available at <http://www.nice.org.uk/CG132> (accessed April 2012).
- 229 The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999; 340: 977–987.
- 230 Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev* 2005; (4)CD005479.
- 231 Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990–2006. *Br J Obstet Gynaecol* 2008; 115: 1078–1086.
- 232 Cavasin H, Dola T, Uribe O *et al.* Postoperative infectious morbidities of cesarean delivery in human immunodeficiency virus-infected women. *Infect Dis Obstet Gynecol* 2009; 2009: 827405.
- 233 Parisaei M, Anderson J, Erskine KJ, Gann S. Experience of delivering women with HIV in an inner city London hospital 1994–2004. *Int J STD AIDS* 2007; 18: 527–530.
- 234 Morrison JJ, Rennie JM, Milton P. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol* 1995; 102: 101–106.
- 235 Minkoff H, Burns DN, Landesman S *et al.* The relationship of the duration of ruptured membranes to vertical transmission of human immunodeficiency virus. *Am J Obstet Gynecol* 1995; 173: 585–589.
- 236 The International Perinatal HIV Group. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS* 2001; 15: 357–368.
- 237 Garcia-Tejedor A, Perales A, Maiques V. Duration of ruptured membranes and extended labor are risk factors for HIV transmission. *Int J Gynaecol Obstet* 2003; 82: 17–23.
- 238 Haile-Selassie H, Masters J, de Ruiter A, Tookey P. Duration of ruptured membranes and vertical transmission of HIV: data from national surveillance in the UK and Ireland. *5th Annual Conference of the Children's HIV Association*. Cardiff, Wales. May 2011 [Abstract O5]. Available at <http://www.chiva.org.uk/professionals/health/events/previous/conference11/oral.html> (accessed April 2012).
- 239 Chi BH, Mudenda V, Levy J, Sinkala M, Goldenberg RL, Stringer JS. Acute and chronic chorioamnionitis and the risk of perinatal human immunodeficiency virus-1 transmission. *Am J Obstet Gynecol* 2006; 194: 174–181.
- 240 Mofenson LM, Lambert JS, Stiehler ER *et al.* Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. *N Engl J Med* 1999; 341: 385–393.
- 241 Wabwire-Mangen F, Gray RH, Mmiro FA *et al.* Placental membrane inflammation and risks of maternal-to-child transmission of HIV-1 in Uganda. *J Acquir Immune Defic Syndr* 1999; 22: 379–385.
- 242 National Institute of Health and Clinical Excellence. Induction of Labour. CG70. 2008. Available at <http://www.nice.org.uk/CG70> (accessed April 2012).
- 243 Brookfield K, Dutherly L, Cotter A. Rupture of membranes greater than four hours is not a risk factor for perinatal HIV transmission in the era of combination antiretroviral therapy. *Am J Obstet Gynecol* 2011; 204 (Suppl 1): S42–S43.
- 244 Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to reduce neonatal morbidity and mortality: RCOG Greentop Guideline 7. 2010. Available at <http://www.rcog.org.uk/files/rcog-corp/GTG%207.pdf> (accessed April 2012).
- 245 Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev* 2010; (8)CD001058.
- 246 Frenkel LM, Cowles MK, Shapiro DE *et al.* Analysis of the maternal components of the AIDS clinical trial group 076 zidovudine regimen in the prevention of mother-to-infant transmission of human immunodeficiency virus type 1. *J Infect Dis* 1997; 175: 971–974.
- 247 Bhadrakom C, Simonds RJ, Mei JV *et al.* Oral zidovudine during labor to prevent perinatal HIV transmission,

- Bangkok: tolerance and zidovudine concentration in cord blood. Bangkok Collaborative Perinatal HIV Transmission Study Group. *AIDS* 2000; 14: 509–516.
- 248 Colgrove RC, Pitt J, Chung PH, Welles SL, Japour AJ. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS* 1998; 12: 2281–2288.
- 249 Kully C, Yerly S, Erb P *et al.* Codon 215 mutations in human immunodeficiency virus-infected pregnant women. Swiss Collaborative 'HIV and Pregnancy' Study. *J Infect Dis* 1999; 179: 705–708.
- 250 Eastman PS, Shapiro DE, Coombs RW *et al.* Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol 076. *J Infect Dis* 1998; 177: 557–564.
- 251 Masquelier B, Chaix ML, Burgard M *et al.* Zidovudine genotypic resistance in HIV-1-infected newborns in the French perinatal cohort. *J Acquir Immune Defic Syndr* 2001; 27: 99–104.
- 252 Palumbo P, Holland B, Dobbs T *et al.* Antiretroviral resistance mutations among pregnant human immunodeficiency virus type 1-infected women and their newborns in the United States: vertical transmission and clades. *J Infect Dis* 2001; 184: 1120–1126.
- 253 Welles SL, Pitt J, Colgrove RC *et al.* HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant transmission in the Women and Infants Transmission Study. *AIDS* 2000; 14: 263–271.
- 254 Nielsen-Saines K, Watts H, Goncalves Veloso V *et al.* Phase III randomized trial of the safety and efficacy of three neonatal ARV regimens for prevention of intrapartum hiv-1 transmission: NICHHD HPTN 040/PACTG 1043. *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA. February 2011 [Abstract124LB].
- 255 Taha TE, Kumwenda N, Gibbons A *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission on HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; 362: 1171–1177.
- 256 Moodley D, Moodley J, Coovadia H *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; 187: 725–735.
- 257 Taha TE, Kumwenda NI, Hoover DR *et al.* Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA* 2004; 292: 202–209.
- 258 Haile-Selassie H, Townsend C, Tookey P. Use of neonatal post-exposure prophylaxis for prevention of mother-to-child HIV transmission in the UK and Ireland. *HIV Med* 2011; 12: 422–427.
- 259 Mandelbrot L, Landreau-Mascaro A, Rekacewicz C *et al.* Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; 285: 2083–2093.
- 260 Boucher FD, Modlin JF, Weller S *et al.* Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr* 1993; 122: 137–144.
- 261 Mirochnick M, Nielsen-Saines K, Pilotto JH *et al.* Nelfinavir and lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J* 2011; 30: 769–772.
- 262 Tremoulet AH, Capparelli EV, Patel P *et al.* Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; 51: 4297–4302.
- 263 Hirt D, Urien S, Rey E *et al.* Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates. *Antimicrob Agents Chemother* 2009; 53: 1067–1073.
- 264 Jullien V, Urien S, Chappuy H *et al.* Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. *J Clin Pharmacol* 2005; 45: 257–264.
- 265 Benaboud S, Ekouevi DK, Urien S *et al.* Population pharmacokinetics of nevirapine in HIV-1-infected pregnant women and their neonates. *Antimicrob Agents Chemother* 2011; 55: 331–337.
- 266 Mirochnick M, Dorenbaum A, Blanchard S *et al.* Predose infant nevirapine concentration with the two-dose intrapartum neonatal nevirapine regimen: association with timing of maternal intrapartum nevirapine dose. *J Acquir Immune Defic Syndr* 2003; 33: 153–156.
- 267 Mirochnick M, Nielsen-Saines K, Pilotto JH *et al.* Nevirapine concentrations in newborns receiving an extended prophylactic regimen. *J Acquir Immune Defic Syndr* 2008; 47: 334–337.
- 268 Chadwick EG, Capparelli EV, Yogev R *et al.* Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS* 2008; 22: 249–255.
- 269 Chadwick EG, Yogev R, Alvero CG *et al.* Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS* 2011; 25: 643–649.
- 270 Chadwick EG, Pinto J, Yogev R *et al.* Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J* 2009; 28: 215–219.

- 271 Urien S, Firtion G, Anderson ST *et al.* Lopinavir/ritonavir population pharmacokinetics in neonates and infants. *Br J Clin Pharmacol* 2011; **71**: 956–960.
- 272 Simon A, Warszawski J, Kariyawasam D *et al.* Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV infected mothers. *JAMA* 2011; **306**: 70–78.
- 273 US Food and Drug Administration. FDA Drug Safety Communication: serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution. 2011. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm#.Tu-NUvkvx9yw.email> (accessed April 2012).
- 274 Vankandondera J, Luchters S, Hassink E. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA). *2nd International AIDS Society Conference on HIV Pathogenesis and Treatment*. Paris, France. July 2003 [Abstract LB07].
- 275 Capparelli EV, Mirochnick M, Dankner WM *et al.* Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr* 2003; **142**: 47–52.
- 276 Wiznia A, Church J, Emmanuel P *et al.* Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; **26**: 799–805.
- 277 Zhang X, Nieforth K, Lang JM *et al.* Pharmacokinetics of plasma enfuvirtide after subcutaneous administration to patients with human immunodeficiency virus: inverse Gaussian density absorption and 2-compartment disposition. *Clin Pharmacol Ther* 2002; **72**: 10–19.
- 278 Desfrere L, de Oliveira I, Goffinet F *et al.* Increased incidence of necrotizing enterocolitis in premature infants born to HIV-positive mothers. *AIDS* 2005; **19**: 1487–1493.
- 279 Van Rompay KK, Otsyula MG, Marthas ML, Miller CJ, McChesney MB, Pedersen NC. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother* 1995; **39**: 125–131.
- 280 Tsai CC, Emau P, Follis KE *et al.* Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV<sub>mac</sub> infection depends critically on timing of initiation and duration of treatment. *J Virol* 1998; **72**: 4265–4273.
- 281 Bottiger D, Johansson NG, Samuelsson B *et al.* Prevention of simian immunodeficiency virus, SIV<sub>sm</sub>, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS* 1997; **11**: 157–162.
- 282 Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J* 2011; **30**: 408–412.
- 283 Lahoz R, Noguera A, Rovira N *et al.* Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J* 2010; **29**: 376–379.
- 284 Lallemand M, Jourdain G, Le Coeur S *et al.* A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **343**: 982–991.
- 285 Salisbury D. *Immunisation against Infectious Disease*. London, Department of Health, 2006: 161–184. Available at [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_079917](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917) (accessed April 2012).
- 286 Coutsooudis A, Dabis F, Fawzi W *et al.* Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004; **189**: 2154–2166.
- 287 Dunn DT, Newell M-L, Ades AE, Peckham C. Estimates of the risk of HIV-1 transmission through breastfeeding. *Lancet* 1992; **340**: 585–588.
- 288 Nduati R, Richardson BA, John G *et al.* Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. *Lancet* 2001; **357**: 1651–1655.
- 289 Read D, The Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J Infect Dis* 2004; **189**: 2154–2166.
- 290 Nduati R, John G, Mbori-Ngacha D *et al.* Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA* 2000; **283**: 1167–1174.
- 291 Taylor GP, Anderson J, Clayden P *et al.* British HIV Association and Children's HIV Association position statement on infant feeding in the UK 2011. *HIV Med* 2011; **12**: 389–393.
- 292 WHO, UNICEF, ANAIDS, UNFPA. *HIV and Infant Feeding: A Guide for Healthcare Managers and Supervisors*. Geneva, WHO, 2004. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9241591234/en/index.html](http://www.who.int/maternal_child_adolescent/documents/9241591234/en/index.html) (accessed April 2012).
- 293 Homsy J, Moore D, Barasa A *et al.* Breastfeeding, mother-to-child HIV transmission, and mortality among infants born to HIV-infected women on highly active antiretroviral therapy in rural Uganda. *J Acquir Immune Defic Syndr* 2009; **53**: 28–35.
- 294 Kilewo C, Karlsson K, Ngarina M *et al.* Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus Study. *J Acquir Immune Defic Syndr* 2009; **52**: 406–416.

- 295 Marazzi MC, Nielsen-Saines K, Buonomo E *et al.* Increased infant human immunodeficiency virus-type one free survival at one year of age in sub-Saharan Africa with maternal use of highly active antiretroviral therapy during breast-feeding. *Pediatr Infect Dis J* 2009; **28**: 483–487.
- 296 Peltier CA, Ndayisaba GF, Lepage P *et al.* Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *AIDS* 2009; **23**: 2415–2423.
- 297 Chasela CS, Hudgens MG, Jamieson DJ *et al.* Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med* 2010; **362**: 2271–2281.
- 298 Fawzy A, Arpadi S, Kankasa C *et al.* Early Weaning increases diarrhea morbidity and mortality among uninfected children born to HIV-infected mothers in Zambia. *J Infect Dis* 2011; **203**: 1222–1230.
- 299 Kafulafala G, Hoover DR, Taha TE *et al.* Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in Malawi. *J Acquir Immune Defic Syndr* 2010; **53**: 6–13.
- 300 World Health Organization. Guidelines on HIV and infant feeding 2010: principles and recommendations for infant feeding in the context of HIV and a summary of evidence. 2010. Available at [http://www.who.int/maternal\\_child\\_adolescent/documents/9789241599535/en/](http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/) (accessed April 2012).
- 301 Kilewo C, Karlsson K, Massawe A *et al.* Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr* 2008; **48**: 315–323.
- 302 Shapiro RL, Ndung'u T, Lockman S *et al.* Highly active antiretroviral therapy started during pregnancy or postpartum suppresses HIV-1 RNA, but not DNA, in breast milk. *J Infect Dis* 2005; **192**: 713–719.
- 303 Valea D, Tuaille E, Al TY *et al.* CD4+ T cells spontaneously producing human immunodeficiency virus type I in breast milk from women with or without antiretroviral drugs. *Retrovirology* 2011; **8**: 34.
- 304 House of Lords Select Committee on HIV and AIDS in the United Kingdom. *No Vaccine, No Cure: HIV and AIDS in the United Kingdom*. London, The Stationery Office Limited, 2011: Available at <http://www.publications.parliament.uk/pa/ld201012/ldselect/lddaids/188/188.pdf> (accessed April 2012).
- 305 Coutoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS* 2001; **15**: 379–387.
- 306 Centers of Disease Control and Prevention (CDC). Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures – worldwide, 1997–2000. *MMWR Morb Mortal Wkly Rep* 2001; **49**: 1153–1156.
- 307 Lambert JS, Harris DR, Stiehm ER *et al.* Performance characteristics of HIV-1 culture and HIV-1 DNA and RNA amplification assays for early diagnosis of perinatal HIV-1 infection. *J Acquir Immune Defic Syndr* 2003; **34**: 512–519.
- 308 Burgard M, Blanche S, Jasseron C *et al.* Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. *J Pediatr* 2012; **160**: 60–66.
- 309 Burgard M, Blanche S, Mayaux M *et al.* Impact of neonatal prophylaxis on early diagnosis in newborns. *10th Conference on Retroviruses and Opportunistic Infections*. Boston, MA. February 2003 [Abstract 868].
- 310 Nastouli E, Atkins M, Seery P, Hamadache D, Lyall H. False-positive HIV antibody results with ultrasensitive serological assays in uninfected infants born to mothers with HIV. *AIDS* 2007; **21**: 1222–1223.
- 311 Frange P, Burgard M, Lachassinne E *et al.* Late postnatal HIV infection in children born to HIV-1-infected mothers in a high-income country. *AIDS* 2010; **24**: 1771–1776.
- 312 Department of Health. Children's HIV National Network (CHINN) Review 2005. 2006. Available at [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_4139815.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4139815.pdf) (accessed April 2012).
- 313 Wood C, Kumalo P, Ainsworth J, Govind A, Meates M. Disclosure, discordance and decisions: the psychosocial impact of antenatal HIV testing. 2002. *6th International Congress On Drug Therapy in HIV Infection*. Glasgow, UK. November [Abstract P319].
- 314 Wood C, Ellison G. What have clinicians learnt from working with HIV/AIDS? A medical perspective from London. In: Ellison G, Parker M, Campbell C, eds. *Learning from HIV/AIDS*. Cambridge, Cambridge University Press, 2003: 105–137.
- 315 Siriwasin W, Shaffer N, Roongpisuthipong A *et al.* HIV prevalence, risk, and partner serodiscordance among pregnant women in Bangkok. Bangkok Collaborative Perinatal HIV Transmission Study Group. *JAMA* 1998; **280**: 49–54.
- 316 Guilen AC, Fogarty L, O'Campo P, Anderson J, Keller J, Faden R. Women living with HIV: disclosure, violence, and social support. *J Urban Health* 2000; **77**: 480–491.
- 317 Stein MD, Freedberg KA, Sullivan LM *et al.* Sexual ethics. Disclosure of HIV positive status to partners. *Arch Int Med* 1998; **158**: 253–257.
- 318 WHO Department of Gender, Women and Health; WHO Cluster of Family and Community Health. Gender



- dimensions of HIV status disclosure to sexual partners: rates, barriers and outcomes for women. World Health Organization. 2003. Available at [http://www.who.int/gender/documents/women\\_and\\_girls/9241590734/en/](http://www.who.int/gender/documents/women_and_girls/9241590734/en/) (accessed April 2012).
- 319 General Medical Council. Confidentiality: disclosing information about serious communicable diseases. General Medical Council. 2009; Available at [http://www.gmc-uk.org/Confidentiality\\_disclosing\\_info\\_serious\\_communicable\\_diseases\\_2009.pdf\\_27493404.pdf](http://www.gmc-uk.org/Confidentiality_disclosing_info_serious_communicable_diseases_2009.pdf_27493404.pdf) (accessed April 2012).
- 320 Serovich JM. Helping HIV-positive persons to negotiate the disclosure process to partners, family members, and friends. *J Marital Fam Ther* 2000; 26: 365–372.
- 321 Freeman E, Glynn J, for the Study Group on Heterogeneity of HIV epidemics in African Cities. Factors affecting HIV concordancy in married couples in four African cities. *AIDS* 2004; 18: 1715–1720.
- 322 Benn P, Fisher M, Kulasegaram R. UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure (2011). *Int J STD AIDS* 2011; 22: 695–708.
- 323 UK Chief Medical Officers' Expert Advisory Group on AIDS. HIV and Infant Feeding: guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS. Department of Health. 2004. Available at [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4089892](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4089892) (accessed April 2012).
- 324 Creighton S, Sethi G, Edwards SG, Miller R. Dispersal of HIV positive asylum seekers: national survey of UK healthcare providers. *BMJ* 2004; 329: 322–323.
- 325 National AIDS Trust and British HIV Association. The dispersal process for asylum seekers living with HIV: advice for health care and voluntary sector professionals. National AIDS Trust. 2006. Available at <http://www.nat.org.uk/Media%20Library/Files/PDF%20documents/NAT-Dispersal-Process-For-Asylum-Seekers.pdf> (accessed April 2012).
- 326 National AIDS Trust and British HIV Association. Detention, removal and people living with HIV: advice for health care and voluntary sector professionals. National AIDS Trust. 2009. Available at [http://www.nat.org.uk/Media%20Library/Files/Policy/Poverty%20and%20Social%20Disadvantage/NAT%20and%20BHIVA%20Booklet%20on%20HIV%20and%20Removal%20Centres%20\(June%202009\)%20EMAIL-1.pdf](http://www.nat.org.uk/Media%20Library/Files/Policy/Poverty%20and%20Social%20Disadvantage/NAT%20and%20BHIVA%20Booklet%20on%20HIV%20and%20Removal%20Centres%20(June%202009)%20EMAIL-1.pdf) (accessed April 2012).
- 327 British HIV Association, Children's HIV Association, British Association for Sexual Health and HIV. 'Don't forget the children'. Guidance for the HIV testing of children with HIV-positive parents. Children's HIV Association. 2009. Available at <http://www.chiva.org.uk/files/guidelines/dont-forget.pdf> (accessed April 2012).
- 328 British Psychological Society, British HIV Association, Medical Foundation for AIDS and Sexual Health. Standards for psychological support of adults living with HIV. MedFASH. 2011. Available at <http://www.bhiva.org/StandardsForPsychologicalSupport.aspx> (accessed April 2012).
- 329 National Institute of Health and Clinical Excellence. Antenatal and Postnatal Mental Health: clinical Management and Service Guidance. CG45. 2007. Available at <http://guidance.nice.org.uk/CG45/NICEGuidance/pdf/English> (accessed April 2012).
- 330 Moodley D, Pillay K, Naidoo K *et al*. Pharmacokinetics of zidovudine and lamivudine in neonates following coadministration of oral doses every 12 hours. *J Clin Pharmacol* 2001; 41: 732–741.
- 331 Frasca K, Fisher RG, McGuire E. Alternative dosage of zidovudine in infants exposed to maternal human immunodeficiency virus infection. *Pediatr Infect Dis J* 2009; 28: 1131–1132.
- 332 Alimenti A, Burdge DR, Ogilvie GS, Money DM, Forbes JC. Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy. *Pediatr Infect Dis J* 2003; 22: 782–789.
- 333 Durand-Gasselin L, Pruvost A, Dehee A *et al*. High levels of zidovudine (AZT) and its intracellular phosphate metabolites in AZT- and AZT-lamivudine-treated newborns of human immunodeficiency virus-infected mothers. *Antimicrob Agents Chemother* 2008; 52: 2555–2563.
- 334 Hirt D, Pruvost A, Ekouevi DK *et al*. Very high concentrations of active intracellular phosphorylated emtricitabine in neonates (ANRS 12109 trial, step 2). *Antimicrob Agents Chemother* 2011; 55: 2953–2960.
- 335 Shetty AK, Coovadia HM, Mirochnick M *et al*. Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *J Acquir Immune Defic Syndr* 2004; 34: 482–490.
- 336 Jullien V, Urien S, Hirt D *et al*. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother* 2006; 50: 3548–3555.
- 337 Verweel G, Burger DM, Sheehan NL *et al*. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir Ther* 2007; 12: 453–458.
- 338 Simonds RJ, Lindegren ML, Thomas P *et al*. Prophylaxis against *Pneumocystis carinii* pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States. Pneumocystis carinii Pneumonia Prophylaxis Evaluation Working Group. *N Engl J Med* 1995; 332: 786–790.

## Appendix 1: Summary of the modified GRADE system

BHIVA revised and updated the Association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment,

Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

---

### 1A

Strong recommendation.  
High-quality evidence.  
Benefits clearly outweigh risk and burdens, or vice versa.  
Consistent evidence from well-performed, randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.  
Strong recommendations, can apply to most patients in most circumstances without reservation.  
Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.

### 1B

Strong recommendation.  
Moderate-quality evidence.  
Benefits clearly outweigh risk and burdens, or vice versa.  
Evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk.  
Strong recommendation and applies to most patients.  
Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

### 1C

Strong recommendation.  
Low-quality evidence.  
Benefits appear to outweigh risk and burdens, or vice versa.  
Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.  
Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.

### 1D

Strong recommendation.  
Very low-quality evidence.  
Benefits appear to outweigh risk and burdens, or vice versa.  
Evidence limited to case studies. Strong recommendation based mainly on case studies and expert judgement.

### 2A

Weak recommendation.  
High-quality evidence.  
Benefits closely balanced with risks and burdens.  
Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.  
Weak recommendation, best action may differ depending on circumstances or patients or societal values.

### 2B

Weak recommendation.  
Moderate-quality evidence.  
Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens.  
Evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk.  
Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.

### 2C

Weak recommendation.  
Low-quality evidence.  
Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens.  
Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.  
Weak recommendation; other alternatives may be reasonable.

### 2D

Weak recommendation.  
Very low-quality evidence.  
Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.  
Evidence limited to case studies and expert judgment.  
Very weak recommendation; other alternatives may be equally reasonable.

---

## A1.1 References

- 1 BHIVA guideline development manual, 13th September 2011. Available at <http://www.bhiva.org/guidelinedevelopmentmanual.aspx> (accessed April 2012).
- 2 Guyatt GH, Oxman AD, Kunz R *et al*. Going from evidence to recommendations. *BMJ* 2008; 336: 1049–1051.
- 3 Development and Evaluation (Short GRADE) Working Group. The grading of recommendations assessment. Available at <http://www.gradeworkinggroup.org> (accessed April 2012).

## Appendix 2: Systematic literature search

### A2.1 Questions and PICO criteria

Databases: Medline, Embase, Cochrane Library

Conference abstracts:

- IAS Conference on HIV Pathogenesis and Treatment.
- International AIDS Conference.
- Conference on Retroviruses and Opportunistic Infections.
- European Conference on Clinical Aspects and Treatment of HIV Infection.
- International Congress on Drug Therapy in HIV Infection.
- British HIV Association Annual Conference.
- Children's HIV Association conference (CHIVA).
- International Workshop on HIV Paediatrics.
- International Conference on Antimicrobial Agents and Infectious Disease (ICAAC).
- American Association for the Study of Liver Disease (AASLD).
- European Association for the Study of the Liver (EASL).

Date parameters:

- Databases: July 2011.
- Conference abstracts: 2008–July 2011.

Five systemic literature searches were undertaken from published work and conference abstracts up until July 2011 as described in the BHIVA guidelines development manual. The population was defined as HIV-positive women covering five areas.

Search questions were set by the Writing Group within each search as listed below

### A2.2 Search 1: safety and efficacy of antiretrovirals in pregnancy

**Study design:** Systematic reviews (SRs), RCTs, observational, risk, economic

**Population:** HIV-positive women

**Intervention:** starting ART during pregnancy

**Comparator:** none

**Outcomes:** death, AIDS, non-AIDS co-morbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance.

### 1. Conceiving on HAART

Should existing ARV medication be changed? Is there a difference between maternal and infant outcomes between zidovudine and non-zidovudine-containing regimens?

Is there robust evidence in humans of excess birth defects in infants who were conceived on, or exposed in the first trimester to, efavirenz?

### 2. Naïve to HAART: mother needs ART for herself

Which ARV regimen should be recommended?

What gestation should this start?

Should she continue this after delivery?

### 3. Naïve to HAART: mother does not need HAART for herself

Which ARV regimen should be recommended?

What gestation should this start?

Should she continue this after delivery?

If she stops treatment how should this be managed?

### 4. Late-presenting woman not on treatment

Which ARV regimen should be recommended?

### 5. Pharmacokinetics

Should ARV dosages be altered in pregnancy?

### A2.3 Search 2: hepatitis viruses coinfection

**Study design:** SRs, RCTs, observational, risk, economic

**Population:** HIV/HBV/HCV coinfecting women

**Intervention:** starting ART during pregnancy

**Comparator:** none

**Outcomes:** death, AIDS, non-AIDS co-morbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance.

### 1. Hepatitis B

Which ARV regimen should be recommended?

Should this be continued after delivery?

What is the preferred mode of delivery for women with HBV coinfection?

Should all infants born to hepatitis B coinfecting mothers receive (a) hepatitis B vaccination; (b) hepatitis B immune globulin?

Should pregnant women with HBV be vaccinated against HAV?

### 2. Hepatitis C

Which ARV regimen should be recommended?

Should this be continued after delivery?

What is the preferred mode of delivery for women with HCV coinfection?

Should pregnant women with HCV be vaccinated against HBV and HAV?

Is there a place for treating hepatitis C in pregnancy to prevent MTCT of hepatitis C?

Should these women be monitored in any additional way compared to those not coinfecting?

Should the HCV be treated?

#### A2.4 Search 3: delivery, fetal monitoring and obstetric issues

**Study design:** SRs, RCTs, observational, risk, economic

**Population:** HIV-positive women

**Intervention:** obstetric delivery and fetal monitoring

**Comparator:** none

**Outcomes:** death, AIDS, non-AIDS co-morbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

##### 1. Mode of delivery

At what level would a HIV viral load be 'safe' for vaginal delivery?

When should a CS be performed?

What ART should be given during delivery?

##### 2. Obstetric procedures

When should VBAC be regarded as 'safe'?

Is it safe to perform ECV, induction of labour, instrumental delivery, episiotomy in HIV-positive pregnant women?

What fetal monitoring tests should be performed during delivery?

##### 3. Trisomy/anomaly screening tests, amniocentesis and chorionic villus sampling

Which tests are most appropriate for use in HIV-positive women?

What should be the ARV management of a woman requiring amniocentesis or chorionic villus sampling who is not yet on ART?

##### 4. Ruptured membranes

What is the optimum ART and obstetric management for women presenting with both term and preterm ROMs?

#### A2.5 Search 4: paediatric issues

**Study design:** SRs, RCTs, observational, risk, economic

**Population:** HIV-exposed infants

**Intervention:** ART and prophylaxis for neonates

**Comparator:** none

**Outcomes:** death, AIDS, non AIDS co-morbidities, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance.

##### 1. Infant post-exposure prophylaxis

Which drugs should be used for infant PEP and for how long?

Should PCP prophylaxis be administered to the neonate?

##### 2. Infant feeding

Is an update required to the BHIVA position statement?

If mother breastfeeds, how frequently should mother and baby be monitored and what tests should be used?

How should infants be fed (breast or bottle)?

##### 3. Infant testing

What tests should be undertaken on the neonate and when?

#### A2.6 Search 5: investigations and monitoring in pregnancy

**Study design:** SRs, RCTs, observational, risk, economic

**Population:** HIV-positive women

**Intervention:** starting ART during pregnancy

**Comparator:** none

**Outcomes:** death, AIDS, non AIDS co-morbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance.

##### 1. HIV monitoring

What baseline tests should be recommended for HIV-positive women?

How often should they be repeated?

How should we investigate and manage abnormal liver function in pregnancy?

##### 2. Sexual health

When should we recommend sexual health screening and how often?

How should we manage genital infections in HIV-positive pregnant women?

## Appendix 3 Search protocols (main databases search)

### A3.1 Search 1: when to initiate antiretroviral therapy

Component	Description
Review area	<b>Safety and efficacy of antiretrovirals in pregnancy</b>
Objectives	To assess the benefits and risks of ART in pregnancy
Populations	HIV-positive women who are pregnant, HIV-positive women of child-bearing age
Interventions	ART (all drugs)
Comparisons/aspects covered by search	Between antiviral regimens and historical data where appropriate
Outcomes	To be decided by Writing Groups
Study designs	SRs, RCTs, observational studies, risk, economic
Exclusions	Animal studies, letters, editorials, comments, case reports, non-English studies
How the information was searched	Databases: Medline, Embase, Cochrane Library, Conference abstracts 2008–2011 Language: restrict to English only Date parameters: –July 2011
Search terms and date searched	HIV + all preg/obs + ARVs
Search results	Published abstracts: 239 Conference abstracts: 105
Key papers	Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. <i>AIDS</i> 2008; <b>22</b> : 973–981. Tariq S, Townsend CL, Cortina-Borja M <i>et al.</i> Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000–2009. <i>J Acquir Immune Defic Syndr</i> 2011; <b>57</b> : 326–333. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. <i>AIDS</i> 2011; <b>25</b> : 2301–2304.

### A3.2 Search 2: hepatitis coinfection

Component	Description
Review area	<b>Hepatitis B and C coinfection</b>
Objectives	To assess the benefit of ART on coinfecting pregnant women
Populations	HIV positive, HBV and or HCV coinfecting pregnant women
Interventions	ART Anti-hepatitis therapy
Comparisons/aspects covered by search	Risks of each/all drugs to mother and fetus
Outcomes	To be decided by Writing Groups
Study designs	SRs, RCTs
Exclusions	Animal studies, letters, editorials, comments, case reports, non-English studies
How the information was searched	Databases: Medline, Embase, Cochrane Library, Conference abstracts: 2008–2011 Language: restrict to English only Date parameters: –2011
Search terms and date searched	HIV + preg/ obs/ neonates + hepatitis
Search results	Published abstracts: 31 Conference abstracts: 2
Key papers	Brook G, Main J, Nelson M <i>et al.</i> British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. <i>HIV Med</i> 2010; <b>11</b> : 1–30.

## A3.3 Search 3: fetal monitoring and obstetric issues

Component	Description
Review area	<b>Fetal monitoring and obstetric issues</b>
Objectives	To establish the safest mode of delivery for mother and child in most obstetric scenarios where the mother is HIV positive
Populations	HIV-positive pregnant women
Interventions	Modes of delivery Fetal monitoring Management of obstetric complications
Comparisons/aspects covered by search	Comparisons of outcomes by modes of delivery, choice of ARV drugs, routes of delivery and duration.
Outcomes	To be decided by Writing Groups
Study designs	SRs, RCTs
Exclusions	Animal studies, letters, editorials, comments, case reports, non-English studies
How the information was searched	Databases: Medline, Embase, Cochrane Library Conference abstracts: 2008–2011 Language: restrict to English only Date parameters: 2008–current
Search terms and date searched	HIV + specific preg/ obs/ procedures delivery, fetal monitoring
Search results	Published abstracts: 196 Conference abstracts: 41
Key papers	European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. <i>Clin Infect Dis</i> 2005; <b>40</b> : 458–465. Warszawski J, Tubiana R, Le Chenadec J <i>et al</i> . Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. <i>AIDS</i> 2008; <b>22</b> : 289–299. Boer K, England K, Godfried MH, Thorne C. Mode of delivery in HIV-positive pregnant women and prevention of mother-to-child transmission: changing practices in Western Europe. <i>HIV Med</i> 2010; <b>11</b> : 368–378.

## A3.4 Search 4: paediatric issues

Component	Description
Review area	<b>Management of the child born to an HIV-positive mother</b>
Objectives	Establish optimum management of the child to prevent acquisition of maternal HIV
Populations	Children born to HIV-positive mothers
Interventions	Neonatal prophylaxis, treatment of mother Formula feeding
Comparisons/aspects covered by search	Strategies involving the above
Outcomes	To be decided by Writing Groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, non-English studies
How the information was searched	Databases: Medline, Embase, Cochrane Library Conference abstracts: 2008–2011 Language: restrict to English only Date parameters: 2008–current
Search terms and date searched	HIV + neonates and infant feeding
Search results	Published abstracts: 464 Conference abstracts: 45
Key papers	Connor EM, Sperling RS, Gelber R <i>et al</i> . Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. <i>N Engl J Med</i> 1994; <b>331</b> : 1173–1180. Brooks Jackson J, Musoke P, Fleming T <i>et al</i> . Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18 month follow-up of the HIVNET 012 randomised trial. <i>Lancet</i> 2003; <b>362</b> : 859–868. Haile-Selassie H, Townsend C, Tookey P. Use of neonatal post-exposure prophylaxis for prevention of mother-to-child HIV transmission in the UK and Ireland. <i>HIV Med</i> 2011; <b>12</b> : 422–427.

## A3.5 Search 5: investigations and monitoring in pregnancy

Component	Description
Review area	<b>Investigations and monitoring in pregnancy in HIV-positive women</b>
Objectives	To establish which additional investigations are needed for an HIV-positive woman in pregnancy and how often they should be undertaken
Populations	HIV-positive pregnant women
Interventions	STI screening, monitoring of virological response to ART, monitoring of toxicity of medication
Comparisons/aspects covered by search	Risk of each/all drugs
Outcomes	To be decided by Writing Groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, non-English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Conference abstracts:2008–2011 Language: restrict to English only Date parameters: –2011
Search terms and date searched	HIV + specific tests in pregnancy e.g. LFTs/BV/herpes
Search results	Published abstracts: 152 Conference abstracts: 25
Key papers	UK National Screening Committee. Infectious Diseases in Pregnancy Screening Programme: 2008–2009 Annual Report. NHS Screening Programmes

## Appendix 4

**A4.1 Antiretroviral therapies for which sufficient numbers of pregnancies with first trimester exposure have been monitored to detect a twofold increase in overall birth defects**

To date such an increase has not been detected. (Data from the Antiretroviral Pregnancy Registry <http://www.apregistry.com>, accessed 27 April 2012; data to end July 2011.)

Abacavir  
Atazanavir  
Efavirenz  
Emtricitabine  
Indinavir  
Lamivudine\*  
Lopinavir  
Nevirapine  
Ritonavir\*  
Stavudine  
Tenofovir  
Zidovudine\*

\*Sufficient data to detect a 1.5-fold increase in overall birth defects.

## A4.2 Advisory Committee Consensus

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause. The Registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with its population-based comparator, the MACDP. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counselling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Health care providers are encouraged to report eligible patients to the Registry at <http://www.APREgistry.com>.