

Guidelines for the management of HIV infection in pregnant women 2012

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1. 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 co-infection 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; 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 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 prior to 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 the guideline development.

1.3 Dissemination and implementation

The following measures have/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. The writing committee will however continue to meet regularly to consider new information from high quality studies and publish amendments and addendums to the current recommendations prior to the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

2. Recommendations and auditable outcomes

2.1 Recommendations

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 prior to initiation of treatment (as per the *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*[REF], 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 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 viral load 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 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 viral load of <50 HIV RNA copies/mL at 36 weeks the following interventions are recommended: Grade 1C

- Review adherence and concomitant medication
- Perform resistance test if appropriate
- Consider therapeutic drug monitoring (TDM)
- Optimise to best regimen
- Consider intensification

Section 5: Use of antiretroviral therapy in pregnancy

5.1 Conceiving on HAART

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:

(1) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta. Grading: 2D

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

5.2 Naïve to HAART: mother needs ART for herself

5.2.1 Women requiring ART for their own health should commence treatment as soon as possible as per the *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*[REF]. Grading: 1A

5.2.2 Although there is most evidence and experience in pregnancy with zidovudine Grading: 2C

plus lamivudine, tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable nucleoside backbones.

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 less than 250 cells/ μ 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 HAART: mother does not need HAART 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 viral load is <100 000 HIV RNA copies/mL plasma. Grading: 1C

5.3.4 Zidovudine monotherapy can be used in women planning a caesarean section who have a baseline VL of <10 000 HIV RNA copies/mL and a CD4 of >350 cells/ μ 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 viral load 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 mother to child transmission (PMTCT) without waiting for further/formal serological confirmation. Grading: 1D

5.5 Elite controllers

- 5.5.1** Untreated women with a CD4 cell count ≥ 350 cells/ μ L and a viral load of <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** Antiretroviral 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/ μ L as per adult treatment guidelines. Grading: 1B
- 5.6.3** ART should be continued in all women who commenced HAART for MTCT with Grading: 1B

a CD4 cell count of between 350 and 500 cells/ μ l during pregnancy who are co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) in accordance with adult treatment guidelines.

- 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/ μ 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/ μ l unless there is discordance with her partner or co-morbidity as outlined in Section 6. Grading: 2B

Section 6: HIV and hepatitis virus co-infections

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** Liver function tests 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, liver function tests 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** Since there is no evidence of any adverse effect on maternal or neonatal health if women become pregnant while taking antiretroviral therapy active against HBV these should be continued. Grading: 1C
- 6.1.6** In all HAV non-immune HBV co-infected 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/ μ l when an additional dose may be indicated. Grading: 1D
- 6.1.7** Tenofovir and emtricitabine should form the backbone of an antiretroviral Grading: 1B

- regimen in naive patients with wild-type HIV/HBV infection and no contraindication to any drug.
- 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 antiretroviral 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 co-infection. Grading: 2D
- 6.1.12** Where the CD4 cell count is <500 cells/ μ L HAART should be continued postpartum if HBV co-infection exists because of the increased risk of HBV progressive disease. Grading: 1B
- 6.1.13** Where the CD4 cell count is >500 cells/ μ 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/ μ 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 viral load on HAART. Grading: 2C
- 6.1.18** Neonatal immunization with or without HBIG should commence within 24 hours of delivery. Grading: 1A

6.2 Hepatitis C virus

- 6.2.1** On diagnosis of new HCV infection, confirmation of HCV viraemia with Grading: 1C

- quantitative viral load (VL) and genotype, assessment of hepatic inflammation and function and concomitant liver disease should be performed.
- 6.2.2** Liver function tests 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** Co-infected 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 co-infected 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/ μ 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/ μ L, HAART should be continued if active HCV co-infection 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/ μ 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/ μ 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/ μ 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

Section 7: Obstetric management

7.1 Ante-natal care

- 7.1.1 Fetal ultrasound imaging should be performed as per national guidelines Grading: 1D

- regardless of maternal HIV status.
- 7.1.2 The combined screening test for trisomy 21 is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing. Grading?
- 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 viral load 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 hours prior to 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 viral load <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 viral load results at 36 weeks.
 - For women with a plasma viral load 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 viral load of 50-399 HIV RNA copies/mL at 36 weeks, PLCS should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.
 - Where the viral load 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 Caesarean section (VBAC) should be offered to women with a viral load <50copies/ml. Grading: 1D

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

7.3 Management of spontaneous rupture of membranes

- 7.3.1** In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited. Grading: 1C
- 7.3.2** If maternal HIV viral load 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 viral load of 50-999 HIV RNA copies/mL, immediate Caesarean section should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views. Grading: 1C
- 7.3.4** If maternal HIV viral load is ≥ 1000 RNA copies/mL plasma immediate Caesarean section is recommended. Grading: 1C
- 7.3.5** The management of prolonged premature rupture of membranes (PPROM) at ≥ 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 optimised
 - 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 viral load of >10,000 HIV RNA copies/mL plasma who present in labour, or with ruptured membranes or who are admitted for planned CS Grading: 1C
- For untreated women presenting in labour or with ruptured membranes in whom the current viral load is not known. Grading: 1B
- In women on zidovudine monotherapy undergoing a PLCS intravenous zidovudine can be considered. Continued oral dosing is a reasonable alternative.

Section 8 Neonatal management

8.1 Infant post-exposure prophylaxis (PEP)

8.1.1 Zidovudine monotherapy is recommended if maternal viral load is <50 HIV RNA copies/mL at 36 weeks' gestation or thereafter prior to delivery (or mother delivered by PLCS whilst on zidovudine monotherapy). Grading: 1C

8.1.2 Infants <72 hours old, born to untreated HIV-positive mothers, should immediately initiate three drug therapy for four weeks. Grading: 1C

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

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

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

8.2. Pneumocystis pneumonia (PCP) prophylaxis

8.2.1 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 viral load at 36 weeks gestational age or at delivery is >1,000 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 antiretroviral therapy, 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 viral load chooses to breast feed, this should not constitute grounds for automatic referral to child protection teams. Maternal HAART should be carefully monitored and continued until one 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 viral load, and monthly testing of the infant for HIV by PCR for HIV DNA or RNA (viral load). Grading: 1D

8.5 Infant testing

- 8.5.1** HIV DNA PCR (or HIV RNA testing) should be performed on the following occasions:
- During the first 48 hours and prior to 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

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

- 1 Proportion of pregnant women newly diagnosed with HIV having a sexual health screen.
- 2 Proportion of newly diagnosed women, requiring HAART for their own health, starting treatment within 2 weeks of diagnosis.
- 3 Proportion of women who have commenced ART by beginning of week 24 of pregnancy.
- 4 Proportion of women with a baseline HIV viral load >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).
- 5 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.
- 6 Proportion of women with hepatitis B virus co-infection who have liver function tests performed 2 weeks after commencing HAART to detect evidence of antiretroviral hepatotoxicity or IRIS.
- 7 Proportion of women with hepatitis C virus co-infection who have liver function tests performed 2 weeks after commencing HAART to detect evidence of antiretroviral hepatotoxicity or IRIS.
- 8 Proportion of women who have invasive prenatal diagnostic testing performed before their HIV status is known.

- 9 Proportion of emergency Caesarean sections performed and their indication.
- 10 Proportion of infants <72 hours old, born to untreated HIV-positive mothers, initiating three-drug therapy within 2 hours of delivery.
- 11 Proportion of routine neonatal PEP commenced within 4 hours of delivery.
- 12 Proportion of infants born to HIV-positive mothers who have HIV antibody testing for seroreversion performed at age 15–24 months.

3. Introduction

One of the major successes in the management of HIV-positive patients has been the prevention of MTCT 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 randomized controlled trials regarding the use of antiretroviral therapy (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 committee 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 Caesarean sections 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 Caesarean sections. Linked to this is the proposed starting gestation for women temporarily taking highly active antiretroviral therapy (HAART) in pregnancy, which has been brought forward depending on baseline viral load. It is anticipated that this will result in a larger proportion of women achieving a viral load of <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 hepatitis B virus or hepatitis C virus co-infection. For the first time these guidelines have addressed the issue of continuation of HAART post delivery in women with a baseline CD4 cell count of more than 350 cells/ μ L.

The paediatric section provides further guidance on infant post-exposure prophylaxis (PEP), drug dosing and safety. It is clear that there exists an urgent need for paediatric syrup preparations for a

wider variety of antiretroviral 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 amongst 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 (one in every 449). Prevalence in London was about one in 350 in 2000, rising to one in 250 by 2003 and has been relatively stable since then. In the rest of England, about one in 3500 women giving birth was HIV positive in 2000, rising to one in 700 by 2006, and remaining stable since then. In Scotland prevalence increased from about one in 2150 in 2000 to one 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 around 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 (one 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 less than 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 viral load, there were only three transmissions, 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 prior to delivery: the proportion of those who were taking zidovudine monotherapy dropped from around 20% in 2002–2003 to less than 5% since 2006, and only about 2% in 2009–2010. Over the same period the proportion of women delivering by elective Caesarean section (CS) declined from about two-thirds to just over one-third, while vaginal deliveries increased from less than 15% of all deliveries to almost 40%. Although planned vaginal delivery is now common for women who are on HAART with undetectable viral load close to delivery, the increase in planned vaginal deliveries may have contributed to a rise in reported emergency CS, from around 20% to about 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 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 around 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. Due 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 prior to 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 still 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 prior to 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 around 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 antiretroviral 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

3.5 National Study of HIV in Pregnancy and Childhood (NSHPC)

This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, based at the Institute of 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 (www.nshpc.ucl.ac.uk), the CHIPS website (www.chipscohort.ac.uk), or email NSHPC (nshpc@ich.ucl.ac.uk).

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

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 four-fold 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, hepatitis B virus (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 viral load 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 to HIV-uninfected women.

Viral load in cervicovaginal specimens has been shown to correlate with HIV-1 MTCT [18]. Genital tract viral load will usually mirror the plasma viral load [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 viral load [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 viral load provide some reassurance that the 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 viral load 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 (CVL) showed that HSV-2 shedding was associated with increased risk of intrapartum HIV transmission and that the effect was independent of CVL and plasma HIV viral load. This study was however 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 to HIV-negative women 30.8% *versus* 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 rupture of membranes 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 mother-to-child transmission 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, the 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 randomized controlled trials 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 around 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), followed by a test of cure. Partner notification should take place where indicated, to avoid re-infection.

With regard to cervical cytology, HIV-positive pregnant women should be managed as per the Guidelines for the NHS Cervical Screening Programme 2010 [48]. Routine cytology should be

deferred until after the 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 prior to initiation of treatment (as per BHIVA Adult Guidelines), 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 viral load should be performed 2–4 weeks after commencing HAART, at least once every trimester, at 36 weeks and at delivery. Grading: 1C
Performing a viral load 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 liver function tests should be performed as per routine initiation of HAART and then at each antenatal visit. Grading: 1C

Hepatotoxicity may occur as a result 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 viral load of <50 copies/mL at 36 weeks the following interventions are recommended:

Grade 1C

- **Review adherence and concomitant medication**
- **Perform resistance test if appropriate**
- **Consider therapeutic drug monitoring (TDM)**
- **Optimise to best regimen**
- **Consider intensification**

For a woman who conceives on HAART that is not fully suppressive or loses virological control during the 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. Use of antiretroviral therapy in pregnancy

5.1 Conceiving on HAART

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:

(1) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta. Grading: 2D

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

Despite the lack of licence for the use of antiretroviral therapy 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 antiretroviral therapy exposure. This prospective database records rates of congenital birth defects in babies born to women with first-trimester exposure to antiretroviral therapy in comparison to 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 antiretroviral 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 greater than 1.5-fold higher than the general population has been excluded. Amongst 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 two-fold 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 had microphthalmia; and the third had 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 cases reported compared to 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 two-fold increase in risk of overall birth defects and no such increases have 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 preterm delivery. 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 antiretroviral 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 IeDEA 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 T1/T2/T3. 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 also accepted reports up to 6 months 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 pregnancy without additional precautions and considerations over and above those of other antiretroviral therapies.

Non-pregnant adults 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 less than 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 viral load, whether antiretroviral therapy is taken in pregnancy and the time on therapy prior to 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 viral load less than 50 HIV RNA copies/mL at delivery)[63]. However, as newer therapies become established, the degree of transplacental transfer of the components of combination should be considered.

While ritonavir-boosted protease inhibitor therapy can maintain suppression of viral load, 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 protease inhibitor 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 HAART: mother needs ART for herself

5.2.1 Women requiring ART for their own health should commence treatment as soon as possible as per the adult treatment guidelines. Grading: 1A

When considering the optimal time to start HAART, the theoretical considerations for avoiding medication during pregnancy, and the first trimester in particular, must be considered in the light of the increasing safety data on first-trimester exposure to ART, the risk to maternal health (and fetal exposure to opportunistic infections), the risk of MTCT and the time required to achieve an undetectable viral load 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 on the basis of 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 prior to, 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 on the basis of safety, tolerability and efficacy (BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012 [REF]). 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, transplacental 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 less than 250 cells/ μ 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, the BHIVA treatment guidelines [REF] 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 since 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 of less than 250 cells/ μ 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, preterm delivery (see below) and pharmacokinetics during the third trimester (discussed separately) several ritonavir-boosted protease inhibitors 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 viral load was longer in women initiating protease inhibitor-based HAART; however, in this study 80% of these women were taking nelfinavir [82]. In a more recent study, treatment with a boosted protease inhibitor resulted in more rapid viral suppression (to <50 HIV RNA copies/mL) than nevirapine, except in the highest viral load quartile [83]. In another multicentre, study nevirapine-based HAART reduced viral load 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 viral load rather than then 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 (PTD)

The data on the association of HAART and PTD are conflicting. Some studies implicate boosted protease inhibitors, 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 protease inhibitor [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 to 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 to those on a non-boosted PI regimen (HR 2.03; 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 antiretroviral regimens in breastfeeding populations in relation primarily to HIV MTCT. The Mma Bana study from Botswana randomly allocated 560 women at 26–34 weeks' gestation, with CD4 cell counts >200 cells/ μ 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/ μ 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 protease inhibitors. 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 PROMISE study (NCT01061151), with 6000 women randomly allocated to either 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 α_1 acid glycoprotein; renal sodium reabsorption increases; and changes occur in the metabolic enzyme pathway in the liver, including changes in CYP450. Caution should be exercised if women fall pregnant on unlicensed doses and consideration given to performing therapeutic drug monitoring (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].

Amongst 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 that are in the therapeutic range [113]. There are currently no data on the pharmacokinetics of etravirine and rilpivirine in pregnant women.

Protease inhibitors 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 twice daily (b.d.) (lopinavir 600 mg/ritonavir 150 mg) achieved similar area under the curve levels to non-pregnant adults taking the standard dose of two tablets b.d. [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 tablets 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 area under the curve (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 to 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. Therapeutic drug monitoring 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, whilst dosing twice a day produced levels more comparable to 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_{24h}) in the third trimester and postpartum was 1.37 (0.15–3.49) $\mu\text{g/mL}$ and 2.59 (<0.09–3.96) $\mu\text{g/mL}$ 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 b.d. [124]. The mean trough levels (C_{24h}) in the third trimester and postpartum were 1.46 (0.66–2.33) $\mu\text{g/mL}$ and 2.24 (1.17–5.32) $\mu\text{g/mL}$, 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_{50} (0.146 $\mu\text{g/mL}$) 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, therapeutic drug monitoring 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, therapeutic drug monitoring 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 whilst 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 HAART: mother does not need HAART 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 amongst 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 viral load is <100 000 HIV RNA copies/mL plasma. Grading: 1C

The prolonged half-life of NNRTIs make 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 a randomized controlled trial (RCT) in pregnant women with a CD4 cell count >200 cells/ μ l (with no viral load 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 viral loads <400 HIV RNA copies/mL plasma despite baseline viral loads >100 000 in 15% and 13%, respectively, with significantly more women in the NRTI-only group achieving viral load <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]. Preterm delivery (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. Fixed-dose combination zidovudine, lamivudine, 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 to other highly active combinations of antiretroviral therapy when the baseline viral load is greater than 100 000 HIV RNA copies/mL plasma (BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012[REF]). Although these groups are not comparable, the Writing Group recommend restricting the use of zidovudine, lamivudine and abacavir for PMTCT to women with baseline viral loads <100 000 HIV RNA copies/mL plasma.

5.3.4 Zidovudine monotherapy can be used in women planning a Caesarean section who have a baseline VL of <10 000 HIV RNA copies/mL and a CD4 cell count of >350 cells/ μ L. Grading: 1A

The 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-breast breastfeeding, low CS rate, baseline CD4 cell count >200 **cells/ μ 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 pre-labour CS 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 viral load of <10 000 HIV RNA copies/mL plasma, based on these and other data and on the published relationship between viral load and transmission [132]. No transmissions were observed in the UK and Ireland amongst the 464 pregnancies managed by zidovudine monotherapy and PLCS between 2000 and 2006 reported to the NSHPC. The median delivery viral load 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

Viral load data also influence recommendations relating to mode of delivery (see below). Major determinants of the probability of achieving a viral load <50 HIV RNA copies/mL plasma by the time of delivery are the baseline untreated viral load and the time available to achieve this target. In the Mma Bana study, the viral loads <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 viral load <1000 HIV RNA copies/mL plasma and in 86% (lopinavir/ritonavir-based) to 90% (abacavir/lamivudine/zidovudine) if baseline viral load >100, 000 HIV RNA copies/mL. When therapy was initiated therapy at 31–34 weeks, only 78% of mothers on PI-based therapy had achieved this target [66]. Data from a UK multicentre 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 viral load in the upper quartile (>32, 641 HIV RNA copies/mL) with only 46% achieving <50 HIV RNA copies/mL by 36 weeks gestational age (the data point used to make most delivery management decisions) and this fell to 37% for viral loads >100, 000 HIV RNA copies/mL [133]. For all viral loads greater than 10, 000 HIV RNA copies/mL,

treatment initiation later than 20.3 weeks' gestation was associated with significantly less likelihood of successful viral load 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 viral load of >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 viral load 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 viral load of <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, viral load and viral resistance tests will impact on this choice.

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

Where the viral load 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 antiretrovirals [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 hours 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 a Caesarean section should be considered. If delivery occurs less than 2 hours 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 viral load 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 (POCT) should be performed. Women who have previously tested negative in pregnancy but who have ongoing risk for HIV should also have a POCT if presenting in labour. If the test is positive (reactive) a confirmatory test should be sent but treatment to prevent mother-to-child transmission should commence immediately. Where POCT 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, viral load 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 ≥ 350 and a viral load of < 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 viral load assays on more than one occasion. It is estimated that one in 300 HIV-positive individuals are elite controllers [140].

In the absence of data from randomized controlled trials on elite controllers, recommendations are based on randomized controlled trial and observational data on all pregnant HIV-positive women.

In the original zidovudine monotherapy study (ACTG 076) the transmission rate if maternal viral load was < 1000 HIV RNA copies/mL was 1% (range 0–7%)[61]. Treatment reduced transmission even among women with low or undetectable HIV viral load, 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 viral load < 1000 HIV RNA copies/mL at delivery was associated with a relatively low risk of transmission and that antiretroviral 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 mother-to-child transmission 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 antiretroviral therapy. The Writing Group therefore recommends vaginal delivery for all elite controllers on antiretroviral therapy.

5.6 Stopping ART postpartum

5.6.1 The discontinuation of NNRTI-based HAART postpartum should be according to the BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012 [REF]. Grading: 1C

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

5.6.2 Antiretroviral 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/ μ 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 is sparse and has 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 the results from CD4-guided interruption studies (SMART [149] and TRIVICAN [150] in particular) although the interruption of ARV given for MTCT 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 the internationally accepted treatment guidelines for all adults as well as incorporating the evidence available from the limited data there is 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, a randomized study (the HAART Standard Version of the Promoting Maternal and Infant Survival Everywhere [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/ μ L during pregnancy who are co-infected with HBV or HCV in accordance with the *BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012*[REF]. Grading: 1B

There is evidence that continuing ART in patients co-infected 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/ μ 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/ μ L. Moreover two recent retrospective reviews in women discontinuing ARV 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/ μ 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 had previous ARV exposure and 36% had a pre-ARV CD4 cell count of < 350 cells/ μ L. Lastly, in a large cohort of women who were enrolled in South America and followed up for 6–12 weeks after discontinuation of ARVs given to prevent MTCT, significant falls in the CD4% were seen as would be expected [146].

Other studies have shown no detriment in discontinuing treatment postnatally on disease progression. 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/ μL , 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/ μL who received zidovudine monotherapy during pregnancy. More persuasively, among women with CD4 cell counts >350 cells/ μL 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 antiretroviral treatment after delivery [148]. Finally, in an audit to document postpartum disease-free survival of HIV-positive women taking ARV during pregnancy, 40% of mothers (nadir CD4 cell count median 317 cells/ μL) 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/ μL and the majority having counts between 201 and 500 cells/ μL (66%) at cART commencement. 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/ μL has detrimental effects but it is conceivable that treatment at this stage may prevent future morbidity. In view of this, where the patient preference is to continue therapy and the physician believes that there is no potential contraindication, in particular poor adherence postpartum, we believe that 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 women with a baseline CD4 cell count >350 cells/ μL and an HIV viral load >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 of >500 cells/ μ l unless there is discordance with her partner or co-morbidity as outlined in Section 6: HIV and hepatitis virus co-infections. Grading: 2B

Only one cohort study has demonstrated benefit in starting therapy in adults who have a CD4 cell count >500 cells/ μ L (NA-ACCORD)[151]: specifically, this was not observed in the ART-CC analysis [158]. In addition, several small CD4-guided interruption studies using a higher threshold than SMART of commencing below 350 cells/ μ L (TRISTAN [159], STACCATO [160]) and seroconversion treatment studies have not shown significant clinical benefit with fixed courses of early treatment [161]. Lastly, durable CD4 cell count benefits have been demonstrated in women receiving short-term ARV therapy to prevent MTCT when initiating above 500 cells/ μ L indicating no short-term harm in this strategy and possible benefits [162].

6. HIV and hepatitis virus co-infections

6.1 Hepatitis B

The combination of HIV, chronic hepatitis B virus (HBV) infection and pregnancy presents unique management questions. Referral to the local designated specialist should be undertaken to ensure that all aspects of care, including the effects of HBV/HIV on pregnancy, effects of pregnancy on the course of co-infection, drug management for both HBV and HIV, and prevention of mother-to-infant transmission for both viruses are addressed. The prevalence of HBV co-infection in pregnant women tends to reflect that of the adult population (Europe/Africa 4–10%)[163–166] 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)[166] Up to one-third of HBsAg are wild type (HBeAg-positive) and, depending on region, up to 6% co-infected with hepatitis delta virus. Rates of HBV/HIV co-infection 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% amongst Asian women in the USA vs. 0.6% in white women)[167]. 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 MSM). Although plausible because of higher levels of HBV-DNA in co-infected women, there is no evidence of increased MTCT in co-infection 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 log₁₀. 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, a higher rate of chronicity (20–80% compared to 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-HBeAb and anti-HBsAb, faster progression to cirrhosis, and a higher incidence of lamivudine resistance [168].

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 Liver function tests 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, liver function tests 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 (HBcAb/HBeAg status) and level of the virus (HBV DNA), the degree of inflammation and synthetic function (ALT, AST, albumin, INR), an assessment of fibrosis, and the 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 co-infection (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 [169]. 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 liver function tests (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 Since there is no evidence of any adverse effect on maternal or neonatal health if women become pregnant while taking antiretroviral therapy 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 as 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) was 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 co-infected 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 co-infection 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 [170] and international guidelines [171].

6.1.6 In all HAV non-immune HBV co-infected 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/ μ 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 co-infected pregnant women [172,173]. 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/ μ 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 antiretroviral regimen in naive patients with wild-type HIV/HBV infection and no contraindication to any 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 antiretroviral 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 co-infection. Grading: 2D

All HBV/HIV co-infected 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 likelihood of HBV resistance in co-infected 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 co-infected patients and may induce HBeAg seroconversion although, as for other antivirals, this may be less likely in co-infection. 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 [170].

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 co-infected patients. In co-

infected patients naïve to antivirals, in an RCT, combining emtricitabine with tenofovir has been shown to be more effective than emtricitabine alone (median TWAC decrease was $-5.32 \log_{10}$ IU/mL in the tenofovir/emtricitabine group vs. -3.25 IU/mL in the emtricitabine group: $P=0.036$)[174].

Further studies comparing emtricitabine/lamivudine with lamivudine alone produced similar results [175]. In addition, the PROMISE study includes a substudy examining pregnant women with CD4 cell counts >350 cells/ μ L randomly allocated to either tenofovir/emtricitabine or zidovudine/lamivudine and lopinavir/ritonavir with outcome measures of pregnancy HBV viral loads, HBV transmission, pregnancy outcomes, and postpartum ALT and HBV viral load. 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 HBV co-infection.

6.1.12 Where the CD4 cell count is <500 cells/ μ L, HAART should be continued postpartum if HBV co-infection exists because of the increased risk of HBV progressive disease. Grading: 1B

6.1.13 Where the CD4 cell count is >500 cells/ μ 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/ μ 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

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) co-infection should receive ARVs if their CD4 cell count is <500 cells/ μ L [171,172]. 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/ μ 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 co-infected 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 co-infection. In those with CD4 cell counts over 500 cells/ μ 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 co-infection.

Inflammatory flares, which may be severe, particularly in persons with cirrhosis can occur as a result of viral escape and HBV viraemia, if drugs with anti-HBV activity 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 [176].

Similarly, hepatitis flares among HIV/HBV co-infected 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 [177] 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 viral load on HAART. Grading: 2C

No data exists to support any benefit from PLCS in mothers with HBV/HIV co-infection 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 pre-labour Caesarean section versus vaginal delivery could effectively reduce the rate of mother-to-infant transmission of HBV (RR 0.41; 95% CI 0.28–0.60)[178]. However, methodological concerns including lack of information on randomization procedure, lack of allocation concealment and lack of blinding make the role of PLCS for preventing mother-to-child transmission 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)[179]. Similarly, a single RCT in women positive for HBsAg and with an HBV DNA $>10^6$ 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 the lack of any cohort or RCT data to support the use of CS in co-infection argue against advocating this in co-infected 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, the efficacy of lamivudine, tenofovir and emtricitabine as part of HAART in reducing HBV DNA in non-pregnant co-infected patients, and the use of tenofovir with either lamivudine or emtricitabine as standard practice in co-infected patients, collectively provide further reason against recommending CS in those co-infected.

6.1.18 Neonatal immunization with or without HBIG should commence within 24 hours 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 and HBeAg -positive is 70–90% and for women who are HBsAg-positive but HBeAg-negative, 10–40%. By coadministering 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 their 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 more than 1.1×10^7 IU/mL. Antiretroviral therapy with HBV activity (lamivudine/emtricitabine, tenofovir) can reduce this risk to a negligible level [180].

6.2 Hepatitis C virus (HCV)

Antenatal prevalence of HCV mono-infection ranges from less than 1 to about 2.5% increasing to 3–50% in co-infection 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 [181,182]. Several meta-analyses and systematic reviews have shown the overall rate of mother-to-child transmission for HCV approximates 5% (range 2–10%) if the mother is anti-HCV-positive only. Co-infection is associated with a significant increase in HCV transmission (OR up to 2.82) compared to HCV mono-infection [183–185]. In addition a higher rate of MTCT is seen in mothers who are co-infected and HCV viraemic compared to those who are co-infected and non-viraemic (OR 2.82) as well as to HCV viraemic but HIV-negative (OR 1.97)[183,184]. 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 co-

infected with HIV and HCV than from those infected with HIV only (OR 1.82) where a modest association was found with HCV viral load [186]. Numerous studies have shown that the height of the HCV viral load correlates with the risk of HCV MTCT and it is likely there is a linear relationship between VL and transmission as for HIV [187,188]. Invasive obstetric procedures, internal fetal monitoring, prolonged rupture of membranes and female infant sex have also been associated with transmission but breastfeeding and CS do not pose an additional risk in mono-infected mothers [189,190]. Effective HAART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia [190,191]. No correlation with HCV genotype or interleukin-28 polymorphisms and transmission has been identified [192–194]. 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 [195].

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 Liver function tests 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 viral load), the genotype and subtype, the degree of inflammation and synthetic function (ALT, AST, albumin, INR), an assessment of fibrosis, and the 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 co-infection (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 [169]. 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 ante-natal 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 viral load through pregnancy at 4-weekly intervals. In chronically infected patients there is unlikely to have been significant change in the HCV viral load. However, the prenatal viral load will give some idea as to the likelihood of MTCT risk 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 recognised that a small number of co-infected 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 viral load assay should be performed.

6.2.3 Co-infected 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 bocepravir 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 the male partners of women who are pregnant. Hence, active treatment during pregnancy can only be considered once directly acting anti-viral 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 [196]. Given the evidence from animal data, women with co-infection 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 co-infected 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 [197]. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HBV or HAV immunization, including in HCV co-infected pregnant women [198,199]. 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 prior to delivery [200]. 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 less than 300 cells/ μ 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/mL should receive three doses of HAV vaccine over 6–12 months instead of the standard two [201].

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 study mothers who underwent CS compared with mothers who gave birth vaginally (OR 1.1 [202] to OR 1.19 [185]). In the first European Paediatric Hepatitis Network cohort, a subgroup analysis of women co-infected 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)[185]. However in a later analysis from the EPHN ($n=208$, 15.0%) no such association was found (OR 0.76; 95% CI 0.23–2.53)[190]. 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 viral load 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 viral

load in this group, which may go some way to explaining this. Also, in a small French cohort of co-infected women (29% on HAART), rate of transmission did not differ significantly between children born by vaginal delivery or CS [203]. HAART should be given to all HCV/HIV co-infected pregnant women, regardless of CD4 cell count or HIV viral load because of the evidence of increased HIV transmission in co-infected mothers.

6.2.7 Where the CD4 cell count is <500 cells/ μ L, HAART should be continued if active HCV co-infection 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/ μ 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/ μ 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/ μ 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 ARV or not postpartum depends on both HIV and HCV factors. There is consensus amongst guidelines that all persons with active (HCV-viraemic) co-infection should receive HAART if their CD4 cell count is <500 cells/ μ L [154,204,205]. In those women with CD4 cell counts of 350–500 cells/ μ L who have cleared infection either spontaneously (around 25%) or after treatment and with a sustained virological response (SVR) and who have normal liver histology as judged by biopsy or Fibroscan, consideration should be given to continuing cART where the patient expresses a preference to do so. This is because until the completion of the randomized PROMISE trial, which addresses the question of whether to continue HAART postnatally in mothers with CD4 cell counts >400 cells/ μ L, there is equipoise as to correct management. In those with CD4 cell counts over 500 cells/ μ 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 do not get re-infected, these women should have no further histological progression of their liver. In women with CD4 cell counts over 500 cells/ μ 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 co-infection. Furthermore, ART interruption has been associated with accelerated fibrosis in patients with active hepatitis C [206] and that effective HIV suppression improves liver histology even in the absence of effective HCV treatment [207,208].

7. 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 [209] and the NICE antenatal guidelines [210] 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 minimise the number of women who may need invasive testing.

Clinical Guidance 62 (CG62)[210] 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, β HCG and pregnancy-associated plasma protein A (PAPP-A). In the general population this has a detection rate of 92.6% with a false positive rate of 5.2% [211].

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 weeks 0 days and 20 weeks 0 days [210] However, significantly increased levels of β HCG, α FP and lower levels of UE3 (the elements of the 'triple test') have been observed in the HIV-positive population [212–214] while a reduction in β HCG in patients treated with PI-based [215] or with NNRTI-based HAART has been reported. Since Down's syndrome is associated with increased β 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. PAPP-A and nuchal translucency are unaltered by HIV infection or antiretroviral therapy [216] and thus are the preferred screening modality.

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 viral load 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 the viral load 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 viral load.

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 hours prior to 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 amnioscopy [217]. 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 [218]. Viral load data were not reported, but in other settings suppression of viral load reduces transmission.

A further study of nine women in France on HAART in 2008 [219] 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 prior to the procedure. There are no studies and few case reports in the HAART era reporting on chorionic villus sampling (CVS) or

cordocentesis [220]. For evidence relating to choice of antiretroviral therapy to reduce transmission risk associated with amniocentesis, see Section 5.4 on late presentation.

7.1.5 External cephalic version (ECV) can be performed in women with HIV. Grading: 2D

- ECV should be offered to women with a viral load <50copies/mL and a breech presentation at >36+0 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. External cephalic version (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 Caesarean section. 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 [210]. The question of whether ECV might increase the risk of mother to-child transmission of infections such as HIV is important and, in the absence of direct evidence, we have reviewed the relevant biological evidence and concluded that materno-fetal transfusion, as a consequence of this procedure, is extremely rare, and unlikely to be precipitated by ECV [221]. It is also reassuring that in a randomized trial of fundal pressure to expel the baby during Caesarean section, no evidence of materno-fetal transfusion was found [222].

7.2 Mode of delivery

7.2.1 Vaginal delivery is recommended for women on HAART with a HIV viral load <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 viral load results at 36 weeks.
- For women with a plasma viral load 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 viral load of 50–399 HIV RNA copies/mL at 36 weeks, PLCS should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.
- Where the viral load is ≥ 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 viral load <50 HIV RNA copies/ml taking HAART, irrespective of mode of delivery [4,23,223,224]. These studies support the practice of recommending planned vaginal delivery for women on HAART with plasma viral load <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 Caesarean section (0.7%; 17/2286) or planned vaginal delivery (0.7% ;4/559; AOR 1.24; 95% CI 0.34–4.52). Median viral load 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 viral load of <50 HIV RNA copies/mL. Two of the three infants were born by elective (pre-labour) Caesarean section (0.2%, 2/1135) and one by planned vaginal delivery (0.2%, 1/417); 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 viral load thresholds or strata above 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_{10} increase in viral load, 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 viral load of <400 copies/mL there was no significant difference in MTCT rates according to mode of delivery, with 3/747 (0.4%) transmission in the ECS group compared with 3/574 (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 viral load of >10 000 HIV RNA copies/mL and no significant protective effect of elective Caesarean section was seen (OR 1.46; 0.37–5.80). MTCT was low at 0.4% in women delivering with a viral load of <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 viral load of <400 HIV RNA copies/mL, elective Caesarean section 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 amongst 599 women delivering with viral loads of <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 [224].

A potential explanation for the differing conclusions of the effect of mode of delivery on MTCT in women with delivery plasma viral loads of <400 HIV RNA copies/mL in these two studies is that the true value of the plasma viral load 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 viral load 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 viral load assay with a cut-off of <400 HIV RNA copies/mL can necessarily be applied to patients with plasma viral loads 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 viral loads between 50 and 399 HIV RNA copies/mL. Data from the NSHPC UK and Ireland cohort 200–2011 (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 the impact of mode of delivery for women on HAART with plasma viral loads between 50 and 399 HIV RNA copies/mL. In the NSHPC there were seven transmissions among 593 women with documented viral load 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 viral loads between 50 and 399 HIV RNA copies/mL, the risk of MTCT for women intending vaginal delivery is around 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 viral load, the trajectory of the viral load, 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 viral load 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 the conflicting data regarding the effect of mode of delivery on MTCT in women with a viral load of <400 HIV RNA copies/mL, together with the data from the UK study showing a 2.4-fold increased risk of transmission for every \log_{10} increase in viral load associated with mode of delivery, the Writing Group felt that until further data are available, a PLCS should be recommended for all women with a viral load of >400 HIV RNA copies/mL.

7.2.2 In women for whom a 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 (198–1993) 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 [217]. 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)[225]. However prolonged rupture of membranes 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 [226].

In the WITS cohort (1989–1994) artificial rupture of membranes (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)[217]. 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 less than 20% of the cohort taking any antiretroviral therapy for prophylaxis [226].

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 Caesarean section 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 viral load of <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 [227]).

The importance of the use of antiretroviral therapy in the prevention of MTCT 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 viral load have not been performed and are unlikely to be performed in the near future. HIV DNA [228] and HIV RNA [18] in cervicovaginal lavage have been identified as independent transmission risk factors. Large cohort studies from the UK and Ireland, and France have concluded that there is no significant difference in MTCT in women with an undetectable viral load 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 viral load that have been reported in patients with an undetectable viral load on HAART [21,229,230]. 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 rupture of membranes in women on HAART and in those with a VL of <50 HIV RNA copies/mL. An association between MTCT and the 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 viral load, 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 on the basis of viral load.

The data regarding fetal blood sampling and the 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 the use of fetal scalp electrodes or fetal blood sampling confers increased risk of transmission in a woman with an undetectable viral load although this cannot be proven from the current evidence.

Electronic fetal monitoring should be performed according to national guidelines [227]. 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 Vaginal birth after Caesarean section (VBAC) should be offered to women with a viral load <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 a benefit of VBAC and vaginal birth over elective Caesarean section 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 Caesarean section in the face of any difficulty, the outcome of trial of labour for mother and neonate is good, even if scar dehiscence occurs [231].

In the non-HIV population, 70% of VBACs manage a vaginal delivery with a uterine rupture rate of around 0.3%.

Therefore, where a vaginal birth has been recommended on the basis of ART and viral load, 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 viral load at the time of delivery (Grading: 1A) and for women with viral load >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-rupture of membranes and Caesarean section is a proven option for women not requiring treatment for themselves, with a pre-treatment viral load of <10 000 HIV RNA copies/mL plasma.

Observational studies conducted in the early 1990s, prior to the use of HAART, found a reduction in MTCT with PLCS. In 1999, a large international meta-analysis ($n=8533$)[232] and a randomized controlled trial 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 (4 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 viral loads 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 viral load 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 [233]. This review found a higher incidence of minor postpartum morbidity, including fever and anaemia requiring transfusion, amongst HIV-positive women delivered by Caesarean section 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 [223,234] and from case controlled studies in the USA [235] and the UK [236] involving women on HAART with undetectable viral loads 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 viral load is <50 copies/mL, the usual obstetric considerations apply and the 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 Caesarean section [237]. Where the indication for PLCS is prevention of MTCT, the earlier timing reflects the importance of avoiding the onset of labour. In these cases, the risk of MTCT associated with labour and rupture of the membranes 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 [231]. 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 rupture of the membranes (ROM), delivery should be expedited. Grading: 1C

7.3.2 If maternal HIV viral load 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 viral load of 50–999 HIV RNA copies/mL, immediate Caesarean section should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views. Grading: 1C

7.3.4 If maternal HIV viral load is \geq 1000 RNA copies/mL plasma, immediate Caesarean section is recommended. Grading: 1C

In the pre-HAART era several studies [37,39,238] suggested that prolonged duration of ruptured membranes, usually analysed as greater than 4 hours, 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 viral load 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 hour membrane rupture to 19% with >12 hours of membrane rupture [239].

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. Ruptured membranes >6 hours compared to <6 hours was only significantly associated with MTCT in the group of women on no treatment (26.6% vs. 11.9%; $P<0.01$). Corresponding transmission rates for the mono–dual therapy group were 14.3% vs. 7.1% ($P=NS$) and in the women on HAART (0.8% vs. 0.0%; $P=NS$)[240].

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 viral load of <50 HIV RNA copies/mL when comparing those with ROM ≤ 4 hours to >4 hours the MTCT rate was 0.3% (1/326) and 0.0% (0/292), respectively ($P=0.34$). Restricting the analysis to the 386 women with a viral load of <50 copies/mL who delivered vaginally did not alter this conclusion [241]. Therefore, for women on HAART who rupture their membranes at term with a viral load of <50 HIV RNA copies/mL and who do not have an obstetric contraindication to vaginal delivery, a Caesarean section is not recommended.

As both acute and chronic chorioamnionitis have been associated with perinatal transmission [39,242–244], 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 viral load of <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 [245] and the NICE intrapartum guidelines [227] 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 hours for women with a viral load of >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 hours (2/51) and none in the women with ROM ≤ 4 hours (0/43). The two transmitters both had emergency Caesarean sections

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 ruptured membranes >4 hours for those with viral loads ≥ 50 HIV RNA copies/mL, and until further data are available, it is the recommendation of the Writing Group that Caesarean section should be considered for women with a viral load of 50–999 HIV RNA copies/mL at term. Again, if Caesarean section is not undertaken, delivery should be expedited, as above.

Data from the NSHPC for women with a viral load of >1000 HIV RNA copies/mL are sparse at present, with 1/14 (7.1%) transmitting with ROM ≤ 4 hours compared to 3/15 (20%) with ROM >4 hours. A single-centre study from Miami of 707 women on ART showed ROM >4 hours 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 viral load greater than 50 and less than 1000 HIV RNA copies/mL in this group. Until further data are available, an urgent (category 2) Caesarean section is recommended where the viral load is >1000 HIV RNA copies/mL regardless of treatment [246].

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

7.3.5 The management of prolonged premature rupture of membranes 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 PPRM occurs at <34 weeks: Grading: 1C

- **Intramuscular steroids should be administered in accordance with national guidelines**
- **Virological control should be optimised**
- **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 rupture of membranes. Decisions regarding the optimum management of early preterm ROM require the assessment of a number of factors including the exact gestation, the facilities available, maternal viral load and the 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 [247] and (if delivery is to be delayed) oral erythromycin

[248]. Decisions regarding timing of delivery should be made in consultation with the full multidisciplinary team including the neonatal unit.

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

If the maternal viral load is not fully suppressed, consideration should be given to the options available to optimise 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 200mg stat >2hours prior to 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 viral load of >10 000 HIV RNA copies/mL plasma who present in labour, or with ruptured membranes or who are admitted for planned CS. Grading: 1C**
- **For untreated women presenting in labour or with ruptured membranes in whom the current viral load 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 viral load <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 viral load 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 randomized controlled trial 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 i.v. zidovudine are poor. In a prospective study of all women prescribed zidovudine monotherapy during pregnancy prior to the publication of the ACTG 076 findings (1988–1994) in which the 8.8% transmission rate amongst women with CD4 cell counts >200 cells/ μ l is similar to that of the zidovudine monotherapy arm of ACTG 076 (8.3%), intrapartum i.v. zidovudine was not associated with lower rates of transmission [249]. One rationale for intrapartum i.v. zidovudine in ACTG 076 was that labour would be associated with poor absorption of oral therapy. While not strictly comparable, the well-recognised 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 i.v. infusion, transmission was not associated with zidovudine cord blood concentration [250].

Intravenous zidovudine has historically been considered for women whose plasma viral load 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 antiretroviral therapy. However, data from the New York State HIV diagnostic service (1995–1997) suggest that intrapartum i.v. zidovudine alone does not significantly reduce transmission (10%; 95% CI 3.3–21.8%) since, provided neonatal prophylaxis is commenced within 48 hours 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 viral load 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 antiretroviral options for women with viral loads >50 HIV RNA copies/mL who present in labour, or with ruptured membranes 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 viral load 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 viral load 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 viral load at the time of labour or Caesarean section. Oral HAART should be taken at the normal dosing interval.

8. Neonatal management

8.1 Infant post-exposure prophylaxis

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

8.1.1 Zidovudine monotherapy is recommended if maternal viral load is <50 HIV RNA copies/mL at 36 weeks' gestation or thereafter prior to delivery (or mother delivered by PLCS whilst 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 the publication of the results of ACTG 076 [61]. The relative contributions of the antenatal, peripartum and infant components have been difficult to quantify. In ACTG 076 neonatal zidovudine 2mg/kg every 4 hours (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 viral load of <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 post-exposure prophylaxis 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 (~ 0.1%), and although history of zidovudine resistance in maternal virus and infant post-exposure prophylactic 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 [251]. In the Swiss cohort, none of six infants born to mothers harbouring zidovudine-resistant HIV (based on codon 215 analysis only) became infected [252]. 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 viral load at delivery (OR 4.8; with wide 95% CI 0.2–131; P=0.35)[253]. High-level resistance was not reported and the median CD4 cell count in the women was 540 cells/ μ l. In retrospective cohort studies from

France [254] and the USA [255], 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 viral load 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)[256]. 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 antiretroviral, with no history of maternal resistance, for infant post-exposure monotherapy. The established alternatives, nevirapine and lamivudine, have potent antiretroviral 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 viral load <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 underway.

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:

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

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

There is one large randomized controlled trial of combination therapy in neonates born to mothers who did not receive any ART prior to delivery ($n=1684$, in Brazil, Argentina, South Africa and US)[257]. Infants were randomly allocated at less than 48 hours 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 viral load were significantly associated with transmission. For infants uninfected at birth, transmission was two-fold 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 [258]. 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 versus monotherapy short-course regimens to the infant: zidovudine plus lamivudine versus nevirapine [259]; or zidovudine plus nevirapine versus nevirapine [260].

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 hours 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 hours 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 [261]. 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 (5 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% [4/47] vs. 45.5% [5/11], $P=0.002$).

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 viral load at 36 weeks' gestation/delivery is not <50 HIV RNA copies/mL. Grading: 2C

Delivery with a detectable maternal viral load (>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 viral load (>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)[262].

The strength of recommendation is proportionate to the estimated risk of transmission. Thus, benefit of additional neonatal therapy is anticipated at higher viral loads, in circumstances where resistance is suspected or confirmed and where viral load is increasing despite treatment. As with the recommendations regarding PLCS at viral loads <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 viral load is >50 HIV RNA copies/mL at 36 weeks and subsequently a delivery maternal viral load is <50 HIV RNA copies/mL, then it is reasonable to simplify the infant PEP to monotherapy.

Choice of triple combination PEP 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 combinations of ART 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. Due to a lack of neonatal pharmacokinetic and efficacy studies and suitable formulations, ART dosing regimens remain restricted to a small proportion of the antiretroviral drugs

currently manufactured (Table 1). Small pharmacokinetic studies have been performed (zidovudine [263], lamivudine [264,265], tenofovir [139], emtricitabine [266]) and dosing regimens are available for most of the nucleoside analogues and for abacavir from age 1 month [267], 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 [74,268–271]. PK-supported dosing is available for the PIs nelfinavir [264] and ritonavir-boosted lopinavir (based on HIV-1 infected infants initiating therapy in the first 6 weeks of life)[272–274] and a study that included some infants treated from birth [275]. However, evidence of adrenal suppression has been documented in some neonates treated with lopinavir/ritonavir, particularly when preterm [276], 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 [277]. 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 multidrug resistance. Close metabolic monitoring in hospital should be undertaken. Nelfinavir, the only other PI with an infant-dosing regimen, is likely to be withdrawn in the near future. See the CHIVA website for dosing updates (www.chiva.org.uk).

In contrast to the PIs, nevirapine efficiently crosses the placenta (see below) and is well absorbed by the neonate [278]. Neonatal metabolism of nevirapine is induced where there has been antenatal in utero exposure [74,269]; if this drug is given to the neonate when the mother has taken it for 3 or more days, the full dose of 4mg/kg per day should be started at birth, rather than the induction dose of 2 mg/kg per day (Table 1). Owing to its long half-life, nevirapine should be stopped 2 weeks before co-prescribed antiretroviral 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 i.v. use in sick and/or premature neonates, unable to take oral medication, is zidovudine [263,279]. Reduced oral and i.v. dosing schedules for premature infants are available (Table 1). The fusion inhibitor, enfuvirtide does not cross the placenta. Although i.v. 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 [280] and an adult i.v. dosing study [281].

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 on the basis of the history of drug exposure and any previous resistance data in the mother. If the infant is found to be infected, then the first HIV-positive sample should also be tested for the resistance pattern of the transmitted virus.

Intravenous ART in the neonate

The very premature neonate is at risk of necrotising enterocolitis (NEC) 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 NEC, being an infant of a mother with HIV was associated with an increased risk of NEC (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 [282]. Premature infants should be commenced on i.v. 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 antiretroviral that is administered parenterally, usually subcutaneously, in adults and children. An unlicensed i.v. dosing regimen has been adapted for use as part of combination ART in neonates at risk of multiresistant HIV (seek expert advice)[281].

8.1.4 Neonatal PEP should be commenced very soon after birth, certainly within 4 hours. 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 [283–285]. Immediate administration of PEP is especially important where the mother has not received any antiretroviral therapy.

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 [286] and Spain [287] have

demonstrated efficacy and reduced haematological side effects with 4 versus 6 weeks of neonatal zidovudine. In a Thai study, where a short course of 3 days of neonatal monotherapy zidovudine PEP was compared to 6 weeks, there was no significantly increased HIV transmission where the mother received zidovudine monotherapy from 28 weeks' gestation [288]. 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* (PCP) 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 viral load 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 *Pneumocystis pneumonia* (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 viral load should be reviewed before the infant is aged 3 weeks. If the HIV molecular diagnostic test taken in the first 24 hours 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 viral load 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 viral load 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 un-infected at 12–14 weeks. However, infants considered at low risk of HIV transmission (maternal viral load <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 co-infected with hepatitis B virus, immunization against HBV infection should be as per the Green Book and does not differ from management of the HIV-unexposed infant [289]. 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 antiretroviral therapy, 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 [290–292]. RCT evidence from Kenya puts the transmission rate at 16% over 2 years, accounting for almost half the total mother-to-child transmissions [292]. Complete avoidance of breastfeeding removes this risk altogether [292–294] and is the current standard of care in the UK [50,295]. This is in line with previous 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 (AFASS)[296]. Recently, cohort [297–300] and RCT [66,78,301] 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 AFASS, and mortality from formula feeding outweighs additional mortality from HIV transmission by breastfeeding [302,303]. WHO guidance remains that in countries where formula feeding is safe, a national or regional policy decision should be made on feeding policy [304]. Although breastfeeding transmission is reduced by ART, it is not abolished [78,297,299–301,305,306]. There is laboratory evidence that the breast milk of HIV-positive women on ART

contains cells that may shed virus [307]. 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 [308].

8.4.2 In the very rare instances where a mother who is on effective HAART with a repeatedly undetectable viral load 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 [309]. 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 whilst 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 [301], 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 post-exposure prophylaxis is not advised [310].

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 viral load, and monthly testing of the infant for HIV by PCR for HIV DNA or RNA (viral load). 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; viral load 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. **Grading: 1D**

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:

- **During the first 48 hours and prior to 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 done 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 [311]. 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 hours of birth is taken as presumptive evidence of intrauterine transmission. Within the first few weeks of life the 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 [312]. 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 [313]. 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 positive. 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 [314]. 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: 5/4539 cases)[315]. This may be due to covert breastfeeding, premastication of infant food or unknown intrafamilial 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 (www.chiva.org.uk)[316].

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 multidisciplinary team is crucial to support these women as they are often the most isolated and unsupported.

Where, despite all efforts, the multidisciplinary team 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 wellbeing 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. 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. Prevention of MTCT can only be achieved if the pregnant woman embraces the medical interventions appropriately. To maximise the effectiveness of the 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 a multidisciplinary team (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 [317].

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 [318]. The importance of informing appropriate healthcare workers should be emphasized. This includes midwives, general practitioners, health visitors and paediatricians. The process of inpatient 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 [317,319]. Disclosure should be encouraged in all cases but may be viewed as a process that may take some time [320,321]. There are situations where a newly diagnosed HIV-positive woman refuses to disclose to a current sexual partner, or appears to want to delay disclosure indefinitely. This can give rise to very complex professional, ethical, moral and, potentially, legal situations. There is a conflict between the duty of confidentiality to the index patient and a duty to prevent harm to others. Breaking confidentiality in order to inform a sexual partner of the index patient's positive HIV status is sanctioned as a 'last resort' by the World Health Organization (WHO)[322] and General Medical Council (GMC)[323]. 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 Caesarean section, and avoiding breastfeeding. Possible reasons such as the need to 'take vitamins', or having 'obstetric complications' and 'mastitis' may help the women feel more confident in explaining the need for certain procedures to persistent enquirers [324].

Between 20% and 80% of newly diagnosed HIV-positive pregnant women may have partners who are HIV negative, depending on the setting [319,325]. Such couples require advice regarding condom use and post-exposure prophylaxis following sexual exposure [326].

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 [295,327].

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 [328–330].

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 [331].

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 [332].

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 GMC, BMA and Medical Defence Organizations in difficult cases. Legal advice can also be sought from organizations such as the Terrence Higgins Trust (THT) (www.tht.org.uk), or the National AIDS Trust (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 [333].

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

Drug	Dose	Mono/combo	Study	Comments/side effects
Zidovudine (ZDV, AZT)	<p>Oral</p> <p><i>Term</i> (>34 weeks):</p> <ul style="list-style-type: none"> 4 mg/kg twice daily <p><i>Premature</i> (30–34 weeks):</p> <ul style="list-style-type: none"> 2 mg/kg twice daily for 2 weeks then 2 mg/kg three times a day for 2 weeks <p><i>Premature</i> (<30 weeks):</p> <ul style="list-style-type: none"> 2 mg/kg twice daily for 4 weeks <p>Intravenous</p> <p><i>Term</i>: 1.5 mg/kg four times a day</p> <p><i>Prem</i>: 1.5 mg/kg twice daily</p>	Combo (+ lamivudine) Mono Mono Mono Mono Mono*	Moodley 2001 [334] Boucher 1993 [263] Capparelli 2003 [279] Boucher 1993 [263] Frasca 2009 [335]	Anaemia, neutropenia – more common with combination therapy in mother and infant. In French study of zidovudine + 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 in utero and/or zidovudine neonatally [336]
Lamivudine (3TC)	2 mg/kg twice daily	Combo (all with ZDV) Combo (+ nelfinavir)	Mandelbrot 2001 [262] Moodley 2003 [259] Durand-Gasselín 2008 [337] Hirt 2011 [139] Mirochnick 2011 [264]	Anaemia, neutropenia (but less common than with zidovudine). More common with combination therapy in mother and infant.
Abacavir (ABC)	2 mg/kg twice daily	Mono	Jullien 2005 [267]	Hypersensitivity reaction has not been noted in infants (only small numbers treated)
Didanosine (ddI)	60 mg/m ² twice daily	Mono	Wang 1999 [108]	Much better absorbed on an empty stomach. Difficult to separate dosing from feeding. May cause GI symptoms. Variable absorption in neonates
Emtricitabine	2 mg/kg as a single dose (with 13 mg/kg	Combo	Hirt 2011 [338]	Mothers received two tablets of TDF/FTC at onset

(FTC)	of TDF) within 12 hours after birth	(with TDF)		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 [266]	Dose based on PK modelling study
Tenofovir (TDF)	13 mg/kg as a single dose within 12 hours of life. 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).	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.
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 nevirapine. Single-dose regimen: one 2 mg/kg dose 48–72 hours from birth	Mono Mono	Shetty 2004 [339]	Daily dosing regimen from HIVNET 023 (breastfeeding prophylaxis study)
	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 [266]	Mothers received zidovudine 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+	NICHD/HPTN 040/P1043	Nelfinavir 250mg tablets can be dispersed in water.

		3TC)	Mirochnick 2011 [264]	
Lopinavir/ ritonavir	300 mg/m ² twice daily <ul style="list-style-type: none"> • 1–2 kg: 40 mg every 12 hours • 2–6 kg: 80 mg every 12 hours 	Combo	Julien 2006 [340] Verweel 2007 [341] Chadwick 2008 [272] Chadwick 2011 [273] Urien 2011 [275]	Some PK 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 [276]. 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 younger than 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 ² 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	May cause rash, bone marrow suppression. Give to infants aged over 4 weeks born to mothers with a higher risk of transmission

Please see highlights for some reference queries in the list below, thanks

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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 judgment.

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 www.bhiva.org (accessed April 2012).
2. Guyatt GH, Oxman AD, Kunz R *et al*. Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.
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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), randomized control trials (RCTs), observational, risk, economic

Population: HIV-positive women

Intervention: starting antiretroviral therapy 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 antiretroviral 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 antiretroviral 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 antiretroviral 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 antiretroviral regimen should be recommended?

5. Pharmacokinetics

Should ARV dosages be altered in pregnancy?

A2.2 Search 2: hepatitis viruses co-infection

Study design: Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic

Population: HIV/HBV/HCV co-infected women

Intervention: starting antiretroviral therapy 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 (HBV)

Which antiretroviral regimen should be recommended?

Should this be continued this after delivery?

What is the preferred mode of delivery for women with HBV co-infection?

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

Should pregnant women with HBV be vaccinated against HAV?

2. Hepatitis C (HCV)

Which antiretroviral regimen should be recommended?

Should this be continued after delivery?

What is the preferred mode of delivery for women with HCV co-infection?

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 co-infected?

Should the HCV be treated?

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

Study design: systematic reviews (SRs), randomized control trials (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 Caesarean section be performed?

What antiretroviral therapy should be given during delivery

2. Obstetric procedures

When should a vaginal birth after Caesarean (VBAC) be regarded as 'safe'?

Is it safe to perform ECV (external cephalic version), 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 CVS

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

What should be the antiretroviral management of a woman requiring amniocentesis or chorionic villus sampling (CVS) who is not yet on antiretroviral therapy

4. Ruptured membranes

What is the optimum antiretroviral therapy and obstetric management for women presenting with both term and preterm rupture of membranes?

A2.4 Search 4: paediatric issues

Study design: systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic

Population: HIV-exposed infants

Intervention: antiretroviral treatment 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 post-exposure prophylaxis 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?

A2.5 Search 5: investigations and monitoring in pregnancy

Study design: systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic

Population: HIV-positive women

Intervention: starting antiretroviral therapy 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 ART

Component	Description
Review area	Safety and efficacy of antiretrovirals in pregnancy
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	Antiretroviral therapy (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; 22 : 973–981 Tariq S, Townsend CL, Cortina-Borja M, Duong T, Elford J, Thorne C et al. Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000–2009. <i>J Acquir Immune Defic Syndr</i> 2011; 57 : 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; 25 : 2301–2304.

A3.2 Search 2: hepatitis co infection

Component	Description
Review area	Hepatitis B and C co-infection
Objectives	To assess the benefit of antiretroviral treatment on co infected pregnant women
Populations	HIV positive, HBV and or HCV co-infected pregnant women
Interventions	Antiretroviral therapy 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, Bhagani S, Wilkins E, Leen C <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; 11 : 1–30.

A3.3 Search 3: fetal monitoring and obstetric issues

Component	Description
Review area	Fetal monitoring and obstetric issues
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 antiretroviral 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	<p>European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. <i>Clin Infect Dis</i> 2005; 40: 458–465.</p> <p>Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas J-P, Dollfus C <i>et al</i>. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. <i>AIDS</i> 2008; 22:289–299.</p> <p>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; 11: 368–378.</p>

A3.4 Search 4: paediatric issues

Component	Description
Review area	Management of the child born to an HIV-positive mother
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, Kiselev P, Scott G, O'Sullivan MJ 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. <i>N Engl J Med</i> 1994; 331 : 1173–1180. Brooks Jackson J, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M 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. <i>Lancet</i> 2003; 362 :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; 12 :422–427.

A3.5 Search 5: investigations and monitoring in pregnancy

Component	Description
Review area	Investigations and monitoring in pregnancy in HIV positive women
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. liver function tests/ 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 two-fold increase in overall birth defects

To date such an increase has not been detected. (Data from the Antiretroviral Pregnancy Registry 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 www.APRegistry.com.