

# Guidelines for the management of HIV infection in pregnant women 2012

## Writing Group Members:

Dr A de Ruiter (Chair)

Dr GP Taylor (Co Chair)

Dr A Palfreeman (Co Chair)

Ms P Clayden, Dr J Dhar, Dr K Gandhi, Dr Y Gilleece,  
Dr K Harding, Dr P Hay, Ms J Kennedy, Dr N Low-Beer,  
Dr H Lyall, Dr P Tookey, Dr S Welch, Dr E Wilkins

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## **Scope and purpose**

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of HIV-infected pregnant women. The scope includes guidance on the use of ART therapy 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.

### ***Guideline development process***

BHIVA revised and updated the association's guideline development manual in 2011. 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 panel 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 panel. 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 the Appendices. 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 panel members with expertise in the field. Using the modified GRADE system (see Appendix), panel 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 panel members received training in use of the modified GRADE criteria before assessing the evidence. Due 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 have been prefixed with 'R' throughout sections A to E, and numbered sequentially within the text.

Prior to final approval by the writing panel the guidelines were published online for public consultation and external peer review commissioned.

***Patient involvement***

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

## Introduction

One of the major successes in the management of HIV-infected 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 randomised 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 panel 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 recognised 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 recognised 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 vaginal deliveries.

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 cpm 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 count of more than 350 cells/ $\mu$ L.

The paediatric section provides further guidance on infant post-exposure prophylaxis, drug dosing and safety. It is clear that there exists an urgent need for paediatric syrup preparations for a wider variety of antiretroviral drugs as 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.

### ***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 stabilised. 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 relatively stable since then. In the rest of England about one in 3,500 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 2,150 in 2000 to one in 1,150 in 2008<sup>1,2</sup>.

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 2,200) 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<sup>3</sup>. 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 cART and delivered with an undetectable viral load, there were only three transmissions, an MTCT rate of 0.1%<sup>4</sup>. 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<sup>1</sup>.

By 2010 over 98% of all diagnosed women received some form of ART prior to delivery: the proportion of those who were taking ZDV monotherapy (ZDVm) dropped from around 20% in

2002/3 to less than 5% since 2006, and only about 2% in 2009/10. 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%<sup>5</sup>.

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<sup>5</sup>.

### ***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<sup>6</sup>. 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-infected 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<sup>7</sup>. 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<sup>8</sup>. Pregnancies in vertically infected young women are now occurring<sup>9</sup>.

### ***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 a third of infected pregnant women were diagnosed, and most of those were aware of their infection status before they became pregnant<sup>10</sup>. 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<sup>11</sup>. Standards for monitoring antenatal screening were revised and updated in 2010<sup>12</sup>. 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%<sup>13</sup>.

Between 2000 and 2004 the majority of HIV-infected 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<sup>5</sup>.

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<sup>5</sup>.

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<sup>14</sup>. 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<sup>12</sup>.

### ***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 post-natal follow up.

Antiretroviral Pregnancy Registry

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

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

For forms visit: [www.apregistry.com](http://www.apregistry.com)

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

This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, based at the UCL Institute of Child Health, London. HIV-infected children and children born to HIV-infected women are reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, or in the case of some units with large caseloads direct to the NSHPC. 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](http://www.nshpc.ucl.ac.uk) , the CHIPS website [www.chipscohort.ac.uk](http://www.chipscohort.ac.uk) , or e-mail [nshpc@ich.ucl.ac.uk](mailto:nshpc@ich.ucl.ac.uk) .

## Section A: Screening and monitoring of HIV-positive pregnant women

**RA1a. Sexual health screening is recommended in the first trimester and third trimester. Grading: 1C**

**RA1b. Infections found 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<sup>15</sup>. At present, the majority of pregnant HIV-infected women in the UK come from, and mostly acquired HIV in, sub-Saharan Africa where the prevalence of genital infections, particularly in the HIV-infected population, can be high<sup>16</sup>. Data from the unlinked anonymous survey of newborn infant dried blood spots show that, while the prevalence of HIV infection among pregnant women born in sub-Saharan Africa has remained relatively stable in recent years, there has been a fourfold increase in prevalence among women born in Central America and the Caribbean rising from 0.21% in 2000 to 0.78% in 2009<sup>2</sup>. A high prevalence of genital infections in women of Afro-Caribbean origin has been reported<sup>17</sup>.

The diagnosis and treatment of genital infections in any individual have clear benefits, in terms of both individual morbidity and possible infectivity to any sexual partner. In pregnancy, the welfare of the baby is an additional issue. However, apart from the recommendation that all pregnant women should be screened for HIV, HBV and syphilis, asymptomatic pregnant women in the UK are not routinely screened for genital infections.

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth<sup>18, 19</sup>. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with MTCT of HIV and may be interlinked<sup>20-22</sup>. However, a phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission showed no benefit in reducing MCT in the context of single-dose NVP prophylaxis<sup>23</sup>.

Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with bacterial vaginosis (BV) and *Ureaplasma urealyticum*<sup>24, 25</sup>. A strong association between BV and premature delivery has been reported<sup>26, 27</sup>. 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<sup>25</sup>. A study in which mothers received zidovudine from 34 weeks of pregnancy reported that maternal fever > 38C and bacterial vaginosis were associated with in-utero

transmission of HIV with 2.6-fold and 3-fold risks respectively<sup>28</sup>. We do not know how applicable this is in settings where mothers receive HAART 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<sup>26, 27</sup>. 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 pregnant women with asymptomatic BV will prevent PTB and its consequences<sup>29</sup>. However, there is some suggestion that treatment before 20 weeks' gestation may reduce the risk of PTB.

Given that: rates of preterm birth may be increased in mothers treated with HAART (see section in A); and preterm birth is a possible additional risk factor for MTCT of HIV if occurring prior to full virological suppression, it seems reasonable to also screen for and treat BV in this high-risk group. Moreover BV may itself be a risk factor for HIV transmission. Testing can be done easily alongside screening for STIs, which is recommended.

It has long been recognized that genital infections, in particular ulcerative diseases, are associated with sexual transmission of HIV<sup>30, 31</sup>. 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 organisms, and/or ulceration and inflammation<sup>32, 33</sup>. A study from Zimbabwe has shown a correlation between herpes simplex virus type 2 (HSV-2) antibody status and HIV-1 MTCT<sup>34</sup>. 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 ZDV monotherapy from 36 weeks or placebo<sup>35</sup>. 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 ART<sup>36</sup>. 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 to 6.5)<sup>37</sup>. Future studies are needed to evaluate whether valaciclovir can reduce the risk of HIV MTCT during late pregnancy, the intrapartum period, and breastfeeding.

Symptomatic genital HSV should be treated as per non-pregnant women. Continuous suppressive therapy with acyclovir may be required, and is effective and safe<sup>38</sup>.

Organisms associated with BV have been shown to stimulate HIV expression in vitro<sup>39,40</sup>. A study from Kenya demonstrated a reduction in cervical mucosal shedding of HIV-1 RNA following treatment of both gonococcal and chlamydial cervicitis<sup>41</sup>.

Viral load in cervicovaginal specimens has been shown to correlate with HIV-1 MTCT<sup>42</sup>. Genital tract viral load will usually mirror the plasma viral load<sup>43</sup>, 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<sup>44,45</sup> and genetic diversity of virus from the two compartments has been reported<sup>46</sup>. 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<sup>4</sup> and from France<sup>47</sup> showing no difference in MTCT associated with mode of delivery in women with an undetectable viral load providing some reassurance that the potential discordance may not be clinically relevant but further research is warranted.

In the absence of randomized controlled trials, but for the reasons outlined above, it would continue to appear prudent to screen HIV-positive pregnant women for genital infections. This should be done as early as possible in pregnancy and consideration should be given to repeating this at around 28 weeks. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the UK national guidelines, followed by a test of cure. Partner notification should take place where indicated, to avoid re-infection.

In pregnancy, warts are often more severe and less responsive to therapy, which may need to be deferred to the postpartum period. Cytology should be undertaken in pregnancy as for HIV-seronegative women. If an abnormality is detected referral should be made for colposcopy, which can be undertaken irrespective of gestation. If cervical intraepithelial neoplasia (CIN) is seen at colposcopy, it is customary to repeat the colposcopy on one or two occasions during the pregnancy to ensure that there are no signs of invasive cancer developing. Usually, if any abnormality is

detected, treatment is deferred until 6 weeks after delivery, unless invasive cervical cancer is suspected.

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

**RA2a. 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**

**RA2b. HIV sequence analysis should be performed prior to initiation of treatment (as per adult guidelines), except for late-presenting women. Post short-course treatment sequence is recommended to ensure that mutations are not missed with reversion during the off-treatment period. Grading: 1D**

**RA2c. 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 count at baseline and one at delivery. Grading: 2D**

**RA2d. 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. In addition it will add to the currently limited knowledge-base regarding the dynamics of viral load decay with the use of different HAART regimens in pregnancy.

**RA2e. 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**

**RA2f. In the event that a woman who has either conceived on or initiated HAART has not achieved a plasma viral load of <50c/ml at 36 weeks the following interventions are recommended:**

- **Review adherence and concomitant medication**
- **Perform genotype if appropriate**
- **Consider TDM**
- **Optimise to best regimen**
- **Consider intensification**

For a woman who conceives on HAART which is not fully suppressive, this should be undertaken as soon as possible.

If this occurs when the infant is likely to be delivered prematurely (<34 weeks) and may be unable to take medication enterally, intensification should consist of therapies which readily cross the placenta such as double dose tenofovir, raltegravir and single dose nevirapine (see above).

## **Section B: Use of antiretroviral therapy in pregnancy**

### **B1: Conceiving on HAART**

**RB1a: It is recommended that women conceiving on an effective HAART regimen should continue this even if contains efavirenz or does not contain zidovudine. Grading: 1C**

**Exceptions are:**

**1) PI monotherapy should be intensified to include (depending on tolerability and resistance) 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 (ZDV) 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 panel recommend 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 2<sup>nd</sup> and 3<sup>rd</sup> trimester only exposures to the same compounds. The congenital malformation rate observed in babies exposed to a specified drug is presented 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 for 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 2 fold higher rate than in the general population has been excluded)<sup>48</sup>.

There are insufficient data to recommend routinely switching from efavirenz to another agent. The BHIVA and CHIVA Guidelines for the Management of HIV Infection in Pregnancy (2008)<sup>49</sup> recommended that efavirenz be avoided in women who may conceive. This was based on pre-clinical animal studies that had not been conducted on any other ART, the FDA re-classification of efavirenz to category D and the paucity of human data. Three of twenty 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<sup>50</sup>. Subsequently four anecdotal cases of myelomeningocele and two of Dandy Walker syndrome were reported following 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 panel consider that there are insufficient data to support the former position and furthermore recommend that efavirenz can be both continued and commenced in pregnancy.

The data considered were:

- APR<sup>48</sup>

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<sup>51, 52</sup>.

- In 2010, a systematic review and meta-analysis of observational cohorts reported birth outcomes among women exposed to efavirenz during the first trimester<sup>53</sup>. 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.

- Data from the leDEA 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<sup>54</sup>.
- Two publications have reported higher rates of congenital birth defects associated with efavirenz, Brogly, et al (15.6%)<sup>55</sup> and Knapp, et al (12.8%)<sup>56</sup>. The panel has considered these findings and consider 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 were 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 were described by these studies: patent foramen oval (1); gastroschisis (1); polydactyly (1); spina bifida cystica (1); plagiocephaly (1); Arnold Chiari malformation (1) and talipes (1). The reporting of two cases of congenital malformation was duplicated in the two studies. The paper by the NISDI Perinatal Study Group<sup>57</sup> 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)<sup>58</sup>.

Thus it is the recommendation of the panel, 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<sup>59</sup>, 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 per ml plasma (cpm). Analysis of data combined from two observational studies, the European Collaborative Study and the UK and Ireland National Study of HIV in Pregnancy and Childhood, has shown no difference in pregnancy outcomes between ZDV-based and ZDV-sparing HAART<sup>60</sup>. 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<sup>4</sup>. 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 cpm at delivery)<sup>61</sup>. However, as newer therapies become established, the degree of transplacental transfer of the components of combination should be considered (*see also pharmacokinetics section*).

Whilst, 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 peri-exposure protection. In PHPT-5, the addition of boosted lopinavir to ZDVm from 28 weeks gestation was no better than maternal ZDV with or without single dose nevirapine (sdNVP) provided neonatal NVP was administered<sup>62</sup>. The panel 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 contra-indicated in pregnancy due to the risk of maternal lactic acidosis<sup>63</sup>.

## **B2 : Naïve to HAART – mother needs ART for herself**

**RB2a: Women requiring HAART for their own health should commence treatment as soon as possible as per the adult treatment guidelines. Grading: 1A**

**RB2b: In terms of the NRTI backbone there is most evidence and experience in pregnancy with zidovudine plus lamivudine. Tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable alternatives. Grading: 2C**

**RB2c: In the absence of specific contraindications it is recommended that the 3<sup>rd</sup> agent in HAART should be nevirapine if the CD4 count is less than 250 cells/ $\mu$ l or efavirenz or a boosted PI.**

**Grading: 1C**

**RB2d: No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses.**

**Consider 3<sup>rd</sup> trimester TDM particularly if combining tenofovir and atazanavir.**

**If dosing off-licence consider switching to standard dosing throughout pregnancy or regular TDM.**

**Grading: All 1C**

**RB2a: Women requiring HAART 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) and the risk of MTCT. Where the mother is at risk of, or has presented with an OI, initiation of HAART should not be delayed. Where treatment is indicated on the basis of CD4 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.

**RB2b: In terms of the NRTI backbone there is most evidence and experience in pregnancy with zidovudine plus lamivudine. Tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable alternatives. 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<sup>4, 61, 64-66</sup>. The adult prescribing guidelines now recommend tenofovir/emtricitabine or abacavir/lamivudine as first line therapy on the basis of safety, tolerability and efficacy (cross-reference to 2012 Adult guidelines). No studies have compared the safety and efficacy of the three, fixed dose, dual nucleoside/tide, combinations that constitute the backbone of HAART, in pregnancy. Zidovudine-based and zidovudine-sparing regimens are equally safe and efficacious (see B1). 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.

**RB2c: In the absence of specific contraindications it is recommended that the 3<sup>rd</sup> agent in HAART should be nevirapine if the CD4 count is less than 250 or efavirenz 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 adult prescribing guidelines recommended a 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 guidelines committee 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/ $\mu$ l. Nevirapine is well tolerated in pregnancy, with several studies suggesting this to be the case even above the stated CD4 cut-off<sup>67-70</sup>; has favourable pharmacokinetics in pregnancy<sup>71-73</sup> 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<sup>74-76</sup>.

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<sup>65, 77</sup>, atazanavir<sup>78</sup>, saquinavir<sup>79, 80</sup>). In the European Collaborative Study, time to undetectable viral load was longer in women initiating protease inhibitor-based HAART but in this study 80% of these women were taking nelfinavir<sup>81</sup>. In a more recent study, treatment with a boosted protease inhibitor resulted in more rapid viral suppression (to <50 copies) than nevirapine, except in the highest viral load quartile<sup>82</sup>. In another multi-centre study nevirapine-based HAART reduced viral load more rapidly during the first two weeks of therapy than PI-based HAART with nelfinavir, atazanavir or lopinavir (Kay et al, CROI 19, 2012). 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 initiated.

HIV, protease inhibitor therapy and PTD

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

The association between HAART and PTD was first reported by the Swiss Cohort in 1998<sup>58, 83</sup>, and subsequently by a number of other European studies including three analyses from the European Collaborative Study (ECS)<sup>58, 84-86</sup>. 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<sup>87</sup>.

Several large studies from the USA have not found an association between HAART and PTD<sup>88, 89</sup>. In two further studies, one multicentre study from the PSD cohort and one single centre study, an association between PTD and HAART was only found if HAART included a protease inhibitor<sup>90, 91</sup>. Two of the earlier European Collaborative Study reports had also noted that the increased risk of PTD in patients on HAART was particularly marked in patients on PI containing HAART<sup>84, 86</sup>. However a US meta-analysis in 2007 did not find an association between PTD and PI containing HAART<sup>92</sup>, 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<sup>87</sup>. 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<sup>93</sup>. Over 85% of these reports to the APR came from the US.

Most studies which 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)<sup>84, 86, 92, 94</sup>. However the NSHPC UK and Ireland study did not find an association between timing of HAART initiation and PTD<sup>87</sup>. One single centre UK study found the risk to be increased in those initiating HAART in pregnancy compared to those conceiving on treatment<sup>95</sup>.

A 2010 US 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 with non PI containing regimens and did not find an association between PI containing regimens and PTD<sup>96</sup>. 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 (H.R 2.03 1.06-3.89)<sup>97</sup>.

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 US has the highest background PTD rate of any industrialised country, peaking at 12.8% in 2006<sup>98</sup>.

Two randomised 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 randomised 560 women at 26 to 34 weeks, with CD4 counts >200 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% v 11.8%, p=0.003)<sup>99</sup>.

A second study, the Kesho Bora Study randomised 824 women at 28 to 36 weeks, again with CD4 counts >200 cells/mm<sup>3</sup> 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 2 groups (13% with PI v 11% with ZDVm/sdNVP)<sup>100</sup>.

The randomised 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%<sup>101</sup>. 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<sup>78</sup>.

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 randomised study of sufficient power to explore these issues further and the PROMISE study (NCT01061151), with 6000 women randomised to either a PI based combination regimen or zidovudine monotherapy will hopefully provide some answers to these important questions.

**RB2d: No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses. Grading: 1C**

**Consider 3<sup>rd</sup> trimester TDM particularly if combining TDF 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 through-out gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease, notably albumin and  $\alpha_1$  acid glycoprotein; renal sodium re-absorption 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 twice a day dosing during pregnancy.

The pharmacokinetics of most NRTIs (zidovudine<sup>102</sup>, stavudine<sup>103</sup>, lamivudine<sup>104</sup>, abacavir<sup>105</sup>) are not affected by pregnancy significantly and dose adjustment is not required. Renal excretion of didanosine is increased in pregnancy, but dose alteration is probably not required<sup>106</sup>. Tenofovir concentrations in the third trimester were reported to be reduced by about 15% compared with postpartum, but trough levels are adequate<sup>107</sup> although in a population-based study of tenofovir use, pregnant women appear to have 39% more clearance than non-pregnant women<sup>108</sup>. 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<sup>109</sup> (see Paediatric section). New data on emtricitabine show that whilst 3<sup>rd</sup> trimester concentrations are lower than post-partum the absolute concentrations achieved during pregnancy are adequate and dose adjustment is not required<sup>110</sup>.

Amongst the NNRTIs nevirapine has been extensively studied in pregnancy and plasma concentrations are similar to those in non-pregnant adults<sup>71,73</sup>. No dose adjustment is required when using licensed doses. There are no data on nevirapine XR in pregnant women. Efavirenz 600mg daily has been reported in one study of 25 pregnant women to result in 3<sup>rd</sup> trimester plasma concentrations that were similar to 6 – 12 week post-partum concentrations in the same women.

Cord blood to maternal blood ratio was 0.49 resulting in transplacental concentrations that are in the therapeutic range<sup>111</sup>. 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<sup>112</sup>. 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 3 tablet bd (lopinavir 600 mg/ritonavir 150 mg) achieved similar area under the curve levels to non-pregnant adults taking the standard dose of 2 tablets bd<sup>113</sup>. The improved bioavailability of the tablet formulation is also found in pregnant women and this together with the impact on changes in protein binding increases the protein free-fraction in the 3<sup>rd</sup> trimester<sup>114</sup>. 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<sup>115</sup>.

The plasma concentrations of saquinavir tablets when boosted by ritonavir appear to be generally therapeutic and no dose adjustment is routinely required. Inter-patient variability during pregnancy is, however, high<sup>79, 116</sup>.

A study from Italy reported similar third trimester and postpartum atazanavir concentrations at standard 300mg dose with 100mg ritonavir once daily<sup>117</sup>. However, recently 3<sup>rd</sup> trimester 24hr area under the curve concentrations 28% lower than post-partum concentrations were reported from North America. Third trimester concentrations of atazanavir in women taking tenofovir were lower still, being approximately 50% of the post-partum values of women on atazanavir without tenofovir, and 55% of women in the study taking tenofovir failed to achieve the target atazanavir concentration. The authors have therefore recommended that it may be necessary to increase the dose of atazanavir to 400mg (when given with ritonavir 100mg once daily) during the 3<sup>rd</sup> trimester<sup>118</sup>. 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 sub-optimal<sup>78</sup>.

For darunavir, a study from the USA reported reduced troughs and AUC<sub>24hr</sub> with once daily dosing in pregnancy, whilst dosing twice a day produced levels more comparable to those in non-pregnant individuals<sup>119</sup>. 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 (C24h) in third trimester and post-partum was 1.37 (0.15-3.49) mcg/mL and 2.59 (<0.09-3.96) mcg/mL respectively.

Fosamprenavir was studied at a dose of 700mg with ritonavir 100 mg bd<sup>120</sup>. The mean trough levels (C24h) in third trimester and post-partum were 1.46 (0.66-2.33) mcg/mL and 2.24(1.17-5.32) mcg/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 IC50 (0.146 mcg/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 inter-patient 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 ten pregnant women taking raltegravir 400mg twice daily found adequate trough levels in all ten, although levels were very variable and lower than post-partum<sup>121</sup>, whilst in another study of five women 3<sup>rd</sup> trimester concentrations were no lower than post-partum and in the two cord blood samples studied the cord blood : maternal blood ratio was >1.0<sup>122</sup>. No dose adjustment of raltegravir in pregnancy is required.

The pharmacokinetics in pregnancy of enfuvirtide 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<sup>123</sup>. 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 under dosing. Therefore, therapeutic drug monitoring in pregnancy should be considered for all PIs and for new agents where the facility exists in order to add to the presently limited evidence base.

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<sup>124</sup>. 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%, 3TC 300%, tenofovir 300% and ZDV 200%<sup>125</sup>.

### **B3: Naïve to HAART – mother does not need HAART for herself**

**RB3a: In terms of the NRTI backbone there is most evidence and experience in pregnancy with zidovudine plus lamivudine. Tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable alternatives. Grading: 2C**

**RB3b: 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**

**RB3c: Zidovudine monotherapy can be used in women planning a caesarean section who have a baseline VL of <10,000 and a CD4 of >350. Grading: 1A**

**RB3d: Women who do not require treatment for themselves should commence temporary HAART at 14/40 if the baseline VL is >30K (Consider starting earlier if VL > 100,000). All women should have commenced HAART by 24 weeks. Grading: 1C**

**RB3a: In terms of the NRTI backbone there is most evidence and experience in pregnancy with zidovudine plus lamivudine. Tenofovir plus emtricitabine or abacavir plus lamivudine are acceptable alternatives. Grading: 2C**

**RB3b: 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 3<sup>rd</sup> trimester are addressed separately. A fixed dose combination of zidovudine, lamivudine and abacavir is an option in this setting.

In a RCT in pregnant women with CD4 >200 cells/ $\mu$ 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 post-partum for six 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 breast-feeding 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<sup>65</sup>. Preterm delivery (see section RA2b) 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 (cross ref 2012 Adult Guidelines). Although these groups are not comparable the panel recommend restricting the use of zidovudine, lamivudine and abacavir for PMTCT to women with baseline viral loads <100,000 HIV RNA copies/ml plasma.

**RB3c: Zidovudine monotherapy can be used in women planning a caesarean section who have a baseline VL of <10,000 and a CD4 of >350. Grading: 1A**

The data on the efficacy of zidovudine monotherapy for PMTCT are well known: 67% reduction in ACTG 076 in transmission to 8.3% (treatment initiated 14 – 28 weeks, non-breast feeding, low CS rate, baseline CD4 >200)<sup>59</sup>, 50% reduction in Thai study to 9.4% (mean treatment only 25 days and oral zidovudine during labour)<sup>126</sup>; 0.8% transmission women treated with ZDVm and assigned to pre-labour CS in the Mode of Delivery study<sup>127</sup>. Since 2000 BHIVA guidelines have recommended ZDVm plus PLCS for women with CD4 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<sup>128</sup>. No transmissions were observed in UK and Ireland amongst the 464 pregnancies managed by ZDVm and PLCS between 2000 and 2006 reported to the NSHPC<sup>4</sup>.

**RB3d: Women who do not require treatment for themselves should commence temporary HAART at 14/40 if the baseline VL is >30K (Consider starting earlier if VL > 100,000). All women should have commenced HAART by 24 weeks. 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 ( $p < 0.001$ )<sup>47</sup>. 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) ( $p < 0.001$ )<sup>4</sup>.

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 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% (PI-based) - 100% (Trizivir) of mothers with baseline viral load <1000 and in 86% (PI-based) – 90% (Trizivir) if baseline viral load >100,000. Initiating therapy at 31 – 34 weeks only 78% of mothers on PI-based therapy had achieved this target<sup>65</sup>. Data from a UK multicentre study retrospectively analysing therapy outcomes in pregnant women initiating HAART demonstrate very low rates of complete suppression in women with a baseline viral load in the upper quartile (>32,641) with only 46% achieving <50 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<sup>82</sup>. For all viral loads greater than 10,000 treatment initiation later than 20.3 weeks gestation was associated with significantly less likelihood of successful viral load suppression.

**B4: Late-presenting woman not on treatment**

**RB4a. A woman who presents after 28 weeks should commence HAART without delay. Grading: 1B**

**RB4b. If the viral load is unknown or >100K a 3 or 4 drug regimen that includes Raltegravir is suggested. Grading: 2D**

**RB4c. 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**

**RB4d. It is suggested that intravenous zidovudine be infused for the duration of labour and delivery. Grading: 2C**

**RB4e. 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 RA4b) to further load the baby. Grading: 2C**

**RB4f. Women presenting in labour/ROM/requiring delivery without a documented HIV result must be recommended to have a HIV diagnostic point of care test (POCT). A reactive POCT result must be acted upon immediately with initiation of the interventions to PMTCT without waiting for formal serological confirmation Grading: 1D**

**RB4a: A woman who presents after 28 weeks should commence HAART without delay. 1B**

**RB4b If the viral load is unknown or >100K a 3 or 4 drug regimen that includes Raltegravir is suggested. Grading: 2D**

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 cpm by 36 weeks. The HAART regimen selected is normally based on a resistance test. If this is not rapidly available treatment should not be delayed and PI based HAART should be commenced. Where the viral load is unknown or >100,000 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<sup>129, 130</sup>. It is important to note that no adequate or well-controlled studies of raltegravir have been conducted in pregnant women. Pharmacokinetic data presented in Section A2d indicate that no dose change is required in the third trimester.

**RB4c: An untreated woman presenting in labour at term should be given a stat dose of nevirapine 200mg (Grading: 1B) and commence fixed dose zidovudine with lamivudine (Grading: 1B) and raltegravir. Grading: 2D**

**RB4d: 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 count (even if available), should be given **immediately** as this rapidly crosses the placenta and within two hours achieves, and then maintains, effective concentrations in the neonate for up to 10 days<sup>72, 131</sup>. HAART should be commenced immediately with fixed dose zidovudine and lamivudine and with raltegravir as the preferred additional agent as it also rapidly crosses the placenta<sup>132</sup>. Intravenous ZDV can be administered for the duration of labour and delivery<sup>133</sup>. If delivering 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.

**RB4e: If the infant is unlikely to be able to absorb oral medications, e.g. severe prematurity, consider the addition of double dose tenofovir (to the treatment described in RA4b) 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 RA4b. 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<sup>134</sup>.

**RB4f: Women presenting in labour/ROM/requiring delivery without a documented HIV result must be recommended to have a POCT. A reactive POCT result must be acted upon immediately with initiation of the interventions to PMTCT without waiting for 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. Baseline samples for CD4 count, viral load and resistance should be taken. Treatment should be commenced immediately as per RB4b above. Triple therapy should be given to the neonate (see Paediatric section).

## **B5: Elite controllers**

**RB5a: Untreated women with a CD4 count  $\geq$  350 and a viral load of  $<50$ c/ml (confirmed on a separate assay) can be treated with zidovudine monotherapy or HAART (including Trizivir) **1D** and can aim for a vaginal delivery. Grading: 1C**

Elite controllers are defined as the very small proportion of HIV-infected 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-infected individuals are elite controllers<sup>135</sup>.

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

In the original ZDVm study (ACTG 076) the transmission rate if maternal viral load was  $< 1,000$  HIV RNA cpm was 1% (range 0-7%)<sup>59</sup>. 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 ZDV. A meta analysis of transmission outcomes in several major US and European studies also demonstrated that an HIV viral load  $<1000$  HIV RNA cpm at delivery was associated with a relatively low risk of transmission and that antiretroviral prophylaxis offered additional clinically significant protection<sup>136</sup>. Zidovudine has been shown to reduce cervicovaginal shedding of HIV<sup>42</sup> 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  $<50$  cpm. Therefore zidovudine monotherapy is an option in this setting. 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 section A3.

Data on the mode of delivery in elite controllers are sparse and limited to case reports<sup>137</sup>. The benefits of PLCS at various levels of viraemia are discussed in Section C. There are no data to support the use of PLCS for PMTCT when the VL is  $<50$  HIV RNA cpm in women on antiretroviral therapy. The panel therefore recommend vaginal delivery for all elite controllers on antiretroviral therapy.

## **B6. Stopping ART post partum**

**RB6a. When stopping NNRTI-based HAART post-partum the NNRTI washout period should be covered by two weeks PI-based therapy. Grading: 1C**

**RB6b. Antiretroviral therapy (ART) should be continued in all pregnant women who commenced cART with a history of an AIDS-defining illness or with a CD4 count <350 cells/ $\mu$ l as per adult treatment guidelines. Grading: 1B**

**RB6c ART should be continued in all women who commenced cART for MTCT with a CD4 count of between 350 and 500 cells/ $\mu$ l during pregnancy who are co-infected with HBV or HCV in accordance with adult treatment guidelines. Grading: 1B**

**RB6d ART can be continued in all women who commenced cART for MTCT with a CD4 count of between 350 and 500 cells/ $\mu$ l during pregnancy. Grading: 2C**

**RB6e: ART should be discontinued in all women who commenced cART for MTCT with a CD4 count of > 500 cells/ $\mu$ l unless there is discordance with her partner (see above) or co-morbidity as outlined in section B. Grading: 2B**

**RB6a. When stopping NNRTI-based HAART post-partum the NNRTI washout period should be covered by two weeks PI-based therapy. Grading: 1C**

The literature comparing strategies for stopping anti retroviral therapy in pregnant women is limited.

Strategies for stopping treatment should take into consideration the different half lives of the agents used, particularly the long half life of NNRTIs<sup>138, 139</sup>. An observational study of three different non-randomised strategies of discontinuing ARVs in SMART study participants where non nucleoside agents were used demonstrated that stopping all drugs simultaneously was associated with more subsequent resistance than stopping the NNRTIs some days before the nucleosides<sup>140</sup>. The best strategy to prevent subsequent resistance was to prevent functional monotherapy by covering the NNRTI washout period with a PI<sup>141</sup>.

The high rates of NNRTI resistance associated mutations observed in a few weeks post-partum in pregnant women given sdNVP in labour as the only intervention to prevent HIV MTCT<sup>142, 143</sup> can be substantially reduced by short-courses of dual nucleotide RT inhibitor therapy<sup>144</sup>. Four to seven days zidovudine plus lamivudine reduced the prevalence of these mutations from 59.2% with sdNVP alone to 11.7% and 7.3% respectively at six weeks post partum. In another RCT single dose of tenofovir 300mg plus lamivudine 200mg added to standard 3<sup>rd</sup> trimester ZDVm plus sdNVP reduced the prevalence of detectable NNRTI mutations by 53% from 25% to 12%<sup>145</sup>. In a case study of nine patients with on treatment viral loads of less than 50 and electively stopping zidovudine, lamivudine and nevirapine, the median time to clearance of nevirapine was 168 hours. All patients stopped nevirapine five days prior to discontinuing the NRTI backbone and all had wild type virus on consensus sequencing 21 days post therapy<sup>138</sup>.

**RB6b. Antiretroviral therapy (ART) should be continued in all pregnant women who commenced cART with a history of an AIDS-defining illness or with a CD4 count <350 cells/µl as per adult treatment guidelines. Grading: 1B**

Available RCT data to address the question as to whether one should continue or stop cART 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<sup>146</sup> with or without HIV immunoglobulin<sup>147</sup> and from observational studies with their inherent weaknesses<sup>148-151</sup>. Nevertheless, concerns have been raised regarding the discontinuation of ARVs post-partum in light of the results from CD4-guided interruption studies (SMART<sup>152</sup> and TRIVICAN<sup>153</sup> 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 count thresholds for resumption of therapy were used than would be currently based on clinical treatment guidelines. Moreover, these CD4-based treatment randomized control trials (SMART and Trivacan) and the major cohort studies (NA-ACCORD<sup>154</sup>, ART-CC<sup>155</sup>) 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 post-partum 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 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 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.

**RB6c. ART should be continued in all women who commenced cART for MTCT with a CD4 count of between 350 and 500 cells/ $\mu$ l during pregnancy who are co-infected with HBV or HCV in accordance with adult treatment guidelines. 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 (FTC, 3TC, TDF) and the risk of a flare of hepatitis if discontinued. (See Section C – HIV hepatitis Co-infection)

**RB6d. ART can be continued in all women who commenced cART for MTCT with a CD4 count of between 350 and 500 cells/ $\mu$ l during pregnancy. Grading: 2C**

On the basis of the above cohort data the DHSS (2011)<sup>156</sup> and IAS (2010) guidelines<sup>157</sup> for treating adults have now altered their recommendation and advise treating all adults with a CD4 count <500. Moreover two recent retrospective reviews in women discontinuing ARV post-partum found an increased risk of death or opportunistic infection among women stopping therapy after delivery. The Tennessee study reviewed patients who discontinued therapy post-partum (mean nadir CD4 332) in an observational cohort of mothers from 1997-2008<sup>148</sup>. 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 counts. However, there were many potential confounders. In a further retrospective study on mothers discontinuing therapy between 1997 and 2005<sup>150</sup>, more OIs 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 count of < 350 cells. 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<sup>149</sup>.

Other studies have shown no detriment in discontinuing treatment post-natally on disease progression. Data from ACTG 185<sup>147</sup> through 18 months postpartum and from follow-up of women enrolled in the ACTG 076 study<sup>158</sup> suggest that for many women with CD4 counts >350, limited exposure to ZDV 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 counts <350 who received ZDVm during pregnancy. More persuasively, among women with CD4 cell counts >350 cells/mm<sup>3</sup> followed in the Women and Infants Transmission Study (WITS) cohort, there were no significant differences in CD4 count or disease progression at 1 year among those who did or did not continue antiretroviral treatment after delivery<sup>151</sup>. Finally, in an audit to document postpartum disease-free survival of HIV-infected women taking ARV during pregnancy, 40% of mothers (nadir CD4 median 317) given cART to prevent MTCT and who subsequently discontinued went on to commence treatment after a median of 33 months<sup>159</sup>. However, this was a heterogeneous group with 13% of mothers having CD4 counts <200 and the majority having counts between 201 and 500 (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 count is 350-500 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 contra-indication, in particular poor adherence post-partum, 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 96% reduction in transmission between heterosexual discordant couples if the infected partner is treated with HAART<sup>160</sup>. Therefore a women with a baseline CD4 count >350 cells/ $\mu$ l and a HIV viral load >50 RNA cpm can be offered continued therapy with HAART in this setting.

**RB6e: ART should be discontinued in all women who commenced cART for MTCT with a CD4 count of > 500 cells/ $\mu$ l unless there is discordance with her partner (see above) or co-morbidity as outlined in section C. Grading: 2B**

Only one cohort study has demonstrated benefit in starting therapy in adults who have a CD4 >500 (NA-ACCORD)<sup>154</sup>: specifically, this was not observed in the ART-CC analysis<sup>161</sup>. In addition, several

small CD4-guided interruption studies using a higher threshold than SMART of commencing below 350 (TRISTAN<sup>162</sup>, STACCATO<sup>163</sup>) and seroconversion treatment studies have not shown significant clinical benefit with fixed courses of early treatment<sup>164</sup>. Lastly, durable CD4 count benefits have been demonstrated in women receiving short-term ARV therapy to prevent MTCT when initiating above 500 cells indicating no short-term harm in this strategy and possible benefits<sup>165</sup>.

## Section C: HIV and hepatitis virus co-infections

The combination of HIV, chronic hepatitis B virus (HBV) infection and pregnancy presents unique management questions. Aspects of care include 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. The prevalence of HBV co-infection in pregnant women tends to reflect that of the adult population (Europe/Africa 4-10%)<sup>166-169</sup> and is 40% higher than that found in the general population (HIV +ve v HIV -ve: RR 1.40; 95% CI 1.16–1.69)<sup>169</sup>. Up to one-third of HBsAg are wild type (HBeAg-positive) and, depending on region, up to 6% co-infected with hepatitis delta. 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)<sup>170</sup>. 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; ALT levels tend to fall, HBeAg seroconversion occurs in a small minority and may be associated with liver dysfunction, and HBV DNA levels may rise by as much as one log. 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 & proportion HBeAg +ve), higher mortality when compared to HIV or HBV mono-infection, a higher rate of chronicity (20 to 80% as compared to 3-5% in HIV-negative with risk increasing with lower CD4 at 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<sup>171</sup>.

**RC1a. On diagnosis of new HBV infection, confirmation of viraemia with quantitative HBV-DNA, as well as HAV, HCV, and HDV screening is necessary. In addition, tests to assess hepatic inflammation and function (ALT, AST, albumin, INR), liver fibrosis, as well as exclusion of concomitant liver disease should be performed. Grading: 1C**

**RC1b. Liver function tests should be repeated at 2 weeks after commencing CART to detect evidence of ARV hepatotoxicity or IRS and then monitored throughout pregnancy and post-partum. Grading: 1C**

**RC1c. In the immediate period after discontinuing drugs with anti-HBV activity, LFT's and HBV-DNA should be monitored frequently. Grading: 1C**

In a pregnant HIV-infected woman newly diagnosed with HBV (HBVsAg +ve on antenatal screening or diagnosed pre-conception), baseline hepatitis B markers (HBVcore Ab/HBVeAg 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, auto-immune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) immunisation as well as for HDV (hepatitis delta) co-infection (HDV serology). Fibroscan is contraindicated during pregnancy so that where there is suspicion of advanced liver disease, US 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<sup>172</sup>. However, in the absence of decompensated disease and with CART incorporating anti-HBV drugs and close monitoring, most women with cirrhosis do not have obstetric complications from their HBV infection.

Because of the risk of ARV-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat LFTs at 2 weeks post-initiation of CART. Through pregnancy, it is routine to monitor LFTs tests 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. Finally, in those diagnosed late and not receiving HBV treatment incorporated into CART, LFT's may flare shortly after delivery which in some relates to HBVeAg seroconversion and reappearance or a marked increase in HBV-DNA levels. Where acute HBV has been diagnosed, there is no data to support management and each case needs to be managed with specialist advice. Data suggest that 3TC 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 3TC/FTC.

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 CART incorporating TDF and either FTC or 3TC.

**RC1d. Where pegylated IF or adefovir is being used to treat HBV in a woman who does not yet require HIV treatment who discovers they are pregnant, treatment should be switched to a tenofovir-based HAART regimen. Grading: 1C.**

The outcome of the pregnancy should be reported to the Interferon Pregnancy and Antiretroviral Pregnancy Registries.

**RC1e. 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**

If a woman on PEG-IF becomes pregnant it should be discontinued and changed to a tenofovir-based HAART regimen because of the anti-proliferative 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). For tenofovir, emtricitabine, and lamivudine, APR<sup>48</sup> 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, 3TC or FTC), 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, 3TC or FTC: these drugs are recommended as NRTI choices in national<sup>173</sup> and international guidelines<sup>174</sup>.

**RC1f. 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 count is <300/μl when an additional dose may be indicated. Grading: 1D**

Immunisation for HAV uses inactivated vaccines. Data for HAV vaccine in pregnancy are limited. Nevertheless, several guidelines indicate that pregnancy is not a contra-indication for HAV immunisation, including in HBV co-infected pregnant women<sup>175, 176</sup>. For HAV vaccines, patients with higher CD4 counts and on HAART generally show improved responses to vaccination. HIV-infected persons with CD4 counts <300 cells/ $\mu$ l should receive three doses of HAV vaccine over 6–12 months instead of the standard two.

**RC1g. Tenofovir and 3TC/FTC 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**

**RC1h. If tenofovir is not currently being given as part of HAART it should be added. Grading: 1B**

**RC1i. 3TC/FTC may be omitted from the antiretroviral regimen and tenofovir given as the sole anti-HBV agent if there is clinical or genotypic evidence of 3TC/FTC resistant HBV. Grading: 1C**

**RC1j. 3TC or FTC 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**

**RC1k. FTC has potential antiviral benefits over 3TC, 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**

All HBV/HIV co-infected women should receive HAART containing tenofovir with FTC or 3TC treatment during pregnancy unless contraindicated. Although 3TC and FTC 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 3TC or FTC has been demonstrated to be effective at suppressing HBV DNA and may induce HBeAg seroconversion. Combining 3TC/FTC with tenofovir may also reduce the risk of breakthrough HBV viraemia<sup>173</sup>.

FTC is structurally similar to 3TC 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-infected and co-infected patients. In co-infected patients' naïve to antivirals, an RCT combining FTC with tenofovir has been shown to be more effective than FTC alone (median TWAC decrease was -5.32 log<sub>10</sub> IU/mL in the TDF/FTC group vs. -3.25 IU/mL in the FTC group: p=0.036)<sup>177</sup>: further studies comparing TDF/3TC vs. 3TC alone produced similar results<sup>178</sup>. In addition, the PROMISE study includes a sub-study examining pregnant women with CD4 >350 cells/ $\mu$ L randomised to either TDF/FTC or AZT/3TC and lopinavir/r with outcome measures of

pregnancy HBV viral loads, HBV transmission, pregnancy outcomes, and postpartum ALT and HBV viral load. 3TC/FTC-resistant strains will respond to tenofovir.

LFTs should be monitored frequently after starting CART because of the possibility of an inflammatory flare from immune reconstitution (See section A).

**RC1l. Where the CD4 count is <500 cells/ $\mu$ L HAART should be continued if HBV co-infection exists because of the increased risk of HBV progressive disease. Grading: 1B**

**RC1m. Where the CD4 count is >500 cells/ $\mu$ L and there is no indication to treat HBV (HBV-DNA <2000 IU/mL, absence of fibrosis), consideration should be given to continuing anti-HBV treatment with either HAART incorporating TDF and 3TC/FTC or with adefovir monotherapy because of the benefits on reducing the speed of progression of liver disease and to prevent any risk of hepatic flare. Grading: 2C**

**RC1n. If a decision is taken to discontinue therapy careful monitoring of liver function is imperative Grade. Grading: 2D**

**RC1o. Where the CD4 count is >500 cells/ $\mu$ L and there is HBV viraemia and evidence of liver inflammation or fibrosis, either HAART containing TDF and FTC/3TC should be continued, or the patient switched to adefovir. Grading: 2C**

**RC1p. Hepatitis flares that occurred after HAART cessation should be treated by resumption of active anti-HBV treatment before significant liver dysfunction occurs. Grading: 2D**

The decision to continue ARV or not post-partum 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 (HBVsAg +ve and/or HBV-DNA +ve) co-infection should receive ARVs if their CD4 count is <500 cells/ $\mu$ L<sup>174, 175</sup>. Hence, HAART incorporating agents active against HBV (TDF and either 3TC or FTC) should be continued in this group. In those women with CD4 counts of >500 cells/ $\mu$ L with a baseline HBV-DNA >2000 IU/mL and/or evidence of fibrosis on biopsy or Fibroscan, HBV treatment should be continued because of the risk of progressive liver disease if discontinued. Options are to continue HAART incorporating TDF with TDF/FTC or to switch to adefovir monotherapy. Adefovir has been evaluated against HBV in co-infected patients and, although less active than TDF, does not select resistance against 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 counts over 500 cells/ $\mu$ L who received HAART so as 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, either in the form of TDF-based HAART or switching to adefovir monotherapy because of the risk of progression of liver disease in co-infection.

Inflammatory flares from viral escape and HBV viraemia can occur if drugs with anti-HBV activity are stopped, which may be severe, particularly in persons with cirrhosis. In an RCT comparing 3TC with placebo for reducing HBV MTCT in patients with HBV mono-infection, an immediate rise of HBV-DNA levels was observed on discontinuation of 3TC post-partum<sup>179</sup>. Similarly, hepatitis flares among HIV/HBV co-infected patients have been reported upon the discontinuation of 3TC, FTC and tenofovir. In the Swiss HIV observational cohort, liver enzyme elevation occurred in 29% of patients who discontinued 3TC and in 5% this was severe with three patients presenting with fulminant hepatitis<sup>180</sup> at a median time of 6w after discontinuation. Hepatitis flares that occurred after ART cessation should be treated by resumption of active anti-HBV treatment before significant liver failure occurs.

**RC1q. In the absence of obstetric complications, normal vaginal delivery can be recommended if the mother is receiving HAART. Grading: 2C**

No data exists to support any benefit from ECS 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 randomised trials all from China involving 789 people were included) where routine HBV neonatal vaccine and HBIG were used, there was strong evidence that elective caesarian section versus vaginal delivery could effectively reduce the rate of mothers to infant transmission of HBV (RR 0.41, 95% CI 0.28–0.60)<sup>181</sup>. However, methodological concerns including lack of information on randomisation procedure, lack of allocation concealment and lack of blinding make the role of ECS for preventing mother-to-child transmission of HBV uncertain. In addition, a meta-analysis of six RCT where 3TC was used from the third trimester has demonstrated that 3TC is effective in reducing transmission (HR: 0.31 95% CI: 0.15– 0.63)<sup>182</sup>. Similarly, a single RCT in women positive for HBVsAg and with an HBV-DNA >10<sup>6</sup> IU/mL demonstrated that telbivudine was also effective in reducing MTCT for HBV (2.11% vs. 13.4%; p<0.04) and lowering risk of post-partum 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 3TC as well as telbivudine in reducing the rate of intra-partum transmission in mono-infection, the efficacy of 3TC, tenofovir and FTC as part of CART in reducing HBV-DNA in non-pregnant co-infected patients, and the use of tenofovir with either 3TC or FTC as standard practice in co-infected patients, collectively provide further reason against recommending CS in those co-infected.

## **RC1r. Neonatal immunisation with or without HBIG should commence within 24 hours of delivery.**

### **Grading: 1A**

Immuno-prophylaxis with HBV vaccine with or without HBIG given to the neonate has been shown in separate meta-analyses of RCT's to significantly reduce MTCT from HBV mono-infected women. In the absence of neonatal immunisation with HBV vaccine with or without HBIG, the rate of MTCT from a mono-infected mother who is HBVsAg and HBVeAg +ve is 70–90% and for women who are HBsAg positive but HBeAg negative, 10-40%. By co-administrating 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 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 immunisation with vaccine and HBIG have been reported in infants born to mothers with HBV DNA concentrations more than  $1.1 \times 10^7$  IU/mL. Antiretroviral therapy with HBV activity (3TC/FTC, tenofovir) can reduce this risk to a negligible level<sup>183</sup>.

### **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<sup>184, 185</sup>. 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<sup>186-188</sup>. 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)<sup>186, 187</sup>. 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<sup>189</sup>. Numerous studies have shown that the height of the HCV viral correlates with the risk of HCV MTCT and it is likely there is a linear relationship between VL and transmission as for HIV<sup>190, 191</sup>. Invasive obstetric procedures, internal fetal monitoring, prolonged rupture of membranes and female infant sex have also been associated with transmission but breast feeding and CS do not pose an additional risk in mono-infected mothers<sup>192, 193</sup>. Effective HAART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia<sup>193, 194</sup>. No

correlation with HCV genotype or IL28 polymorphisms and transmission has been identified<sup>195-197</sup>. 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<sup>198</sup>.

**RC2a. On diagnosis of new HCV infection, confirmation of viraemia with quantitative VL and genotype, as well as HAV and HBV screening is necessary. In addition, tests to assess hepatic inflammation and function (ALT, AST, albumin, INR), liver fibrosis, as well as exclusion of concomitant liver disease should be performed. Grading: 1C**

**RC2b. Liver function tests should be repeated at 2 weeks after commencing HAART to detect evidence of ARV hepatotoxicity or IRS and then monitored throughout pregnancy and post-partum. Grading: 1C**

In a pregnant HIV-infected woman newly diagnosed with HCV, 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, auto-immune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) and HBV (HBVsAb) immunisation as well as for HBV co-infection (HBVsAg). 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<sup>172</sup>. 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 ARV-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 LFTs tests 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 pre-natal 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.

**RC2c. Co-infected mothers with HCV should not be treated for HCV with pegylated interferon with or without ribavirin and all pregnant 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 GT1. 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 birth weight 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<sup>199</sup>. 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.

**RC2d. In all non-immune HCV co-infected women after the first trimester, vaccination against HBV with either a standard (0, 1 and 6 months), accelerated (0, 1, and 4 months), or rapid (0, 1, 2 and 12 months) schedule is recommended: HBsAb level should be measured 6–8 weeks after completion of vaccination. Grading: 2C**

**RC2e. HAV vaccine is recommended as per the normal schedule (0 and 6-12 months) unless the CD4 count is less than 300 cells/ $\mu$ L when an additional dose may be indicated Grading: 2C**

Immunisation for HAV and HBV uses inactivated vaccines. Limited data are available on the use of hepatitis B vaccination in pregnancy and none in HIV-infected persons. Moreover, no randomised trial has been performed on the optimum dosing schedule for use in pregnancy<sup>200</sup>. Data for HAV vaccination are similarly limited. Nevertheless, several guidelines indicate that pregnancy is not a contra-indication for HBV or HAV immunisation, including in HCV co-infected pregnant women<sup>201, 202</sup>. 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 being able to be completed during the course of pregnancy<sup>203</sup>. For both vaccines, patients with higher CD4 counts and on HAART generally show improved responses to vaccination. HIV-infected persons with CD4 counts <300 cells/mL should receive three doses of HAV vaccine over 6–12 months instead of the standard two<sup>204</sup>.

**RC2f. 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 randomised 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<sup>205</sup> – OR 1.19<sup>188</sup>). 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 to 0.80)<sup>188</sup>. However in a later analysis from the EPHN (n=208 15.0%) no such association was found (OR 0.76 CI 0.23–2.53)<sup>193</sup>. 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 (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<sup>206</sup>. HAART should be given to all HCV/HIV co-infected pregnant women, regardless of CD4 count or HIV viral load because of the evidence of increased HIV transmission in co-infected mothers.

**RC2g. Where the CD4 count is <500 cells/μL, HAART should be continued if active HCV co-infection exists because of the increased risk of progressive HCV-related liver disease. Grading: 1B**

**RC2h. Where the CD4 count is >500 cells/μL and there is no HCV viraemia or fibrosis, HAART should be discontinued. Grading: 2C**

**RC2i. Where the CD4 count is >500 cells/μL 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**

**RC2j. Where the CD4 count is between 350 and 500 cells/μL 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 post-partum 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 count is <500 cells/μL<sup>157, 207, 208</sup>. In those women with CD4 counts of 350 to 500 cells/μL 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 randomised PROMISE trial which addresses the question of whether to continue HAART post-natally in mothers with CD4 counts > 400 cells/μL, there is equipoise as to correct management. In those with CD4 counts over 500 cells/μL, who received HAART so as 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 counts over 500 cells/μL 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<sup>209</sup> and that effective HIV suppression improves liver histology even in the absence of effective HCV treatment<sup>210, 211</sup>.

## Section D: Obstetric Issues

### Summary of Recommendations

#### 1. Ante-natal Care

RD1A. Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status. Grading: 1D

RD1B. The integrated 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.

RD1C 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

RD1D If not on treatment and the 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

RD1E External Cephalic Version (ECV) can be performed in women with HIV. Grading: 2D

#### 2. Delivery

RD2A 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

RD2B 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

RD2C Vaginal Birth after Caesarean section (VBAC) should be offered to women with a viral load <50c/ml. Grading: 1D

RD2D 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 regardless of ART (see RC2B above). Grading: 1D

RD2E Where the indication for PLCS is the prevention of MTCT, PLCS should be undertaken at between 38 and 39 weeks gestation. Grading: 1C

#### 3. Management of Spontaneous Rupture of Membranes

RD3A In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited. Grading: 1C

**RD3B** If maternal HIV viral load is < 50 RNA copies/ml plasma immediate induction of labour is recommended, with a low threshold for treatment of intra-partum pyrexia **1C** (for 50 <1000 see indications for PLCS above)

**RD3C** If maternal HIV viral load is  $\geq 1000$  RNA copies/ml plasma immediate caesarean section is recommended. Grading: **1C**

**RD3D** The management of PPROM at  $\geq 34$  weeks is the same as term ROM (RC3A-C above) except women who are 34-37 weeks gestation will require group B streptococcus prophylaxis in line with national guidelines. Grading: **1C**

**RD3E** When PPROM 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

#### **4. Use of intra-partum intravenous infusion of zidovudine**

**RD4A** Intra-partum intravenous Zidovudine (ZDV) infusion is recommended in the following circumstances: Grading: **1C**

- For women with a viral load of >10K who present in labour, or with ruptured membranes or who are admitted for planned CS
- For untreated women presenting in labour or with ruptured membranes in whom the current viral load is not known

## D1. Antenatal Management

### **RD1A. Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status. Grading: 1D**

The National Screening Committee<sup>212</sup> and the NICE antenatal guidelines<sup>213</sup> 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<sup>48</sup> does not support the need for increased surveillance with the most commonly prescribed therapies (list in appendix) though 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/>)

### **RD1B. The integrated 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.**

CG62 (see above) also recommends that all women should be offered screening for trisomy 21. The most effective screening is with the combined test at 11+0 to 13+6 weeks gestation. This includes maternal age, nuchal translucency, beta HCG and pregnancy associated plasma protein A (PAPP-A). In the general population this has a detection rate of 92.6% for a false positive rate of 5.2%<sup>214</sup>.

For women who present too late for the integrated 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 (NICE CG62). However, significantly increased levels of  $\beta$ HCG,  $\alpha$ FP and lower levels of UE3 (the elements of the 'triple test) have been observed in the HIV-positive population<sup>215-217</sup> whilst a reduction in  $\beta$ HCG in patients treated with PI- based<sup>218</sup> or with NNRTI based HAART has been reported. Since Down's syndrome is associated with increased  $\beta$ HCG theoretically HIV infection per se may increase the false positive rate in women and thus increase the number of invasive tests offered compared with the uninfected population but PAPP-A and nuchal translucency are unaltered by HIV infection or antiretroviral therapy<sup>219</sup> the preferred screening modality.

**RD1C 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 <50c/ml.
- The fetal medicine team should discuss management with an HIV physician if the woman is HIV positive and has a detectable viral load.

**RD1D If not on treatment and the 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' which included amniocentesis, cerclage, laser therapy and amnioscopy<sup>220</sup>. 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 AZT 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<sup>221</sup>. 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<sup>222</sup> and 17 women on HAART in Portugal (1996 – 2009) showed no transmissions whilst transmission occurred in 1 of 6 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 reported on chorionic villus sampling (CVS) or cordocentesis<sup>223</sup>. For evidence relating to choice of antiretroviral therapy to reduce transmission risk associated with amniocentesis, see section on late presentation.

**RD1E External Cephalic Version (ECV) can be performed in women with HIV. Grading: 2D**

- ECV should be offered to women with a viral load <50cpm 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<sup>213</sup>. 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<sup>224</sup>. It is also reassuring that in a randomised trial of fundal pressure to expel the baby during caesarean section, no evidence of materno-fetal transfusion was found<sup>225</sup>.

**D 2 Mode of delivery**

**RD2A 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 <50c/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 at 36 weeks, a pre-labour caesarean section (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  $\geq 400$  c/ml at 36 weeks, a 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  $<50$  c/ml taking HAART, irrespective of mode of delivery<sup>4, 47, 226, 227</sup>. These studies support the practice of recommending planned vaginal delivery for women on HAART with plasma viral load  $< 50$  cpm.

Among HIV infected 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 (17/2286 – 0.7%) or planned vaginal delivery (4/559 – 0.7%) AOR 1.24 (95% CI 0.34-4.52). Median viral load on HAART was  $<50$  cpm (IQR 50-184). MTCT was 0.1% (three transmissions) in 2117 women on HAART with a delivery viral load of  $<50$  cpm. 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 cpm plasma, but in the multivariate analysis, controlling for ART, mode of delivery, gestational age and sex, there was a 2.4 fold increased risk of transmission for every log<sub>10</sub> increase in viral load, with lack of ART and mode of delivery strongly associated with transmission<sup>4</sup>.

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  $<400$  cpm 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  $>10,000$  cpm 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  $<50$  cpm but mode of delivery data for this subset were not provided<sup>47</sup>.

In contrast, data from the European Collaborative study of 5238 women delivering between 1985 and December 2007 showed that in 960 women delivering with a viral load of  $<400$  cpm, 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 cpm (MTCT 0.4%) with one delivering vaginally at <34 weeks and one by ECS at 37 weeks, but further analysis was not possible<sup>227</sup>.

A potential explanation for the differing conclusions of the effect of mode of delivery on MTCT in women with delivery plasma viral loads of <400cpm in these two studies is that the true value of the plasma viral load in studies which use assays with a lower limit of detection of 400 cpm, is not known. It is conceivable that there may exist a significant difference in the viral load distribution <400 cpm 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 <400cpm can necessarily be applied to patients with plasma viral loads of 50-399 using current assays with lower limits of detection of 50 cpm 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 399c/ml. Data from the UK and Ireland cohort 2000 – 2011 (P Tookey and C French unpublished data) and from the European Collaborative Study 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 c/ml. In the UK and Ireland cohort there were 7 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 European Collaborative Study cohort, of 405 women the transmission rates were 0.37% (95% CI 0.099-2.06) and 1.46% (95% CI 1.77-5.17) 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 cpm 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 <50cpm 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, together with the data from the UK study showing a 2.4 fold increased risk of transmission for every log<sub>10</sub> increase in viral load associated with mode of delivery, the panel felt that until further data are available, a PLCS should be recommended for all women with a viral load of >400 cpm.

**RD2B. In women in 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 (1985 – 1993) provides data on the risk of various obstetric factors in a predominantly untreated, non-breast-feeding 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<sup>220</sup>. 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 (Relative Risk 1.94 95% CI 1.12 – 3.37)<sup>228</sup>. 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<sup>229</sup>.

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<sup>20</sup>.

Induction has previously been avoided as there were concerns about length of ruptured membranes and risk of MTCT but recent evidence (see section on ROM below) would appear to be reassuring on this point.

Data from the predominantly untreated French cohort (1985-1993) showed no risk with instrumental vaginal delivery (Relative risk 0.8, 95% CI 0.6 – 1.2)<sup>220</sup>. Data from the smaller Swiss cohort (n = 494, 1986 – 1996, transmission rate 16.2%) also failed to identify instrumental delivery as a risk factor (Relative risk 1.82 95% CI 0.81 – 4.08) despite less than 20% of the cohort taking any antiretroviral therapy for prophylaxis<sup>229</sup>.

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 cpm 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<sup>230</sup>).

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<sup>231</sup> and HIV RNA<sup>42</sup> 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<sup>45, 232, 233</sup>. 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 <50cpm. 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, whilst acknowledging the potential for discordance between the plasma and genital tract viral load, the panel 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 panel acknowledges a lack of data from the HAART era, but concluded that it is unlikely that the use of fetal scalp electrode 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<sup>230</sup>. 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.

**RD2C. Vaginal Birth after Caesarean section (VBAC) should be offered to women with a viral load <50c/ml. Grading: 1D**

In the absence of randomised 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<sup>234</sup>. 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.

**RD2D 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 regardless of ART (see RC2B above). Grading: 1D**

Zidovudine monotherapy with a planned pre-labour pre-rupture of membranes caesarean section is a reasonable 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)<sup>235</sup> and a randomised controlled trial of mode of delivery in Europe (n=436)<sup>127</sup> 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 ZDV 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 ZDV monotherapy combined with PLCS was 0% (0 of 467 patients; 95% upper CI 0.8%)<sup>4</sup>. This was not significantly different from the 0.7% transmission rate with HAART plus PLCS (17 of 2337 patients; 95% CI 0.4–1.2%) or the 0.7% rate with HAART plus planned vaginal delivery (four of 565 patients; 95% CI 0.2–1.8%)(3). These findings support the option of ZDV 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 5 studies: the European randomised mode of delivery trial and five observational studies from North America and Europe<sup>236</sup>. 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 delivering vaginally. Low CD4 count and co-morbidities such as diabetes were independent risk factors for postpartum morbidity. This review included women not on HAART.

More recent cohort data from Europe<sup>226, 237</sup> and from case controlled studies in the USA<sup>238</sup> and the UK<sup>239</sup> involving women on HAART with undetectable viral loads have demonstrated very low rates of maternal morbidity, irrespective of mode of delivery.

**RD2E. 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 <50cpml, 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<sup>240</sup>. 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<sup>234</sup>. The risk of TTN at this gestation is approximately 1 in 300 and this risk doubles for every week earlier that delivery occurs.

### **D3. Management of Spontaneous Rupture of Membranes**

**RD3A. In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited. Grading: 1C**

**RD3B. If maternal HIV viral load is < 50 (for 50 - 999 RNA copies/ml plasma see indications for PLCS above) immediate induction of labour is recommended, with a low threshold for treatment of intra-partum pyrexia. Grading: 1C**

**RD3C. If maternal HIV viral load is ≥1000 RNA copies/ml plasma immediate caesarean section is recommended. Grading: 1C**

In the pre HAART era several studies<sup>20, 22, 241</sup> 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 ZDV 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 (Adjusted Odds Ratio 1.02). Transmission increased from 12% with <1 hour membrane rupture to 19% with >12 hours of membrane rupture<sup>242</sup>.

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% ( $p = \text{NS}$ ) and in the women on HAART (0.8% vs 0.0%,  $p = \text{NS}$ )<sup>243</sup>.

The NSHPC study of HIV infected 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 <50c/ml when comparing those with ROM  $\leq 4$  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 cpm who delivered vaginally did not alter this conclusion<sup>244</sup>. Therefore for women on HAART who rupture their membranes at term with a viral load of <50 cpm and who do not have an obstetric contra-indication to vaginal delivery, a caesarean section is not recommended.

As both acute and chronic chorioamnionitis have been associated with perinatal transmission<sup>22, 245-247</sup>, 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 cpm should have immediate induction with a low threshold for the treatment of intra-partum pyrexia. The NICE induction of labour guidelines<sup>248</sup> and the NICE intra-partum guidelines<sup>230</sup> 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 >50c/ml are more difficult to interpret as the numbers are currently small. In women with VL 50-999 there were two transmissions with ROM >4 hours (2/51) and none in the women with ROM  $\leq 4$  hours (0/43). The two transmitters both had emergency caesarean section 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  $\geq 50$  c/ml, and until further data are available, it is the recommendation of the panel that emergency caesarean section should be considered for women with a viral load of 50-999c/ml at term. Again, if an emergency caesarean section is not undertaken, delivery should be expedited, as above. Data from the NSHPC for women with a viral load of >1000c/ml are very sparse at present, with 1/14 (7.1%) transmitting with ROM  $\leq 4$  hours compared to 3/15 (20%) with ROM >4 hours.

A single centre study from Miami showed that in 707 women on ART, ROM > 4 hours was associated with an increased risk of MTCT if the VL was > 1000c/ml. There was no association at < 1000c/ml but it is not possible to determine the number of women with a viral load >50 c/ml but <1000 in this group. Until further data are available, an emergency caesarean section is recommended where the viral load is >1000c/ml regardless of treatment<sup>249</sup>.

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

**RD3D. The management of PPROM at  $\geq 34$  weeks is the same as term ROM (RC2A-C above) except women who are 34-37 weeks gestation will require group B streptococcus prophylaxis in line with national guidelines. Grading: 1C**

**RD3E. When PPROM 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 RCOG guidelines<sup>250</sup> and (if delivery is to be delayed) oral erythromycin<sup>251</sup>. Decision 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 A) 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.

#### **D4. Use of intra-partum intravenous infusion of zidovudine**

**RD4A. Intra-partum intravenous zidovudine (ZDV) infusion is recommended in the following circumstances:**

- **For women with a viral load of >10K 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**

**There are no data to support the use of intra-partum intravenous zidovudine infusion in women on HAART with a viral load <10K.**

**The use of intravenous zidovudine is suggested for women taking zidovudine monotherapy as per RC2D above. The use of intravenous zidovudine for women on HAART with a viral load of >50c/ml and <10K can be considered regardless of mode of delivery. However, continued oral dosing of their current regimen is a reasonable alternative.**

The effectiveness of ZDV monotherapy in preventing MTCT was first demonstrated in the ACTG 076 randomised controlled trial of non-breast feeding women in which ZDV 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%<sup>59</sup>. IV zidovudine has therefore been included in the management of all women treated with ZDVm. However the data on the contribution of IV ZDV are poor. In a prospective study of all women prescribed ZDVm during pregnancy prior to the publication of the ACTG 076 findings (1988 – 1994) in which the 8.8% transmission rate amongst women with CD4 counts >200 cells/ $\mu$ l is similar to that of the ZDVm arm of ACTG076 (8.3%), intra-partum IV ZDV was not associated with lower rates of transmission<sup>252</sup> (Frenkel et al. JID 1997). One rationale for IP IV ZDV in ACTG076 is that labour will be associated with poor absorption of oral therapy. Whilst not strictly comparable, the well recognised rapid absorption of sdNVP during labour suggests that the impact of labour on absorption may be over-estimated. PK data from a RCT of oral

ZDVm v placebo indicate that adequate (therapeutic) ZDV concentrations are achieved in cord blood with oral dosing (median 252 ng/ml). Although the concentrations are lower than have been reported with IV infusion transmission was not associated with ZDV cord blood concentration<sup>253</sup>. 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 A) 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 IV 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%)<sup>133</sup>.

From the French data there is no evidence that intra-partum intravenous zidovudine further reduces the risk of MTCT in women on HAART unless maternal HIV viral load is >10,000 copies/ml<sup>47</sup>. However, individual circumstances vary, and intravenous intra-partum zidovudine may be considered as one of a number of maternal intra-partum antiretroviral options for women with viral loads >50 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 of > 10 K. 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 panel recommend the immediate administration of oral agents (see section A) with intravenous zidovudine as an option.

In women on zidovudine monotherapy undergoing a PLCS intravenous zidovudine can be considered. Continued oral dosing is a reasonable alternative.

In women on HAART with a viral load of >50c/ml and < 10K, 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.

## Section E: Neonatal management

### E1. Infant post-exposure prophylaxis

**RE1a. Zidovudine monotherapy is recommended if maternal viral load is <50 HIV RNA copies/ml at 36 weeks gestation/delivery (or mother delivered by PLCS whilst on ZDVm), irrespective of the mother's viral resistance pattern or drug history. Grading: 1C**

**RE1b. Infants <72 hours old, born to untreated HIV-positive mothers, should initiate three drug therapy immediately. Grading: 1C**

**RE1c. Three drug infant therapy is recommended for all circumstances where maternal viral load at 36 weeks gestation/delivery is not <50 HIV RNA copies/ml. Grading: 2C**

**RE1d. Neonatal PEP should be commenced very soon after birth, certainly within 4 hours. Grading: 1C**

**RE1e. Neonatal PEP should be continued for 4 weeks. Grading: 1C**

**RE1f. PCP prophylaxis, with co-trimoxazole, should be initiated from age 4 weeks in:**

- 1) all HIV infected infants – Grading: 1C**
- 2) in infants with an initial positive molecular diagnostic test result (and continued until HIV infection has been excluded) – Grading: 1C**
- 3) infants whose mother's viral load at 36 weeks gestational age/delivery is >1000 HIV RNA copies/ml or unknown (and continued until HIV infection has been excluded) – Grading: 2D**

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

**RE1a: Zidovudine monotherapy is recommended if maternal viral load is <50 HIV RNA copies/ml at 36 weeks gestation/delivery (or mother delivered by PLCS whilst on ZDVm), irrespective of the mother's viral resistance pattern or drug history. Grading: 1C**

Zidovudine monotherapy for the infant has been part of the PMTCT strategy since the publication of the results of ACTG 076<sup>59</sup>. The relative contributions of the ante-natal, peri-partum and infant components have been difficult to quantify. In ACTG 076 neonatal zidovudine 2mg/kg every 4 hours (5 doses) was given for six 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 cpm. 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 (ZDV) monotherapy is the neonatal treatment of choice, whatever the maternal ART combination. For infants born to mothers on fully suppressive ART, ZDV monotherapy post exposure prophylaxis remains reasonable even where the mother has a previous history of ZDV exposure with resistance (thymidine-associated mutations - TAMs). On HAART the risk of transmission in the mother with fully suppressed viral replication is extremely low (~ 0.1%), and the risk of transmission of ZDV resistant virus is concomitantly very low. Data from the era when only maternal ZDV monotherapy was available indicate preferential transmission of wild-type over ZDV-resistant virus. Established alternatives, such as nevirapine and lamivudine have a low barrier to resistance, whilst dosing and safety issues with newer therapies are outlined below (Section on Neonatal Triple Therapy). Therefore neonatal ZDVm in this setting is considered safer with lower risk of multidrug resistance should transmission have occurred. With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred, another advantage of ZDV. Where a low transmission risk mother (see Section B) chooses ZDV monotherapy plus PLCS then the infant should also receive ZDV monotherapy<sup>4</sup>.

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

1. Post delivery infant only prophylaxis: mother found to be HIV-infected after delivery, this is only effective if given within 48 - 72 hours of birth
2. Detectable maternal viraemia (> 50 copies) 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

**RE1b: Infants <72 hours old, born to untreated HIV-positive mothers, should initiate three drug antiretroviral therapy immediately for 4 weeks. Grading: 1C**

There is one large randomised 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)<sup>254</sup>. Infants were randomized at less than 48 hours of age to: 6 weeks ZDV monotherapy; or 6 wks ZDV with 3 doses of NVP in the 1st week of life; or 6 wks ZDV, with NFV and 3TC 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 2 fold higher in the ZDV alone arm compared to the multiple ARV arms ( $p=0.034$ ). There was no significant difference in transmission rates between the two multiple ARV arms and neonatal neutropaenia was significantly higher in the 3-drug arm.

In a randomized African (NVAZ) study babies born to mothers presenting at delivery received single-dose NVP or single-dose NVP and one week of ZDV. Of those HIV negative at birth, 34 (7.7%) who received NVP plus ZDV and 51 (12.1%) who received NVP alone were infected ( $P=0.03$ ) – a protective efficacy of 36% for the dual combination<sup>255</sup>. 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: ZDV plus 3TC versus NVP<sup>256</sup>; or ZDV plus NVP versus NVP<sup>257</sup>.

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 ZDV when this was started within 48 hours of birth<sup>133</sup>. 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<sup>258</sup>. 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 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] versus 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.

**RE1c: Where vaginal delivery is planned and maternal viral load at 36 weeks gestation/delivery is not <50 HIV RNA copies/ml three drug infant therapy given for 4 weeks is suggested.**

**Grading: 2C**

Delivery with a detectable maternal viral load (>50 copies) 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 cpm); 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 randomised trials of combination therapy PEP for infants where mothers are receiving HAART. In a French study, transmission rates with dual therapy (AZT+3TC) to both the neonate and mother 1.6% were lower than ZDV monotherapy reported in historical controls 6.8% (OR 0.22, 95% CI 0.2 – 0.5)<sup>259</sup>.

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 favourable trends can be considered in the risk assessment. Despite the lack of data, NSHPC data indicate a trend towards increasing use of triple neonatal PEP.

#### 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 (ZDV<sup>260</sup>, 3TC<sup>261, 262</sup>, TDF<sup>134</sup>, FTC<sup>263</sup>) and dosing regimen are available for most of the nucleoside analogues and for abacavir from age one month<sup>264</sup>, whilst limited study of didanosine in neonates suggests that the pharmacokinetics are highly variable<sup>106</sup>. The pharmacokinetics of nevirapine in neonates has been described in more detail<sup>73, 265-268</sup>. PK supported dosing is available for the PIs nelfinavir<sup>261</sup> and ritonavir-boosted lopinavir (based on HIV-1 infected infants initiating therapy in the first 6 weeks of life)<sup>269-271</sup> and a study that included some infants treated from birth<sup>272</sup>. However, evidence of adrenal suppression has been documented in some neonates, treated with lopinavir/ritonavir, particularly when preterm<sup>273</sup> 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<sup>274</sup>. The panel therefore recommend that this PI should be avoided in infant PEP, where possible, and should only be prescribed to preterm neonates in exceptional circumstances. 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. Nelfinavir powder for neonates may be difficult to obtain and is complicated to administer. Thus, it is at present difficult to administer protease inhibitor based PEP to HIV-exposed infants. See CHIVA website for dosing updates ([www.chiva.org.uk](http://www.chiva.org.uk)).

In contrast to the PIs, NVP efficiently crosses the placenta (see below) and is well absorbed by the neonate<sup>275</sup>. Neonatal metabolism of NVP is induced where there has been antenatal in utero exposure<sup>73, 266</sup>; if this drug is given to the neonate, when the mother has taken it for three or more days, the full dose of 4mg/kg per day should be started at birth, rather than the induction dose of 2mg/kg per day (Table 1). Owing to its long half-life NVP should be stopped 2 weeks before co-prescribed antiretroviral drugs with shorter half-lives to reduce the risk of NVP monotherapy exposure and the development of NNRTI resistance should transmission have occurred.

The only licensed ART available for intravenous (IV) use in sick and/or premature neonates, unable to take oral medication, is ZDV<sup>260, 276</sup>. Reduced oral and IV dosing schedules for premature infants are available (Table 1). The fusion inhibitor, enfuvirtide does not cross the placenta. Although IV enfuvirtide (T20) has been given to a small number of infants born to mothers with multidrug resistant HIV no formal neonatal PK studies for enfuvirtide have been conducted to date. The dose used has been adapted from a paediatric subcutaneous treatment study<sup>277</sup> and an adult IV dosing study<sup>278</sup>.

For infants born to ART-naïve women, or where drug resistance is unlikely, ZDV, 3TC and NVP 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<sup>279</sup>. Premature infants should be commenced on IV ZDV, but once enteral feeding is established, ZDV may be changed to enteral and the premature dosing regimen should be used (Table 1). Enfuvirtide (T20) is the only other antiretroviral which is administered parenterally, usually subcutaneously, in adults and children. An unlicensed IV dosing regime has been adapted for use as part of combination ART in neonates at risk of multi-resistant HIV (seek expert advice)<sup>278</sup>.

**RE1d 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<sup>280-282</sup>. Immediate administration of PEP is especially important where the mother has not received any antiretroviral therapy.

**RE1e Neonatal PEP should be given for 4 weeks. Grading: 1C**

In the original ACTG 076 study ZDV was administered for 6 weeks after birth and this subsequently became standard of care<sup>59</sup>. Simplification to zidovudine twice daily for four weeks has become common practice in the UK and data from the NSHPC suggest that regimen adopting this strategy remain highly effective<sup>4</sup>. Recent cohort studies from Ireland<sup>283</sup> and Spain<sup>284</sup> have demonstrated efficacy and reduced haematological side effects with 4 versus 6 weeks of neonatal ZDV. In a Thai study, where a short course of 3 days of neonatal monotherapy ZDV PEP was compared to 6 weeks there was no significantly increased HIV transmission where the mother received ZDV monotherapy from 28 weeks gestation<sup>285</sup>. 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.

**RE1f. PCP prophylaxis, with co-trimoxazole, should be initiated from age 4 weeks in:**

- 1) all HIV infected infants – Grading: 1C**
- 2) in infants with an initial positive molecular diagnostic test result (and continued until HIV infection has been excluded) – Grading: 1C**

**3) infants whose mother's viral load at 36 weeks gestational age/delivery is >1000 HIV RNA copies/ml 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 PCR 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 PCR 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 PCR is negative, and the maternal delivery viral load is <1000 copies/mL, there is no need to start co-trimoxazole prophylaxis and the baby can be seen routinely for a second PCR 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 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.

#### Immunisation

Infants born to HIV-infected mothers should follow the routine national primary immunisation schedule, except that BCG vaccine should only be given when the exclusively formula-fed infant is confirmed HIV un-infected at 12-14 weeks.

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.

## **E2: Infant Feeding**

**RE2a: All mothers known to be HIV infected, 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<sup>286-288</sup>. RCT evidence from Kenya puts the transmission rate at 16% over 2 years, accounting for almost half the total mother to child transmissions<sup>288</sup>. Complete avoidance of breastfeeding removes this risk altogether<sup>288-290</sup> and is the current standard of care in the UK<sup>49, 291</sup>. 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 AFASS<sup>292</sup>.

Recently, cohort<sup>293-296</sup> and RCT<sup>65, 77, 297</sup> 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<sup>298, 299</sup>. WHO guidance remains that in countries where formula feeding is safe, a national or regional policy decision should be made on feeding policy<sup>300</sup>. Although breastfeeding transmission is reduced by ART, it is not abolished<sup>77, 293, 295-297, 301, 302</sup>. There is laboratory evidence that the breast milk of HIV-infected women on ART contains cells which may shed virus<sup>303</sup>. 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<sup>14</sup> 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<sup>304</sup>.

**RE2b. In the very rare instances 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**

Breastfeeding whilst 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, whilst the African data do not warrant a change in the recommendation not to breastfeed, 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 whilst breastfeeding than for them to be breastfeeding without disclosing this. Data from Africa show that mixed feeding carries a higher risk of HIV transmission than exclusive breastfeeding<sup>305</sup>. 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.

**RE2c. 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. Whilst serious adverse events were not reported in the infants given nevirapine for up to 6 months<sup>297</sup> 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<sup>306</sup>.

**RE2d: 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 cDNA or RNA (viral load). Grading: 1D**

Where a woman chooses to breastfeed against the medical advice in D2a, 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 which affects her ability to take or absorb ART, or she develops mastitis, she should be advised again to stop breastfeeding. **Grading: 1D**

**RD2e: All infants born to mothers infected with HIV should have an antibody test at age 18 months. Grading: 1C**

The potential for breastfeeding emphasises 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-infected women should have a negative HIV antibody test documented at age 18 months (see RD3 below).

### **E3: Infant testing**

**RE3a HIV DNA PCR (or HIV RNA testing) should be performed on the following occasions.**

- A) During the first 48 hours and prior to hospital discharge**
- B) 2 weeks post infant prophylaxis (6 weeks of age)**
- C) 2 months post infant prophylaxis (12 weeks of age)**
- D) On other occasions if additional risk (e.g. breast-feeding)**

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

#### 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<sup>i</sup>, 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<sup>307</sup>. 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 intra-uterine 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-infected infants are likely to be detected<sup>308</sup>. In view of the genomic diversity of HIV a maternal sample should always be amplified with, or prior to, the first infant sample to confirm that the primers used detect the maternal virus. If a maternal virus cannot be detected by the HIV viral diagnostic test used then a different primer set and / 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<sup>309</sup>. For this reason, the 2<sup>nd</sup> and 3<sup>rd</sup> HIV molecular tests are performed at 2 weeks and 2 months after stopping PEP, i.e. usually at 6 weeks and 12 weeks of age. If all tests are negative and the baby is not being/has not been breastfed, then parents can be informed that the child is not HIV infected. For infants at high risk of infection an additional early HIV test maybe undertaken at 2–3 weeks of age. For infants breast feeding from

mothers on HAART (see above), HIV viral diagnostic tests should be undertaken at least monthly on mother and infant, and twice on the infant, ideally between 2-8 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 newer combined tests are highly sensitive and may give a positive HIV result until up to 2 years of age<sup>310</sup>. 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)<sup>311</sup> This may be due to covert breast feeding, premastication of infant food or unknown intra-familial exposure.

If any of the infant HIV tests are found to be positive, an immediate repeat on a new sample should be requested to confirm infection. When an infant is found to be HIV infected, 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 Network) and contacts for local paediatricians can be found on the CHIVA website [www.chiva.org.uk/](http://www.chiva.org.uk/)<sup>312</sup>.

### **Child protection**

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

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

## Section F: Psychosocial context

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.

**RF1. 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 (CAB) workers, interpreters, community midwives, clinical nurse specialists and health visitors<sup>313</sup>.

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<sup>314</sup>.

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

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<sup>313, 315</sup>. Disclosure should be encouraged in all cases but may be viewed as a process that may take some time<sup>316, 317</sup>. 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)<sup>318</sup> and General Medical Council (GMC)<sup>319</sup>. 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<sup>320</sup>.

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

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<sup>291, 323</sup>.

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<sup>324-326</sup>.

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<sup>327</sup>.

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<sup>328</sup>.

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](http://www.tht.org.uk)).

Postnatal depression is relatively common in the general population, tends to be under-diagnosed and is a risk in HIV-positive women. Women with, or at risk of, antenatal depression should be assessed early and referred onward appropriately<sup>329</sup>.

**Table 1. Infant doses of antiretroviral therapy**

<b>Drug</b>	<b>Dose</b>	<b>Mono/com bo</b>	<b>Study</b>	<b>Comments/side effects</b>
Zidovudine (ZDV, AZT) ( <i>Retrovir</i> )	<p><b><u>Oral</u></b>  <i>Term</i> (&gt; 34 weeks):</p> <ul style="list-style-type: none"> <li>• 4mg/kg twice daily</li> <li>• 2mg/kg four times a day</li> <li>• 3mg/kg three times a day*</li> </ul> <p><i>Prem</i> (30-34 weeks):</p> <ul style="list-style-type: none"> <li>• 2mg/kg twice daily for 2 weeks then 2mg/kg three times a day for 2 weeks</li> </ul> <p><i>Prem</i> (&lt; 30 weeks):</p> <ul style="list-style-type: none"> <li>• 2mg/kg twice daily for 4 weeks</li> </ul> <p><b><u>Intravenous</u></b>  <i>Term</i>: 1.5mg/kg four times a day  <i>Prem</i>: 1.5mg/kg twice daily</p>	<p>Combo (+ 3TC)  Mono  Mono  Mono  Mono  Mono  Mono*</p>	<p>Moodley 2001  Boucher 1993<sup>260</sup>  Capparelli 2003<sup>276</sup>  Capparelli 2003<sup>276</sup>  Boucher 1993<sup>260</sup>  Capparelli 2003<sup>276</sup>  Frasca 2009<sup>330</sup></p>	<p>Anaemia, neutropenia – more common with combination therapy in mother and infant. In French study of zidovudine + lamivudine a small proportion of infants either required 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<sup>331</sup></p>
Lamivudine (3TC) ( <i>Epivir</i> )	2 mg/kg twice daily	<p>Combo (all with ZDV)   Combo (+ nelfinavir)</p>	<p>Mandelbrot 2001<sup>259</sup>  Moodley 2003<sup>256</sup>  Durand-Gasselin 2008<sup>332</sup>  Hirt 2011  Mirochnick 2011</p>	<p>Anaemia, neutropenia (but less common than with ZDV). More common with combination therapy in mother and infant.</p>
Abacavir (ABC) ( <i>Ziagen</i> )	2 mg/kg twice daily	Mono	Jullien 2005 <sup>264</sup>	Hypersensitivity reaction not been noted in infants (only small numbers treated)
Didanosine (ddI) ( <i>Videx</i> )	60mg/m <sup>2</sup> twice daily	Mono	Wang 1999 <sup>106</sup>	Much better absorbed on an empty stomach. Difficult to separate dosing from feeding. May cause GI symptoms. Variable absorption in neonates

Emtricitabine (FTC) ( <i>Emtriva</i> )	2 mg/kg as a single dose (with 13 mg/kg of TDF) within 12 hours after birth	Combo (with TDF)	Hirt 2011 <sup>333</sup>	Mothers received 2 tablets of TDF/FTC at onset of labour and then one tablet daily for 7 days postpartum. This dose resulted in high FTC levels in neonates. Can cause neutropenia, anaemia
	1mg/kg as a single dose immediately after birth.	Combo (with AZT and NVP)	Hirt 2009 <sup>263</sup>	Dose based on PK modelling study
Tenofovir (TDF) ( <i>Viread</i> )	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 <sup>134</sup>	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) ( <i>Viramune</i> )	Daily dosing regimen: 200mg to mother in labour, then 2mg/kg once a day for 1 <sup>st</sup> week then 4mg/kg once a day for 2 <sup>nd</sup> week. Single dose regimen: 200mg to mother in labour, then one 2mg/kg dose at 48-72 hours from birth	Mono Mono	Shetty 2004 <sup>334</sup>	Daily dosing regimen from HIVNET 023 (breastfeeding prophylaxis study)
	2 mg/kg as a single dose on the first day of life plus zidovudine 4 mg/kg every 12 h for 7 days.	Combo (with ZDV)	Hirt 2009	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) ( <i>Viracept</i> )	50-75mg/kg twice daily	Combo (with ZDV+3TC)	NICHD/HPTN 040/P1043 Mirochnick 2011 <sup>261</sup>	Nelfinavir 250mg tablets can be dispersed in water.

		Combo (+3TC)		
Lopinavir/ritonavir ( <i>Kaletra</i> )	300mg/m <sup>2</sup> twice daily <ul style="list-style-type: none"> <li>• 1-2 kg: 40mg every 12 hours</li> <li>• 2-6kg: 80mg every 12 hours</li> </ul>	Combo	Julien 2006 <sup>335</sup> Verweel 2007 <sup>336</sup> Chadwick 2008 <sup>269</sup> Chadwick 2011 <sup>270</sup> Urien 2011 <sup>272</sup>	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 <sup>273</sup> . FDA recommendation (August 2011): The use of <i>Kaletra</i> 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 <i>Kaletra</i> 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 ( <i>Seprin</i> )	900mg/m <sup>2</sup> once daily Mon/Wed/Fri < 6 months: 120mg once daily Mon/Wed/Fri 6 -12 months: 240mg 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

## Appendix 1: GRADE

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (3) has developed an approach to grading evidence that moves away from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for the association's guideline development.

The advantages of the modified GRADE system are: i) The grading system provides an informative, transparent summary for clinicians, patients and policy makers by combining an explicit evaluation of the strength of the recommendation with a judgment of the quality of the evidence for each recommendation; ii) The two-level grading system of recommendations has the merit of simplicity and provides clear direction to patients, clinicians and policy makers.

A Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients. Most clinicians and patients should and would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'we recommend'.

A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Most clinicians and patients would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'we suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences and where appropriate resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded A through to D.

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials, or overwhelming evidence of some other sort (such as well-executed observational studies with very strong effects). Grade A implies confidence that the true effect lies close to the estimate of the effect.

Grade B evidence means moderate-quality evidence from randomized trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.

Grade C evidence means low-quality evidence from observational evidence, or from controlled trials with several very serious limitations.

Grade D evidence on the other hand is based only on case studies or expert judgment and there is likely to be little confidence in the effect estimate.

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