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8. Obstetric management

8.1 Antenatal management

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

The National Screening Committee [1] and the NICE antenatal guidelines [2] 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 living 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 [3] does not support the need for increased surveillance with the most commonly prescribed therapies (listed in Appendix 3), although with newer medication the knowledge base is inevitably limited (see also section 6). APR reports on the frequency and nature of birth defects and ART are updated every 6 months (www.apregistry.com).

8.1.2	The combined screening test for fetal aneuploidies and non-invasive prenatal testing (NIPT) for those who screen as high risk is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing.	1A

NICE antenatal guidelines [2] also recommend that all women should be offered screening for trisomies 13, 18 and 21. The most effective screening is with the combined test at 11+0 to 13+6 weeks' gestation. This includes maternal age, nuchal translucency, β-human chorionic gonadotrophin (βHCG) and pregnancy-associated plasma protein A (PAPP-A). In the general population this has a detection rate of 92.6% with a false-positive rate of 5.2% [4].

For women who present too late for the combined test, the most clinically effective and cost-effective serum screening test for Down's syndrome (triple or quadruple test) should be offered between 15 weeks 0 days and 20 weeks 0 days [2]. However, significantly increased levels of βHCG and α-fetoprotein and lower levels of unconjugated oestriol (the elements of the 'triple test') have been observed in women with HIV [5-7] while a reduction in βHCG in patients treated with PI-based [8] or NNRTI-based cART has been reported. Down's syndrome is associated with increased βHCG, therefore HIV infection *per se* may increase the false-positive rate in women and thus increase the number of invasive tests offered compared with the general population [9]. PAPP-A and nuchal translucency are unaltered by HIV infection or ART [10] and thus are the preferred screening modality for women presenting between 15 and 20 weeks' gestation.

In 2016 the National Screening Committee recommended that NIPT of free fetal DNA in maternal serum should be offered to all pregnant women in the UK who are stratified as high risk after the combined test or serum screening tests [11]; at the time of writing, widespread implementation of this has yet to be adopted. NIPT has been shown to be highly effective at screening for fetal aneuploidy, with a lower false-positive rate and higher positive predictive values than standard screening [12]. The adoption of NIPT for women stratified as high risk following screening will further reduce the number of women to whom invasive prenatal diagnostic tests are offered.

8.1.3	Invasive prenatal diagnostic testing should not be performed until after the HIV status of the woman is known, and should ideally be deferred until HIV viral load has been adequately suppressed to <50 HIV RNA copies/mL.	1C

Limited data suggest that amniocentesis is safe in women on cART [13-15]. There are minimal data on other forms of prenatal invasive testing. It is now possible to use NIPT to screen for Down's syndrome and other common aneuploidies. All clinicians performing a prenatal invasive test should know the woman's HIV status, and if

necessary delay the invasive test until the HIV result is available. Where possible, amniocentesis should be deferred until the viral load is <50 HIV RNA copies/mL. The fetal medicine team should discuss management with an HIV physician in cases where a woman has a detectable HIV viral load.

8.1.4	If not on cART and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence cART to include raltegravir and be given a single dose of nevirapine 2–4 hours prior to the procedure.	1D

The French Paediatric HIV Infection Study Group observed an increased risk of HIV transmission (RR 1.9; 95% CI 1.3–2.7; *P*=0.003) with 'antenatal procedures' that included amniocentesis, cerclage, laser therapy and amnioscopy [16]. This study was conducted between 1985 and 1993 and, of the 1632 mother–infant pairs (overall transmission 19%), only 100 women had received zidovudine, mostly for advanced HIV infection.

There are few studies on the safety of invasive testing in the cART era. A study of 9302 pregnancies in France in 2009 (including 166 during which an amniocentesis was performed) showed that the risk of vertical transmission of HIV in the untreated group increased from 16% to 25% in women who had an amniocentesis; in those on zidovudine alone the risk increased from 3% to 6% and in those on cART there were no transmissions in 81 women who underwent amniocentesis [17]. Viral load data were not reported, but in other settings suppression of viral load reduces transmission.

A further study of nine women on cART in France (in 2008) [15] and 17 women on cART in Portugal (1996–2009) showed no transmissions, whereas transmission occurred in one of six women either not diagnosed with HIV prior to amniocentesis, or not treated prior to the procedure. There are no studies and few case reports in the cART era examining chorionic villus sampling or cordocentesis [18]. For evidence relating to choice of ART to reduce transmission risk associated with amniocentesis, see section 6.4.

8.1.5	External cephalic version (ECV) can be offered to women with plasma viral load <50 HIV RNA copies/mL.	2D

ECV for breech presentation can be performed at term from 37+0 weeks of gestation in women with an undetectable plasma viral load. In nulliparous women, ECV may be offered from 36+0 weeks of gestation, in line with current guidance.

There is less obstetric risk to the baby and woman when the fetus is head-down at the time of birth. ECV is a procedure by which the fetus, which is lying bottom first, is manipulated through the woman'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 pregnant woman living with HIV. For the general maternity population, ECV is recommended [2]. There is a low rate of complications, with an estimated 0.5% incidence of immediate caesarean section [2].

The question of whether ECV might increase the risk of vertical transmission of infections such as HIV is important; however, there is currently no direct evidence to support this. The incidence of fetomaternal haemorrhage after ECV has been estimated at 2.4%, this represents the new presence of fetal blood cells in the maternal circulation after the procedure [19]. It has been postulated that, due to the structure and function of the placenta, the risk of maternal blood entering the fetal circulation due to ECV is much lower [19]. It is also reassuring that in a randomised trial of fundal pressure to expel the baby during caesarean section, no evidence of maternal–fetal transfusion was found [20]. It is the writing group's opinion, therefore, that ECV can be offered to women with a breech presentation who have a plasma viral load <50 HIV RNA copies/mL.

8.2 Mode of delivery

For women taking cART, a decision regarding recommended mode of delivery should be made after review of plasma viral load results at 36 weeks.

8.2.1	For women with a plasma viral load of <50 HIV RNA copies/mL at 36 weeks, and in the absence	1C

	of obstetric contraindications, planned vaginal delivery should be supported.	
8.2.2	For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, pre-labour CS (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.	1C
8.2.3	Where the viral load is ≥400 HIV RNA copies/mL at 36 weeks, PLCS is recommended.	1C

Published cohort data from the UK and other European countries have shown vertical transmission rates of <0.5% in women with plasma HIV RNA <50 HIV RNA copies/mL taking cART, irrespective of mode of delivery [21-25]. These studies support the practice of recommending planned vaginal delivery for women on cART with plasma viral load <50 HIV RNA copies/mL.

The most recent analysis from the NSHPC UK and Ireland surveillance study investigated vertical transmission of HIV in women delivering between 2000 and 2011 (*n*=2000) [26] and found that the overall transmission rate in women with undetectable viral load (<50 HIV RNA copies/mL) was 0.09%, and 0.06% (4/6345) when two *in utero* transmissions were excluded; there was no significant difference between CS and planned vaginal delivery (0.11% *vs* 0.15%; *P*=0.53). For all modes of delivery, risk of transmission was significantly higher when viral load was 50–399 HIV RNA copies/mL than when fully suppressed (<50 HIV RNA copies/mL). Among 1033 women with viral load of 50–399 HIV RNA copies/mL, vertical transmission rates were 0.8% following CS and 1.6% following planned vaginal delivery (*P*=0.39). Women delivering by CS had a slightly shorter duration of cART than those who had planned vaginal deliveries in this group (median 12.4 *vs* 13.9 weeks; *P*=0.007). Excluding five *in utero* transmissions, the vertical transmission rate among women with viral load of 50–399 HIV RNA copies/mL was 0.26% (2/777) following CS and 1.1% (2/188) following planned vaginal delivery (*P*=0.17).

A recent analysis from the ANRS French Perinatal cohort examined CS in 8977 women delivering on cART between 2000 and 2010, and found no difference in unadjusted vertical transmission rates by mode of delivery in 3075 women delivering at term (>37 weeks) with a viral load <50 HIV RNA copies/mL (0.3% for vaginal delivery, 0.3% for CS and 0.3% for non-CS; *P*=1.00). For 707 women who delivered at term with viral load of 50–399 HIV RNA copies/mL, there was also no difference in transmission by mode of delivery (1.0%, 1.0% and 2.5% respectively; *P*=0.24). The authors did not comment on the timing of transmission in the infants diagnosed with HIV [27].

Older data were reported from the ANRS French Perinatal cohort of 5271 women delivering between 1997 and 2004, of whom 48% were on cART. In women on cART with a delivery viral load <400 HIV RNA copies/mL there was no significant difference in vertical transmission rates according to mode of delivery, with 0.4% (3/747) transmission in the CS group compared with 0.5% (3/574) transmission in the vaginal delivery group (*P*=0.35). The effect of mode of delivery was also analysed for women delivering with a viral load >10,000 HIV RNA copies/mL and no significant protective effect of CS was seen (OR 1.46; 95% CI 0.37–5.80). Vertical transmission of HIV was low at 0.4% in women delivering with a viral load <50 HIV RNA copies/mL but mode of delivery data for this subset were not provided [25].

By contrast, data from the European Collaborative Study of 5238 women delivering between 1985 and 2007 showed that in 960 women delivering with a viral load <400 HIV RNA copies/mL, PLCS was associated with an 80% decreased risk of vertical transmission after adjusting for cART and prematurity (adjusted OR 0.2; 95% CI 0.05–0.65). There were only two transmissions among 599 women delivering with viral load <50 HIV RNA copies/mL (transmission rate 0.4%) with one delivering vaginally at <34 weeks and one by emergency CS at 37 weeks, but further analysis was not possible [21].

A potential explanation for the differing conclusions of the effect of mode of delivery on vertical transmission in women with delivery plasma viral load <400 HIV RNA copies/mL in these two studies is that there may be a significant difference in the viral load distribution <400 HIV RNA copies/mL between studies. This highlights the fact that it is not possible to infer that vertical transmission rates from studies using a viral load assay with a cut-off value <400 HIV RNA copies/mL can necessarily be applied to patients with plasma viral loads of 50–399 HIV RNA copies/mL using current assays with lower limits of detection of 50 HIV RNA copies/mL or less.

Although neither of the most recent UK and French analyses showed a statistically significant difference in vertical

transmission by mode of delivery for women with plasma viral loads between 50 and 399 HIV RNA copies/mL, in the UK/Ireland dataset the risk of vertical transmission for women delivering vaginally is about twice that of those delivering by CS, and this rises to four-fold when *in utero* transmissions are excluded. The writing group therefore recommends that CS 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.

Multiple observational studies and a randomised controlled trial established the benefit of CS in women not on effective ART, reducing the risk of vertical transmission by two-thirds in the pre-cART era. More recent observational studies only included very small numbers of women delivering vaginally with a viral load >400 HIV RNA copies/mL, due to the evolution of recommended clinical practice. Studies to date do not provide data to determine the viral threshold above which CS should definitely be recommended. However, given the conflicting data regarding the effect of mode of delivery on vertical transmission in women with a viral load <400 HIV RNA copies/mL, together with the data from the UK study showing a 2.4-fold increased risk of transmission for every 1 $\log_{10}$ unit increase in viral load associated with mode of delivery, the writing group continues to recommend CS for all women with a viral load ≥400 HIV RNA copies/mL.

8.2.4	In women for whom a vaginal delivery has been planned and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negative population, apart from duration of ruptured membranes (see section 8.3).	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-cART era have been reviewed, and show little or no risk for many of these procedures. Scant data are available from the cART era.

The French cohort (1985–1993) provides data on the risk of various obstetric factors in a predominantly untreated, non-breastfeeding population. Procedures, classified as amniocentesis and other needling procedures, cerclage, laser therapy and amnioscopy, were associated with an increased risk of transmission (RR 1.9; 95% CI 1.3–2.7).

Fetal skin lesions (RR 1.2; 95% CI 0.7–1.8) and episiotomy/tear (RR 1.0; 95% CI 0.7–1.3) were not associated with transmission [16]. In a retrospective study from Spain, predominantly in the pre-cART era, HIV transmission occurred in 26.3% of infants exposed to fetal scalp monitoring (electrodes or pH sampling or both) compared with 13.6% exposed to neither type of monitoring (RR 1.94; 95% CI 1.12–3.37) [28]. 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 [29]. In the Women and Infants Transmission Study (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 [30].

Induction has previously been avoided as there were concerns about the duration of ruptured membranes and risk of vertical transmission but recent evidence (see section 8.3) appears to be reassuring with regard to these concerns.

Data from the predominantly untreated French cohort (1985–1993) showed no risk with instrumental vaginal delivery (RR 0.8; 95% CI 0.6–1.2) [16]. Data from the smaller Swiss cohort (*n*=494; 1986–1996; transmission rate 16.2%) also failed to identify instrumental delivery as a risk factor for transmission (RR 1.82; 95% CI 0.81–4.08) despite less than 20% of the cohort taking any ART for prophylaxis [29].

The NSHPC recently reported data on operative vaginal deliveries in women in the cART era between 2008 and 2016; of 3023 vaginal deliveries, 251 infants were delivered with forceps or vacuum [13]. Infection status was available for 222/233 infants who had reached 18 months of age: one infant was diagnosed with HIV, but timing of infection is unclear and there were other risk factors present. This is consistent with previously reported transmission rates in this population, and numbers are too small to draw further conclusions.

In the absence of trial data for women with HIV infection who undergo an operative vaginal delivery, evidence to support a benefit of any type of operative vaginal delivery compared to CS for women or their infants is limited to expert judgement and extrapolation from other datasets, and is subject to inherent biases. There are theoretical