Human immunodeficiency virus in pregnancy

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Abstract
Most human immunodeficiency virus (HIV) infection in women of childbearing age occurs in resource poor countries. However, increasing numbers of infected women are known to reside in the UK. In developed countries, with appropriate healthcare, HIV infection in adults may be regarded as a chronic manageable condition and mother-to-child transmission (MTCT) can be almost totally prevented.

Despite great improvements in antenatal testing in the UK, the greatest single contributor to MTCT is failure to diagnose HIV in pregnancy. Once diagnosed, HIV in pregnancy is best managed by a specialist multidisciplinary team, who can maximise the mother’s health and reduce the risk of MTCT to less than 1%.

The British HIV Association has recently published its 2008 guidelines for the management of HIV in pregnancy. Avoidance of breastfeeding and appropriate use of antiretrovirals with or without pre-labour Caesarean section remain the main interventions minimising the risk of MTCT.

Keywords antiretrovirals; breastfeeding; epidemiology; HIV; pregnancy; pre-labour Caesarean section

Epidemiology of HIV
Globally, the World Health Organization estimates that 33.2 million people were living with human immunodeficiency virus (HIV) by the end of 2007, with 15.5 million of these being women, most of whom were of childbearing age. The majority of these live in resource poor countries, especially in Africa.

In the UK, in 2006, over 52,000 people were reported to have accessed care for HIV infection, however, with many infections not clinically recognised, as many as 77,000 people were estimated to be living with HIV.

The UK has exceptionally good data on HIV infection in pregnancy. A programme of unlinked anonymous HIV-testing surveys has included a survey of dried infant blood spots and antenatal rubella bloods since the late 1980s. Testing dried infant blood spots for HIV antibody provides information on the mother’s HIV status due to the passive transfer of immunoglobulin IgG antibodies. These surveys have given robust estimates of HIV prevalence in pregnancy, largely free of participation bias. Combining these estimates with reports from the National Study of HIV in Pregnancy and Childhood (NSHPC) – a voluntary confidential notification scheme completed by obstetricians and paediatricians with high response rates and co-ordinated by the Royal College of Obstetricians and Gynaecologists and British Paediatric Surveillance Unit – has provided an accurate assessment of the number of undiagnosed infections.

In 2006, one in 440 pregnant women in England and Scotland was HIV-positive. This overall figure masks ethnic and regional differences, with women born in sub-Saharan Africa having a prevalence of 2.1% inside London and of 3.5% outside London. The overall prevalence outside London increased 8-fold between 1997 and 2006, with much of this being attributed to the policy of dispersal of asylum seekers, many of whom originate from countries with a high HIV prevalence. Whilst remaining low, the prevalence of HIV amongst UK-born women also increased. In the UK, in 2006, more than nine out of 10 infections were diagnosed before delivery.

Testing for HIV in pregnancy
Late diagnosis of HIV infection in adults in the UK remains a significant cause of morbidity and mortality despite advances in antiretroviral (ARV) therapy. In one large London hospital, from 2001 to 2005, 12 out of 25 mothers of babies diagnosed with HIV infection had not had an antenatal HIV test. These were women who had received antenatal care in the UK.

Since 1999, it has been UK policy to recommend a HIV test to all women as part of their antenatal care. Obstetric units should ensure that all women understand the advantages to their own, and their baby’s health of diagnosing HIV infection early. Policies of offering, recording uptake and reasons for declining HIV tests need to be established in all antenatal units. Re-offering the test to women who decline the first time should be routine. All healthcare staff must be familiar and comfortable with the offer and recommendation of the HIV test to ensure that it is an integral part of antenatal care. In ensuring confidentiality of the result, units must also ensure that staff who may need to act upon the result have easy access to the information. Units are encouraged to audit their performance across all of these parameters.

A small number of babies born to women who have tested negative for HIV early in pregnancy have become infected. Maternal incident infection with HIV during pregnancy actually confers an even greater risk of mother-to-child transmission (MTCT) due to the concomitant higher viral load (VL). Whilst no recommendation for universal repeat testing has been made, where a mother is known to be at higher risk (e.g. continuing unprotected sexual intercourse with an untested partner who has a history of several partners from a high prevalence country) then a repeat test later in pregnancy should be considered.

Women who present in labour, who have not been tested, or for whom no HIV result is known, should be offered a rapid test and, where positive, this result should be acted upon in advance of confirmation.

Testing partners and children for HIV
Regardless of the mother’s HIV result, raising the issue of HIV testing is a health promotion opportunity and a chance to encourage
testing for her partner too. Staff should be aware of how and where partners can access HIV testing in their area.

Where a mother is found to be positive, it is important to consider testing for her partner (current, and previous where applicable) and for any existing children. The precise timing of this cannot be prescribed but sexual health advisors have expertise in raising these issues and should be able to facilitate rapid testing for all family members.

**Antenatal care**

The antenatal care of women with HIV infection is best provided by a multidisciplinary team consisting of (as a minimum): an obstetrician, a paediatrician, a HIV specialist and a specialist midwife. In addition, a health advisor, social worker, interpreter, Citizen’s Advice Bureau worker and clinical psychologist may need to be involved.

Many women with HIV infection in the UK are recently arrived from sub-Saharan Africa and may have complex cultural, housing, immigration and financial needs. Frustratingly for healthcare providers, medical management of their HIV infection can sometimes seem to be low down the patient’s own perceived list of needs. Providing help and support with these other aspects of their lives is an effective way of ensuring better health outcomes by improving attendance and adherence to medication or other interventions.

**Screening for sexually transmitted infections**

HIV is a sexually transmitted infection and infected women may be both behaviourally and biologically more susceptible to other sexually transmitted infections (STIs). Furthermore, many STIs, particularly ulcerating conditions, may facilitate the transmission of HIV in pregnancy. Some STIs, by causing chorioamnionitis, are also implicated in pre-term delivery (PTD), itself a known risk factor for HIV MTCT transmission. It is, therefore, essential to screen all HIV-positive pregnant women for STIs at least once during their pregnancy and more frequently where continuing risk is identified (e.g. where a sexual partner does not attend for screening and treatment after diagnosis of an STI in the mother). Screening should include testing for Chlamydia trachomatis, *Neisseria gonorrhoea*, syphilis, Trichomonas vaginalis, bacterial vaginosis and hepatitis B and C.

**Factors associated with MTCT of HIV**

These can be divided into maternal and obstetric factors. Maternal STIs, particularly ulcerating genital conditions, have been associated with an increased risk of transmission.

**Obstetric**

Delivery before 34 weeks gestation is associated with an increased risk of transmission. In untreated women, vaginal delivery is associated with an increased risk of transmission with rates increasing with prolonged labours, but in a recent analysis of all deliveries to women in the UK and Ireland, on highly active antiretroviral therapy (HAART) with an undetectable VL, there was no detectable difference in transmission rates between those born by pre-labour Caesarean section (PLCS) and those born by vaginal delivery. Invasive procedures (such as scalp clips) have not been unequivocally proven to increase the risk, but it is biologically plausible that they may enhance MTCT.

**Interventions to reduce MTCT of HIV**

In the absence of any interventions, on average, the MTCT rate of HIV is between 30% and 35%. The three main interventions to prevent MTCT of HIV are the avoidance of breastfeeding, the use of ARV therapy and PLCS. See Table 1 for examples of commonly used ARVs and fixed dose combinations. The relative contribution provided by each of these interventions, and their utilisation, has changed over time as research findings have become available, and, in particular, with the introduction of HAART (see Table 2).

**Evolution of practice from early 1990s**

In the early 1990s, it was recognised that the breast milk of HIV-infected women contained HIV, and that the breastfeeding of infants born to such women contributed substantially to the MTCT of HIV. This provided the first impetus for the introduction of antenatal screening for HIV in the UK as, in the absence of HIV infection, most women were encouraged to breastfeed. Women who were found to be HIV infected were advised to refrain from breastfeeding and to use formula feeding instead, as this was felt to be safe in an environment with a safe water supply. This remains the advice within the UK and most women heed this advice. However, as most affected women in the UK are of sub-Saharan African origin, many women find this intervention problematic. There are strong cultural pressures to breastfeed in this group, many of whom will not have disclosed their HIV status to family and friends, and providing acceptable excuses for formula feeding can be difficult.

In 1994, the results of the Paediatric AIDS Clinical Trials Group (PACTG) 076 study showed that the use of zidovudine (ZDV), given orally to pregnant women from the second trimester onwards, intravenously during labour, and orally to the newborn for the first 6 weeks, reduced the rate of MTCT from 27.7% to 7.9% in a non-breastfeeding population. The use of ZDV in pregnancy became standard of care in resource-rich settings. In 1998, the European Mode of Delivery Study showed that PLCS provided additional protection from MTCT of HIV in women who were not breastfeeding, and who were either on no ARV therapy or on ZDV monotherapy, with MTCT rates of <2%. As a result, in many resource rich countries, the standard of care for pregnant women with HIV became the use of oral ZDV monotherapy for the mother, intravenous ZDV prior to, and during, the PLCS.
The availability of HAART in the late 1990s revolutionised the management and prognosis of patients with HIV. Combinations of drugs allowed the level of HIV in the plasma (the VL) to be brought down to undetectable levels with dramatic reversals in health decline and mortality. HAART swiftly became the standard of care for non-pregnant HIV-positive individuals. With regard to pregnancy, however, physicians were faced with some new questions. Should HAART be used in all pregnant women with HIV? There was little information regarding the potential for toxicity with the use of these drugs in this way both in terms of long- or short-term toxicity for the exposed foetus, as well as pregnancy outcome issues such as PTD.

Remaining uncertainties

Concerns remain that the use of ARVs may result in potential long- or short-term problems for the exposed infant. Laboratory studies have suggested that the use of nucleoside reverse transcriptase inhibitors – of which ZDV is one – may cause some abnormalities, especially in mitochondrial function, which may persist. Follow-up studies of exposed infants have not demonstrated a link with the development of malignancies, but the follow-up period is still relatively short. Three of 20 cynomolgus monkeys exposed in utero to one agent, efavirenz, were born with central nervous system abnormalities raising concerns that this drug should not be used in women of childbearing age. The Antiretroviral Pregnancy Registry, which collects prospective data on birth defects in infants exposed to any of the ARV drugs, has amassed data on around 5000 mother–child pairs worldwide, and provides some reassurance that there do not appear to be any obvious problems in terms of teratogenicity in infants exposed to these drugs in utero. However, there remains a relative paucity of safety information regarding the use of HAART in pregnancy and it is important that we remain vigilant.

With regard to pregnancy outcome, a number of European studies, including one from the UK have shown that there appears to be an increase in PTD in the era of HAART. This has not been the conclusion of most studies from the United States that have examined this. Further studies are ongoing to investigate this, and to look at potential mechanisms for this finding.

An additional question in the HAART era was whether PLCS provided any additional protection in terms of MTCT for babies born to women who had an undetectable plasma VL on HAART. Could these women have a normal vaginal delivery? Did the VL in the genital tract mirror that in the plasma? There is some evidence of compartmentalisation, i.e. viral populations in different body compartments evolving independently, but small studies showed it to be unusual for genital tract VL to be higher than that in plasma, in women fully suppressed on HAART.

Current practice in the UK

Despite unanswered questions regarding the potential toxicity of HAART and safety of vaginal delivery, most HIV-positive pregnant women in the UK receive HAART in pregnancy and, over
the past few years, an increasing number of women have opted for vaginal delivery in the setting of a fully suppressed VL on HAART. Until 2008, there was no evidence that this approach was safe in terms of MTCT of HIV, but there are now two large cohort studies, one from France, and one from the UK and Ireland, which show that this is a reasonable approach. The UK and Ireland cohort of over 5000 women, studied from 2000 to 2006, showed that the MTCT rate was 0.7% in women on HAART, regardless of whether they had an elective Caesarean section (CS) or a planned vaginal delivery. In addition, of over 2000 women with an undetectable VL (<50 copies/ml) around delivery, there were only three transmissions – two delivered by PLCS and one by vaginal delivery, giving a transmission rate of around 0.1% in this group.

Should all pregnant women receive HAART? Clearly those women who are deemed to need HAART for their own health, which is usually based on their CD4 count, should receive it, commencing after the 1st trimester, and should continue after the delivery. There are many women, however, who have a good CD4 count and who only need to take ARVs during the latter part of the pregnancy to prevent MTCT and who then stop. In this group, if the VL is >10,000 c/ml, then the woman should receive HAART, commencing between 20 and 28 weeks, continued until delivery, and there may be the option for a vaginal delivery should the VL reach <50 c/ml near delivery. If the VL is <10,000 c/ml, however, British HIV Association guidelines offer a choice of either HAART with the possibility of an spontaneous vaginal delivery as above, or ZDV monotherapy combined with a PLCS. (See Table 3 for a few clinical scenarios following British HIV Association guidelines.) The UK and Ireland cohort study showed no transmissions in 467 women who were managed in this way, a transmission rate that is, therefore, not inferior to the use of HAART. This approach minimises foetal exposure to drugs, and does not appear to be associated with an increased risk of PTD, but does involve an operative procedure, and is an option only for selected women with favourable baseline CD4 and VL where there is minimal chance of developing resistance mutations and thus compromising future maternal therapeutic options. ZDV monotherapy should be commenced by 28 weeks.

Elective CSs when combined with ZDV monotherapy should be scheduled for 38 weeks, but if a CS is to be performed when the mother’s VL is undetectable on HAART, this can be scheduled for 39 weeks.

An issue of concern is that the proportion of women who undergo an emergency CS has increased in recent years. There may be a number of factors playing a part. Historically, certain obstetric interventions such as the use of scalp clips and instrumental delivery, as well as prolonged rupture of membranes, have been associated with an increased risk of MTCT. These studies were all done in the pre-HAART era. It is not known whether those increased risks still exist in the setting of a fully suppressed VL on HAART. The practical implication of this is that many obstetricians will, understandably, have a lower threshold for performing an emergency CS when complications arise during a planned vaginal delivery. The issue of PTDC could also influence the number of emergency CSs, as women may go into labour early, perhaps when the VL is not yet fully suppressed, when there may be concerns about proceeding with a vaginal delivery from the point of view of HIV transmission.

Women already taking HAART before becoming pregnant

With improving survival for patients with HIV infection, the diagnosis of HIV often antedates conception and many of these women are already on HAART. Where this therapy is effective in terms of maintaining an undetectable VL, with no, or an acceptable, side-effect profile, there is usually no need to change therapy because of pregnancy. Where women conceive on therapies for which greater concerns about potential teratogenicity exist, an early discussion with an experienced clinician is required. It is rarely beneficial to change therapies in these situations and, due to differing half-lives of drugs used, it may be very harmful to stop treatment in an unplanned manner.

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<th>Simplified clinical scenarios following BHIVA guidelines for mothers presenting before 32 weeks gestation</th>
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<td><strong>Scenario</strong></td>
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<td>Mother already on HAART</td>
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BHIVA, British HIV Association; ARV, antiretroviral; HAART, highly active antiretroviral therapy; VL, viral load; ZDV, zidovudine; PI, protease inhibitor; PLCS, pre-labour Caesarean section; SVD, spontaneous vaginal delivery. Early expert advice is strongly recommended for all situations outside of these guidelines.
FURTHER READING

Practice points
• All antenatal units must have clear policies for ensuring that all women are recommended a HIV test as part of their care
• The management of HIV-positive pregnant women is best achieved via a multidisciplinary team
• All HIV-positive women should be screened at least once for sexually transmitted infections during pregnancy
• All HIV-positive women in the UK should be dissuaded from breastfeeding
• All women will be advised to take some ARV regimen
• Recommendations to women regarding planned mode of delivery will depend on the ARV regimen started or continued during pregnancy
• Expert advice from an experienced team of clinicians should be sought early in the management of all pregnant HIV-positive women