Management of HIV infection in pregnancy

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Abstract

Human immunodeficiency virus (HIV) remains an important global infection and cause of significant morbidity and mortality. The majority of new HIV infection occurs in the developing world, where women and their children are greatly affected by the consequences of HIV associated disease. By comparison, in the developed world, women represent a minority of those with new HIV infection. The problems associated with the management of pregnancy and childbirth require specialist care across multidisciplinary teams to ensure the best clinical outcome for mothers and their babies, as well as assuring the confidentiality and safety of patient care and public health. Preventing mother-to-child-transmission (MTCT) has been the goal of research and collaborative guidelines in the UK for much of the past decade and has contributed to reducing MTCT, which is now a rare occurrence in the UK. The global target of eliminating MTCT requires a major and sustained effort to improve access to testing, antiretroviral therapy and expert multidisciplinary care.

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

HIV and women

About 33.3 million people worldwide are infected with HIV and almost half of them are women. Poverty is a major component of new infection with 98% of women with HIV living in resource poor countries. Migration to developed countries, including the UK, should be prioritized as a public health issue.

In the UK, HIV testing uptake has been successful through women attending Genitourinary Medicine clinics and antenatal clinics. However, a significant proportion (27%) of women (especially from sub Saharan Africa) are unaware of their status and present late. One third of all new HIV diagnoses are in late presenters and have a CD4 count of below 200 cells/μl (Box 1). New efforts through community testing pilots, British Association for Sexual Health and HIV guidelines and the *Halve It* campaign aim to reduce the undiagnosed fraction; with earlier therapy, this should further reduce morbidity and new transmissions.

Natural history

The majority of HIV infections are caused by HIV 1 whilst HIV 2 infections are very uncommon. HIV 2 infection occurs mostly in West Africa and has a much lower virulence and transmission.

After infection, viral replication and integration results in a gradual loss of the CD4 lymphocyte count causing immune deficiency, indicated by a cell count less than 350 cells/mm^3. This can lead to a variety of opportunistic infections or subsequently a risk of developing AIDS. The time span from seroconversion illness to AIDS is very variable; some cases develop over a few months whilst for other individuals there is minimal immunosuppression a decade or more after infection.

Management of HIV has been transformed in the past decade by effective combination antiretroviral therapy (ART). This has led to a restoration of immune competence, undetectable viral loads and improved life expectancy. The effect of ART has been to restore quality of life and increase wellbeing. ART has reduced transmission to sexual partners as well as through MTCT.

Mother-to-child-transmission

In the UK, maternal to child transmission of HIV has significantly decreased from 20% to 2% from 1993 to 1998 (Box 2); this was primarily due to a better understanding of management of HIV infection and also the prophylactic use of highly active antiretroviral therapy (HAART). The risk of transmission is highly dependent on the viral load (VL). At a viral load of >100,000 copies/ml there is a 40% risk of transmission. This falls to 1% at 1000 copies/ml and less than 1% at undetectable VL (<50 copies/ml). Management also considers the mode of delivery,

HIV in the UK. Adapted from the Health Protection Agency 2010 report

2010
91,500 people living with HIV in the UK
30,000 women
- 24% unaware of their infection
- 21% for women (antenatal screening programme ↑ detection rate)

6660 new diagnoses
- 50% heterosexually acquired

2150 women

Gradual increase in new diagnoses among people acquiring infection heterosexually in UK
2004 — 740
2008 — 1080
2010 — 1090

Box 1

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MTCT in the UK

- Approximately 1600 pregnancies and 1400 births reported each year
- 80% of pregnant women with HIV are of African origin
- 70% of pregnancies are in previously diagnosed women, many having a second or subsequent pregnancy (20%)
- Very low (<1%) MTCT rates for diagnosed women
- Of approximately 40 HIV infected children each year, only 10 are born to diagnosed women

Box 2

appropriate and timely intervention of post-exposure prophylaxis (PEP) for the infant and avoidance of breastfeeding.

In the UK, over half of pregnant women with HIV present late for antenatal care. 50% present after the first trimester compared to 22% of HIV negative women. Late presentation and later booking have adverse consequences for both mother and child and this situation can be improved with a dedicated and flexible team of specialist midwifes, obstetricians and HIV physicians, who are all in constant communication with each other.

Antenatal testing

The UK introduced routine 'opt out' antenatal HIV testing in 1999; the uptake in 2008 was 92–95%. Testing is performed at booking (12–14 weeks) and no further HIV tests are offered. As there have been a number of HIV seroconversions during pregnancy, the question of whether further HIV testing should be offered later in the pregnancy, especially in high risk groups or in ethnically diverse areas such as London is pertinent. This issue was raised by the perinatal transmission audit, which highlighted the need for health economic data to consider a second HIV test in the third trimester. In the UK, women who refuse antenatal testing do so because they believe they are at risk of HIV. This is, however, based on poor information and patchy knowledge.

It is extremely important to have a dedicated midwife/women's health advisor with close links to HIV teams who can identify high risk pregnant women and offer subsequent tests, educate and arrange appropriate follow up. Psychosocial factors influence antenatal testing and subsequent management, so should be explored at an early stage.

HIV seroconversion is associated with higher viral loads which increases the risk of *in utero* transmission by up to 40%, hence the need for prompt diagnosis, initiation of appropriate antiretrovirals and follow up. Diagnosis of *in utero* transmission can be made by the identification of proviral DNA through amniocentesis or from the cord blood/newborns blood sample at birth, Robust policies should exist in every antenatal unit offering HIV tests, with clear records of uptake and the reasons for declining a test. Reasons for declining should be further explored through a meeting with a dedicated HIV midwife and the obstetrician in charge, with repeat offering of the test. All relevant healthcare staff should have the skills and knowledge to deal with these situations comfortably and receive regular training, peer support and audit in their units.

Methods of MTCT

There are three established ways of MTCT:

- *In utero* transmission is an uncommon mode of transmission as an intact placenta acts as a very effective barrier to the transfer of HIV. Placental transfer of virus can happen with an extremely high viral load which is common in seroconversion illness, advanced late stage disease with very low CD4 and in the presence of opportunistic infections which can upregulate the viral load. The placental barrier can be compromised with severe systemic infections like miliary tuberculosis, falciparum malaria and secondary syphilis where inflammatory endarteritis can distort the integrity of the placenta. Con-comitant use of crack and cocaine can also impair placental function and may increase the risk of MTCT.
- MTCT at the point of delivery is the commonest mode of transmission, and can occur as a result of high viral load at delivery, prolonged rupture of membranes, prematurity, vaginal laceration, vaginal ulceration due to herpes simplex infection or syphilitic ulcers, episiotomy, invasive fetal monitoring and instrumental delivery.
- Postpartum MTCT is almost exclusively due to breast feeding and accounts for up to 40% of transmissions in undiagnosed women. For some women there is a lot of stigma around being unable to breast feed; this can cause great distress, especially in sub Saharan Africa, who see it as a disclosure of their HIV status to friends, families and even partners.

Stigma and mental health conditions in HIV positive pregnant women

Chronic HIV infection, subsequent opportunistic infections, homelessness, stigma, poverty, immigration, disclosure, family and peer pressure and drug use can all contribute to complex mental illness which can affect the engagement of the women with the HIV/Obstetrics team. It can result in late booking and self neglect, and interfere with adherence to ART and follow up. African women, especially from sub Saharan Africa, are the second largest group affected with HIV after men who have sex with men in the UK. About one quarter of HIV positive people in Europe are from Africa (32% in the UK).

Residency status and immigration pose significant problems both in terms of accessing healthcare and right to the care. Undocumented migrants are more likely to be unaware of emergency contraception, to have unintended pregnancy, to present late for their first antenatal visit and to not have an HIV test documented.

The audit on perinatal transmission highlighted that social circumstances aggravated the delivery of optimal care of HIV infected pregnant women and this might have been a contributing factor towards MTCT.

Many HIV positive women are unable to disclose the diagnosis to their partners as they fear violence, separation and rejection. Women may depend on their partners for financial support, right to remain in the UK and accommodation. Disclosure issues are best dealt within a multidisciplinary team approach with the best interests of the women at the centre of discussion. Otherwise, there may be non engagement with

services and even disappearance, resulting in delivery of the baby in suboptimal settings.

Sexually Transmitted Infections (STIs) and pregnant women

British HIV Association (BHIVA) guidelines recommend STI screening on a yearly basis in HIV positive individuals. Women need to be educated about preventing onward HIV transmission and STI's. Any pregnant woman at risk should also be screened for other sexual infections that could potentially affect the unborn child including chlamydia, syphilis, hepatitis, gonorrhoea and herpes. Screening for STI's should be performed twice during pregnancy, once in the first trimester and again in the third trimester. Test of cure should be performed following treatment for any bacterial STI's.

Chronic herpes simplex (HSV) type 2 infection is common in HIV positive women and all women should have type specific HSV serology if they have no previous diagnosis of genital herpes and present with symptoms of genital ulcers. HSV recurrence will increase the local HIV replication and may play a role in MTCT especially when vaginal delivery is anticipated. Prophylactic treatment with aciclovir and appropriate advice will reduce the rate of HSV outbreaks and may reduce the need for emergency Caesarean section. Appropriate partner notification should be performed.

HAART in pregnancy

Antiretroviral drugs have been used extensively in HIV positive women in order to control virus levels and thus reduce MTCT. The repertoire of antiretroviral agents is expanding and there is better understanding about the mode of action, toxicity and interactions of these agents. Very little data has arisen from animal studies for these drugs and most of the experience of use in pregnancy comes from observational studies, pregnancy drug registry and yellow card reporting.

In resource rich countries, triple combination is standard of care and mono or dual therapy is seldom used. In 1994, PACTG 076 was a land mark study which showed that Zidovudine, a nucleoside analogue inhibitor, given orally to pregnant woman in the second trimester, followed by an intravenous infusion during labour and then given orally to newborn for first 6 weeks reduced the MTCT from 27.7% to 7.9%; women did not breast feed. This is called the 076 protocol. Bloodless planned lower segment Caesarean section in conjunction with the 076 protocol reduces the risk of MTCT to 2%. MTCT decreased from 19.6% to 2.2% from 1993 to 1998. This was the standard of care for pregnant women in developed countries and uptake of antiretroviral increased to 97% of live births in 1998. In the late 1990s, introduction of triple combinations antiretroviral or HAART changed clinical practice. HAART enables the plasma viral load to become undetectable and as a result improved survival and reduced morbidity. It is now used in all pregnant women. All children born to mothers who had exposure to antiretrovirals in the UK are followed up for any future potential adverse effects and are placed on the pregnancy registry.

Timing and type of HAART and transmission

A high viral load is the most important risk factor for MTCT and mothers with a viral load of less than 50 copies/ml and who do not breast feed have 0.5% chance of transmitting the virus.

Maternal baseline viral load is an important risk factor and should be taken into consideration when deciding when to initiate treatment in pregnant women (Box 3). UK data presented in 2010, showed that virological control of <50 copies/ml was achieved at the time of delivery in only 37% patients who had a starting viral load >100,000 copies/ml. It is important to start ARV earlier than 20–24 weeks when the baseline viral load is high, the CD4 count is low, in the presence of co-morbidities like hepatitis B/C infection or recurrent genital HSV, and in high risk obstetrics patients such as those with a history of premature delivery. ART should be started as soon as possible if the viral load is higher than 100,000 and in some special circumstances, for example seroconversion illness. Insufficient control of viral load (>500 copies/ml) at 14–32 weeks' gestation is a risk factor for residual MTCT even in mothers on ART with a controlled viral load at delivery.

A longer duration of HAART is associated with reduced MTCT and rates of MTCT are lower in women who became pregnant on HAART, compared to those who start HAART during pregnancy; each week of HAART reduces the odds of transmission by 8%. Studies have shown the different types of HAART used do not influence the rate of MTCT.

Antiretroviral toxicity

The fetus is most vulnerable to toxic drug effects in the first 12 weeks of gestation. Spinal development starts between 6 and 12 weeks and the neural tube is closed by 6 weeks. Previous guidelines advised that efavirenz should not be used in pregnancy. However, systematic review and meta analysis indicates that there is no additional teratogenicity with efavirenz compared to other drugs; it can be both continued and commenced in pregnancy. Zidovudine, lamivudine and ritonavir have been shown to have congenital malformation rates within the expected range. Similarly, an excess in congenital malformations has been excluded with abacavir, tenofovir, emtricitabine, lopinavir, atazanavir nevirapine.

Ongoing surveillance of all children exposed to ART is through the RCOG/NSPH and the international Antiretroviral pregnancy databases.

Amniocentesis, cervical suture and invasive procedures

Most invasive procedures should be avoided in HIV positive pregnant women, however, if an amniocentesis or a cervical suture is necessary, there is a small chance of bleeding and thus

When to start HAART in pregnancy. BHIVA 2012 guidelines

CD4 count
- <350: start ART immediately

Viral load
- <30,000 copies/ml: start ART by 24 weeks
- >30,000 copies/ml: start ART by 14 weeks
- >100,000 copies/ml: start ART immediately

Box 3

of HIV transmission; this risk has to be weighed against the benefit of performing the procedure. It is very important to try and reduce the viral load to below detection and if the woman is not on antiretroviral treatment, it should preferably be commenced prior to any procedure. The French Paediatric HIV Infection Study Group observed a relative risk of HIV transmission of 1.9 with antenatal procedures including amniocentesis, cerclage, laser therapy and amnioscopy. However, this study was conducted between 1985 and 1993 and only a minority had received Zidovudine. If the procedure cannot be delayed until viral suppression is achieved, a HAART regimen including raltegravir should be given along with single dose of nevirapine 2–4 hours prior to the procedure.

Late booking or women presenting in labour who are untested

Late booking or presentation in labour, prior to adequate treatment with HAART (and thus likely detectable viraemia) can lead to MTCT. A national audit of pregnant women with HIV revealed that women who received ART for fewer than 2 weeks were more likely to be first diagnosed with HIV, during their pregnancy. The most common reason for not receiving ART were late booking, a denial of HIV diagnosis and refusal of treatment. Children born to these women had a higher rate of MTCT (13.4%).

If a woman presents after 28 weeks and is subsequently found to be HIV positive she should start treatment without delay. The ART regimen selected is normally based on a resistance test; however, if this is not rapidly available a PI-based regimen (either ritonavir-boosted atazanavir, lopinavir or darunavir) should be initiated immediately. Where the viral load is unknown or >100,000 copies/ml, a fourth drug, raltegravir, may be added to this regimen.

If a woman presents in labour and is not on treatment, she should be given a stat dose of nevirapine as this rapidly crosses the placenta (effective concentrations are achieved within 2 hours and then maintained in the neonate for up to 10 days). Obstetric emergency management is the priority, however if time permits prior to Caesarean section, attending staff should also commence potent therapy which crosses the placenta and results in rapid reduction of viral load, such as an oral combination of zidovudine, lamivudine and raltegravir, with intravenous zidovudine being administered throughout labour. The newborn should then initiate a combination of three drugs, usually zidovudine, lamivudine and nevirapine for 4 weeks, adjusted according to further information available about the maternal pre-natal viral load.

Mode of delivery (see Table 1)

Mode of delivery plays a key role in reducing MTCT and historically, "bloodless" elective Caesarean section was performed. However, Caesarean section has implications on cost and morbidity. Effective control of viral load with HAART has led to more and more women having vaginal deliveries. For women taking HAART, a decision regarding mode of delivery should be made after review of viral load at 36 weeks.

BHIVA guidelines state that a vaginal delivery is recommended for women on HAART with an undetectable viral load. In these women, obstetric management should follow the same guidelines as for the uninfected population. Published cohort data from the UK and other European countries have shown MTCT rates of <0.5% in women with plasma viral load <50 copies/ml taking HAART, irrespective of mode of delivery.

In contrast, data from the European Collaborative study showed that in 960 women delivering with a viral load of <400 copies/ml, elective Caesarean section were associated with an 80% decreased risk of MTCT. As a result of more HIV positive women opting for planned vaginal delivery, there has been a rise in emergency Caesarean sections, possibly due to many obstetricians having a lowered threshold for Caesarean section due to the historic data (detailed below) that prolonged SROM and presence of infection (chorioamnionitis) is associated with increased MTCT.

For women taking zidovudine monotherapy, a Caesarean section is recommended irrespective of the viral load, equally if the viral load >400 copies/ml the recommendation if for Caesarean section regardless of the ART agents.

The timing of Caesarean section is a balance between the risks of transient tachypnoea of the newborn and the likelihood of labour occurring before the scheduled Caesarean section. Where the indication is to prevent MTCT, Caesarean section at 38–39 weeks is considered; the earlier timing reflects the importance of avoiding the onset of labour.

Mode of delivery. BHIVA 2012 guidelines

Viral load at 36 weeks (copies/mL)	< 50	50–399 copies/mL	> 400
	No obstetric complications: • VAGINAL DELIVERY recommended	Consider pre-labour Caesarean section dependent upon: • actual viral load • trajectory of viral load • length of time on treatment • obstetric factors • mother's views	Caesarean section recommended

Table 1

There are no published studies of low level viraemia (ie 50–399 copies/ml) and the risk of MTCT. BHIVA recommends that Caesarean section 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.

In the pre-HAART era, several studies suggested that prolonged duration of ruptured membranes, usually analyzed as greater than 4 hours, in women who were either untreated or receiving ZDV monotherapy, resulted in a significantly increased risk of MTCT. The few studies available from the HAART era do not support this. According to BHIVA guidelines therefore, for any women on HAART who ruptures her membranes at term with a viral load of <50 copies/ml and who does not have an obstetric contra-indication to vaginal delivery, a Caesarean section is not recommended.

Studies have shown an association between both acute/chronic chorioamnionitis and perinatal transmission. Although these studies were largely performed in the pre-HAART era, it is recommended that labour should be monitored carefully for development of infection and managed according to standard guidelines for non-HIV infected patient following delivery.

Pre-term delivery

There is conflicting evidence as to whether HAART is associated with pre-term delivery. A current trial– PROMISE study (NCT01061151) will likely provide some more answers around the use of PI's in pregnancy.

Decisions regarding the optimum treatment of pre-term ROM necessitate assessment of exact gestation, maternal viral load and the presence of other co-morbidities as well as the facilities available.

Consideration of corticosteroids to improve fetal lung maturation and oral erythromycin should be given as per the RCOG guidelines. The viral load should be optimized, if it is not undetectable. A concern that the pre-term infant may not be able to tolerate oral therapy may make it more desirable to load the infant through the transplacental route with maternal therapy.

Treatment to the newborn

Antiretroviral treatment to the newborn is an example of pre-exposure prophylaxis and should be decided before the delivery. The choice of the drugs given to the baby depends on the mother's antiretroviral drug history and known resistance mutations. This treatment should be planned in a multi-disciplinary setting with a paediatrician with interest in HIV disease, obstetrician and HIV physician; there may be need for advice from a virologist.

There are two situations where neonatal PEP (post-exposure prophylaxis) is advised:

- Where the mother is found to be HIV positive after delivery (treatment needs to be given within 72 hours)
- When there is detectable maternal viraemia at birth

For children born to mothers with wild type virus and an undetectable viral load, AZT is usually sufficient. However, when the viral load in not undetectable or the mother has various mutations, ART use becomes more difficult. Choices for newborn are fairly limited given the toxicities of many drugs. Neonatal PEP should be given for 4 weeks.

Breast feeding in HIV positive women

Women who breast feed may transmit HIV by this route, especially if the viral load in plasma and breast milk is high, delivery is pre-mature, breastfeeding is prolonged, or if nipples are cracked. The current standard of care in the UK is to avoid breastfeeding in HIV positive mothers. There may be wide variations between plasma and breast milk viral load, which is why breast feeding should be avoided even in the presence of an undetectable serum viral load. Intestinal permeability is a possible entry site for the virus and mixed feeding is thought to double the risk of HIV transmission secondary to inflammation.

Testing of infants

All infants born to HIV positive mothers should be tested for HIV. HIV DNA PCR (or HIV RNA testing) should be performed during the first 48 hours and prior to hospital discharge, 2 weeks post infant prophylaxis (6 weeks of age), 2 months post infant prophylaxis (12 weeks of age), HIV antibody testing for seroreversion should be done at age 18 months.

Conclusion

HIV is one of the most important communicable diseases in the UK. It is associated with serious morbidity, high costs of treatment and care and significant mortality. To date, 120,000 people have been diagnosed with HIV in the UK, of whom 27,000 have developed AIDS and more than 20,000 have died.

Advances in the management of HIV infection have led to changes in how HIV infection is managed in pregnancy. With undetectable viral loads, antenatal procedures and instrumentation have become safer and vaginal deliveries are a viable first line management option. As more data becomes available, better informed drug choices can be made. The overriding issue when dealing with HIV in pregnancy is to have clear lines of communication with input from the multidisciplinary team. ◆

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Practice points

- All pregnant women must be encouraged to have an HIV antibody test
- All pregnant HIV infected women require multidisciplinary care
- Partner testing and involvement encouraged
- All pregnant HIV infected women should receive antiretroviral drug treatment to prevent MTCT
- Psychological assessment and child protection issues should be addressed early on pregnancy
- All women should be encouraged to aim for vaginal delivery
- A clear, up-to-date and effective labour plan should be made and kept on labour ward, copy with the patient
- A dedicated paediatrician should arrange monitoring of ART, follow up and further testing of the baby

