

Vol. 4 No. 3 Preventing mother to child transmission

By Bridget Haire

If the pregnancy is managed well, having a baby for a woman with HIV in good health now carries only the smallest of risk that the infant will become HIV infected. As life expectancy increases for people living with HIV, women are increasingly wanting to have children. Understanding what the risks are and what the options entail, and working with a medical team that is HIV experienced and prepared to take the mother's wishes and well being as seriously as the infants, facilitates the best result.

HIV transmission from mother to child has been reduced to less than two percent in developed countries due to judicious use of antenatal testing, antiretroviral therapy, pre-labour Caesareans, treatment of the infant after birth (post-exposure prophylaxis) and abstaining from breastfeeding.

For women with HIV considering pregnancy, there is some evidence about the relative benefits of each of the specific interventions. Frustratingly, however, a lot of this evidence comes from observational studies and so it is not considered high-quality scientific evidence. For a woman wanting to minimise interventions while still maximising the protection from HIV for her infant, expert opinion and national and international guidelines come into play.

The best researched package of interventions is known as the 076 protocol, established in 1994 by the ground-breaking PACGT study, which established that treatment with AZT (Retrovir) from the second trimester combined with an intravenous infusion during birth, treatment of the infant for six weeks after birth and pre-labour Caesarean delivery reduced transmission rates from 24 percent to eight (babies were not breastfed). With the advent of effective combination therapy from 1996, the 076 protocol shifted from being standard of care to being the 'minimum' standard of care, with pregnant women increasingly opting to treat with combination therapy – using additional agents added onto the AZT-based regimen.

Other major developments since 1994 include a raft of ethically questionable studies that aimed to find a cheaper option in the developing world. (The ethical questions arise from the use of a placebo arm in these studies, despite the proven efficacy of the 076 regime.) Reducing the post-exposure prophylaxis to infants to four weeks was found to be as effective as the six-week treatment in studies looking at shorter AZT regimens. Single doses of nevirapine (Viramune) - one to the mother during the birth and one to the infant afterwards – reduced HIV transmission to 11-12 percent at six to eight weeks of age.

Transmission factors

HIV can be transmitted from a mother to an infant in the uterus (probably during the third trimester), during birth or after delivery through breastfeeding. Maternal health, obstetric factors and infant prematurity are the three significant factors influencing the likelihood of transmission in the absence of treatment, together with not breastfeeding.

On the whole, the lower the maternal viral load the lower the probability of transmitting HIV to the infant. However, maximally suppressive therapy throughout pregnancy is not always the best or only choice for a mother and her child. Pre-labour Caesarean delivery lowers the incidence of transmission independently of viral load, though it is believed that there may be a viral load nadir below which transmission will not occur^[1]. Antiretroviral therapy in pregnancy is also associated with an increase in prematurity that carries with it various risks and complications, so the goal of viral suppression needs to be balanced with other considerations^[2].

Drug options...when, with and what

AZT remains the best-studied drug for use in pregnancy, and is usually the basis of any combination unless there are specific individual reasons for not doing so. In instances where a woman's HIV status becomes apparent during labour, nevirapine is preferable as it

achieves therapeutic blood levels very quickly.

National and international guidelines on antiretroviral use in pregnancy have moved away from blanket recommendations to treat aggressively in pregnancy, to strategies that seek to balance the optimal treatment for both mother and infant with caution around unnecessary exposure of the foetus to antiretroviral drugs, particularly in early pregnancy.

If a woman is taking a fully suppressive regimen when she becomes pregnant, the advice is to continue unless it contains a drug contraindicated in pregnancy, such as efavirenz. If she is not on therapy and has a viral load that warrants treatment, the advice is to defer treatment until after the first trimester, although in some cases, the benefits may outweigh the risks.

After AZT, nevirapine is the next-best studied anti-HIV drug in pregnancy. The HIVNET 012 study of more than 1,000 mothers and newborns in Uganda between 1997 and 1999 was the main basis for using a single-dose of nevirapine to prevent mother-to-child transmission. A single dose given to the mother at the start of labour and to the neonate cuts transmission by 47%. When AZT/3TC (Combivir) or AZT alone was added to nevirapine at birth, only 4.7% of infants born to infected mothers became infected. Alleged irregularities in the conduct of this study have led to a scientific review, however this review, conducted by the US Institute of Medicine of the National Academies, has ruled that the findings of the study are robust.

Nevirapine is however associated with liver toxicity and women with CD4 counts above 250 may be at increased risk of such side effects. The product information was changed in 2004 to specifically state the increased liver resistance in women and those with CD4 cells above 250, and while it is unknown how pregnancy affects the likelihood of hepatitis, pregnant women are likely to treat with CD4 counts above this level.

Nevirapine is not suitable as a monotherapy in developed countries like Australia as treatment-limiting toxicity can arise after a single dose.

Efavirenz has now been found to be associated with neural tube defects, with reports of four babies born to women who took efavirenz in the first trimester.^[3]

British and American guidelines differ by a factor of ten as to when they consider a viral load warrants treatment. In the UK, it is over 10,000 while in the US it is over 1,000.

Both the British and the American guidelines suggest that women with low viral loads should consider treatment in the second or third trimester to reduce the likelihood of transmission. Either combination therapy or AZT monotherapy, as per the 076 protocol, is indicated, with combination therapy as the preferred option if a woman prefers a vaginal delivery to a pre-labour Caesarean. The use of short-term monotherapy in this context has not been associated with creating resistance (citation), and the advantage is limiting foetal exposure to drugs. For women with pre-existing AZT-resistance, this option would not be an effective strategy, so resistance testing is an important component of choosing monotherapy.

Australian guidelines have not recently been updated but are in development using the US guidelines as a model. The 1997 guidelines state, "Most women should be receiving combination antiretroviral therapy. In women planning pregnancy or currently pregnant, combinations including zidovudine, nevirapine, didanosine, lamivudine and saquinavir currently appear to be the safest options. The lack of clinical efficacy and toxicity data needs to be carefully explained to the women involved".

Treatment breaks and changes

For women on treatment that is fully suppressive of viral load, it's not recommended to change or interrupt therapy for pregnancy unless the regimen contains efavirenz, which is linked to birth defects. Treatment interruption may cause viral rebound at the critical point in gestation where intra uterine transmission could occur. For women taking therapy that is not

fully suppressive, resistance testing and regimen change is indicated.

Obstetric factors

Caesarean section delivery has been shown to be a factor in reducing infant transmission independently of maternal viral load and antiretroviral treatment (European Collaborative Study)^[4]. However, expert opinion is that there is a viral level below which transmission does not occur^[5].

Caesarean delivery is not recommended in countries where surgery is considered risky, with high rates of post-surgical infections, nor to women currently living in developed countries who may return to live in the developing world and have other children there. As post-operative recuperation may be a significant issue for many women regardless of their country of residency – single parents or women with other children or caring responsibilities for example – vaginal delivery remains an important option. For women with very low viral loads who have no known obstetric risk factors, there is no evidence that vaginal delivery poses a significant HIV transmission risk.

The longer the period between rupture of membranes and delivery in a vaginal birth, the greater the chance of HIV transmission. The risk increases by two percent for every hour following two hours after rupture^[6]. In addition, interventions such as forceps, invasive foetal monitoring, and suction caps are likely to increase the risk of transmission (although there is no evidence of the risk of these interventions, this makes logical sense).

Infant treatment

Administration of antiretrovirals to an infant who is not breastfed works on the principle of post-exposure prophylaxis. This enables an infant who may have been exposed to HIV during birth to 'abort' the infection.

In instances where a woman is diagnosed with HIV during labour or after birth, infant treatment is the only intervention other than breastfeeding alternatives to prevent infection, so the highest level of post-exposure prophylaxis is warranted, which is combination therapy rather than AZT monotherapy. This would also apply in instances where a woman with HIV declines any interventions for herself during pregnancy, delivery and birth. While a woman with HIV has the right to refuse treatment on her own behalf, the infant has an independent right to treatment. Legal precedent exists in Australia for the infant treatment to be directly administered regardless of maternal wishes.

Breastfeeding

Formula feeding is recommended for women with HIV in Australia, as it is safe, affordable and sustainable. While in the absence of HIV breastfeeding has significant advantages for the infant, the risk of HIV transmission outweighs these benefits in HIV positive women.

Breastfeeding increases the likelihood of infection by about 15 percent, although this is even higher – twice as high – in women who acquire HIV after giving birth and while breastfeeding.

Studies are ongoing in Africa in populations where alternatives to breastfeeding are not viable to find interventions that reduce the risk of transmission through breastfeeding. The most optimistic finding was that exclusive breastfeeding followed by fast weaning produced better results than mixed feeding (Coutoudis et al., 2001b). The antiretroviral nevirapine also appeared to have some effect. In all studies, however, any breastfeeding increases the incidence of transmission significantly.

Unfortunately, antiretroviral therapy may not lower the incidence of transmission. A South African study has shown that HIV shedding in breastmilk varies between breasts and over time, and that there is only weak correlation between viral levels in blood plasma and breastmilk. The authors of the recent British HIV Association treatment guidelines for HIV in pregnancy describe the shedding of HIV in breastmilk as seemingly 'random'. This could be

due to the interplay of a number of complex factors: breastmilk is in a different viral 'compartment' to the peripheral blood; it contains both cell-free and cell-associated HIV; and trauma to the nipple and clinical and sub-clinical mastitis may increase local virus levels. Studies aimed at finding a way of reducing transmission in breastfeeding populations are ongoing. These include antiretrovirals administered to mothers and infants.

Reducing mother to child HIV transmission in breastfeeding populations is an important humanitarian goal as in many parts of the world there is no safe viable alternative. It is not yet known whether any strategy will reduce the incidence of transmission to the level of infants that are not breastfed however, so choosing to breastfeed in a country where there is an alternative exposes a baby to an unwarranted risk.

Screening policy

Diagnosing HIV before pregnancy or in early pregnancy is obviously important so that interventions can be offered. From a policy perspective, the spectre of universal HIV testing gets raised every few years as a way of ensuring that every HIV positive pregnant women is identified so that she can take advantage of the options to reduce transmission. To date, mandatory testing in pregnancy has been resisted in Australia on the grounds that 'universal' often becomes 'routine', whereby the important risk assessment, medical history-taking and pre and post-test counselling elements of HIV testing may not afforded the priority they need if the shift were made. Were the incidence of late diagnosis in women to rise, this may be subject to review.

Women with HIV have the right to make informed decisions about treatment and delivery options for pregnancy and birth. Decision-making depends on having a good flow of information between the pregnant woman or woman planning pregnancy and her medical team, which should comprise at least an HIV experienced primary care physician and obstetrician. Thorough discussion and evaluation of the risks and benefits of particular interventions needs to be made – for example, with regard to Caesarean delivery and/or commencing antiretroviral treatment, where individual women may have a decided preference one way or another. In weighing up options, minimising the risks of HIV transmission does need to take priority, although other factors such as limiting exposure to drugs in the first trimester if possible and maternal desires regarding delivery are valid concerns.

Data continue to accumulate through long-term observational studies of women with HIV and their pregnancies and children and through formal randomised studies, but many of the latter are being conducted in the developing world so are not applicable to the Australian context. Observational data give a less-than crystal-clear picture of what the best approach is in various situations including treatment history and delivery mode preference, but trends do emerge over time. Women in observational studies are more likely to be on state-of-the-art therapy, better reflecting the options of a woman with HIV in Australia now than formal studies done five to 10 years ago, or studies from Africa.

The HIV positive baby boom, like other baby booms in recent history, is a reflection of optimism in the new world order (in this case the 'world' of effective treatments) of managed infection, increasing life expectancy and greater personal agency. This is very welcome.

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^[1] Rare transmissions have been reported even at plasma viraemia less than 400 RNA copies/ml. Cooper ER, Charurat M, Mofenson LM, Hanson IC, Pitt J, Diaz C *et al*. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr* 2002;29:484-

94.

^[2]European Collaborative Study,. Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS* 2000;14:2913-30.

^[3] Aidsmap, European warning about tenofovir/ddl, and BMS strengthens caution about use of efavirenz during pregnancy, Michael carter, 14 April 2005.

<http://www.nam.org.uk/en/news/F1F997E0-6E4F-4160-B866-A9D2A335E43B.asp>

^[4] Read, J. and International HIV Perinatal Group. Mode of delivery and vertical transmission of HIV-1: a meta-analysis from fifteen prospective cohort studies. Twelfth World AIDS Conference; 1998 June 28 - July 3; Geneva, Switzerland (Abstract No 23275). 1998.

Ref Type: Abstract. The European Mode of Delivery Collaboration. Elective caesarian-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999;353:1035-9.

^[5] Browne et al abstract submitted to BHIVA/BASHH – April 2005.

^[6]The International Perinatal HIV Group. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS* 2001;15:357-68.