Advances in mother-to-child transmission of HIV infection

Zidovudine is now available in state hospitals to prevent mother to child transmission

The pandemic of human immunodeficiency virus (HIV) infection has had a major impact on maternal and child health. Since the beginning of the epidemic an estimated 12 million women and 1.3 million children worldwide are living with the virus. Many of the children were born to infected mothers. The epidemic has claimed the lives of nearly 3 million children (1).

Mother-child transmission (MCT) takes place antepartum while in *utero*, intrapartum during labour and delivery or postpartum through breast milk (2). Published perinatal transmission rates vary widely, with developing countries reporting higher rates compared to developed nations. Most recent reviews quote rates varying from 15 to 43% in the absence of interventions (2). One reason for rising perinatal transmission is the continuing increase of HIV infection in women of childbearing age. This is largely attributable to heterosexual transmission, which at present accounts for 70% of all transmissions (1). In addition, most women, especially those in developing countries, are unaware of their HIV status as they do not receive adequate prenatal care that includes testing facilities. Rising rates of HIV infection have jeopardised national maternal mortality and child survival rates. The need for effective interventions to prevent MCT has become a public health priority.

Effect of pregnancy on the natural history of HIV infection

Data published to date show that pregnancy does not have a major adverse effect on the natural history of HIV infection in women (3). An accelerated progression of the infection has not been reported although the immune function is suppressed during pregnancy as reflected by a decrease in immunoglobulin, reduced complement level and a decrease in cell-mediated immunity (2,3).

Effect of HIV infection on pregnancy

Adverse pregnancy outcomes have been reported from both developed and developing countries with higher rates from the latter (3). As most research studies have been carried out in Africa the majority of reports are in relation to African countries. Both HIV-1 and HIV-2 infection in Africa have been linked to a higher rate of spontaneous abortion (OR = 4.05), stillbirth (OR = 3.91), foetal abnormalities (OR = 1.08), perinatal mortality (OR = 1.79), neonatal mortality (OR = 1.10), infant mortality (OR = 3.69), intrauterine growth retardation (OR = 1.7), low birthweight (OR = 2.09), and preterm delivery (OR = 1.83) (3). Higher rates of ectopic pregnancy have also been reported in HIV infected women although this observation may

be confounded by the effects of concurrent sexually transmitted diseases such as gonorrhoea and *Chlamydia* infection.

Timing of transmission

A statistical model based on a French prospective study has shown that one-third of the infants were infected *in utero*, less than 2 months before delivery. In the remaining two-thirds the time of infection was estimated to be the day of birth (4). Several clinical and laboratory studies have confirmed that a substantial proportion of infection is acquired at childbirth (2). Probable mechanisms of transmission include transplacental maternal-foetal microcirculation of blood and the virus during uterine contractions, and direct contact of the foetus with infected blood or secretions from the maternal genital tract (2), so that interventions during late pregnancy and delivery offer the best chance for reducing the risk of infection.

Infants who escape infection at birth are at risk of infection if breast-fed by infected mothers. A meta-analysis of 9 studies gave an estimate of a relatively constant incidence of about 3.2 infections per 100 person years of breast feeding after 2.5 months of age among infants HIV negative at birth but breast-fed by infected mothers (5).

The rate of postnatal transmission in mothers who had established infection before becoming pregnant is between 8 and 18% (6). A meta-analysis of 5 studies showed an additional transmission risk of 14% (95% CI, 7-22%) through breast-feeding (2,6,7). The chance of transmission through breast milk rises if the mother contracts the infection in the postpartum period, probably because the rate of viral replication is higher in early stages of primary infection and high levels of virus secretion in breast milk (2,6,7). Based on four studies, the estimated risk of postnatal transmission was 29% (95% CI 16-42%) among women who developed primary infection after delivery (2,7).

Risk factors for postnatal transmission include maternal immune deficiency and the presence of HIV infected cells in milk (6). Certain immunologic factors present in breast milk may be protective against postnatal transmission of the virus. The presence of secretory IgA in early breast milk and IgM later, correlates with a reduced risk of transmission. The probable protective role of IgM in breast milk is by providing a protective painting of the mucosal surfaces, preventing viral attachment and entry into submucosal tissues, and by decreasing the viral load in milk by its potential lytic action (6).

Timing of breast-feeding is important, as several studies suggest that the transmission rate in the first few weeks or months of life could be substantially higher than later, because the former includes feeding with colostrum

and early milk which are rich in lymphocytes. Heating breast milk to destroy the virion is adopted as an intervention in some instances. Recent studies have shown a relationship between higher transmission rates and longer duration of breast-feeding (8).

The advent of interventions during the past few years to reduce MCT is making an impact on the incidence of paediatric HIV infection.

Therapeutic interventions

Available evidence suggests that the maternal viral load provides the best indicator of transmission rates. A high antenatal viral load, particularly at the time of delivery, is a risk factor for the transmission of HIV from an untreated mother to the infant (9). Similarly, undetectable or low viral loads are associated with low perinatal transmission (9).

Hence antiretroviral drugs (ARV) given during pregnancy and delivery would lower the transmission rate by reducing viral load. Therapeutic concentrations of the drug in the foetus and neonate may also provide some prophylactic protection during and after exposure to the virus.

Highly active antiretroviral therapy (HAART) is likely to be more effective in preventing transmission due to the reported greater reductions in viral load. No large scale studies in pregnant women are yet available, but several clinical trials have shown that monotherapy with antiretroviral drugs such as zidovudine (ZDV) and nevirapine reduced MCT (10,11).

ZDV monotherapy

The first therapeutic intervention trial investigating the effect of ZDV on MCT during pregnancy was the paediatric AIDS clinical trial group protocol (PACTG 076) in a group of women who did not breast-feed (10). An intensive regimen of ZDV was given orally at 14 to 34 weeks of gestation, intravenously during labour and delivery, and as an oral syrup to the baby for first 6 weeks of life. The intervention achieved a 66% reduction in transmission rate. Based on these findings the use of ZDV to reduce MCT is now standard practice in many developed countries.

Short course ZDV therapy

Since transmission is thought to occur in most cases towards the end of pregnancy a short course of ZDV was tried in a randomised controlled trial in Bangkok (12). It showed that ZDV 300 mg twice daily from 36 weeks of gestation and every 3 hours orally from the onset of labour until delivery, resulted in 50% lowered risk of transmission. Newborns were not given any therapy (12). All women were counselled not to breast-feed. Women in the Bangkok study were asymptomatic and had a relatively intact immune system. Whether the ZDV therapy would be as effective in an asymptomatic population is not known.

The safety and efficacy of the Bangkok regimen was assessed in African women who were breast-feeding their infants, as breast-feeding is the norm in many developing countries. This study showed that the efficacy of ZDV therapy at age 1 month was 44%, only slightly lower than

50% decrease in the Bangkok study (13). However, at three months this figure had fallen to 37%, probably because of postnatal transmission from continued breast-feeding.

Another study in Africa went a step further by giving women ZDV 300 mg twice a day orally for 7 days post-partum, in addition to an antepartum dose of 300 mg twice daily orally from 36 weeks of gestation until labour, and a single 600 mg oral dose at the beginning of labour. It showed a 38% in reduction in MCT at six months of age in spite of breast-feeding (14). But the findings of these two African studies do not allow conclusions to be drawn on the efficacy of a single dose therapy at labour *versus* repeated dosing during labour and one week therapy post-partum, as the effect may have been influenced by maternal CD₄ counts, independent of treatment effect.

Short course therapy with other ARV

In Kampala, the safety and efficacy of nevirapine, was compared with ZDV in HIV infected women (11). Nevirapine is rapidly absorbed when given orally, and passes quickly through the placenta, achieving high levels in the placenta. Nevirapine 200 mg orally was given at the onset of labour as a single oral dose to mothers and 2 mg/kg orally to babies within 72 hours of birth. In the comparison group ZDV 600 mg orally was given to the mother as a single dose at the onset of labour and 300 mg 3-hourly until delivery and 4 mg/kg orally twice a day to babies for 7 days after birth. Mothers were allowed to breast-feed. Nevirapine lowered the risk of HIV-1 transmission during the first 14 to 16 weeks of life by nearly 50% (11).

Most of the trials mentioned above have looked at the short term efficacy of antiretroviral therapy. The impact of these regimens on long term survival and on later transmission associated with breast-feeding needs further investigation.

Caesarean delivery

Several studies have suggested a protective effect of elective caesarean section (CS) on reducing the risk for perinatal transmission (15,16), as this bypasses the infected vaginal canal during childbirth. Delivery by CS decreases the rate of MCT by 50%. Another potential benefit of planned CS would be to decrease the risk of prolonged rupture of membranes which doubles the risk of MCT (15,16). The protective effect of elective CS was found to be additive with ZDV therapy (16). Future research should address whether any added benefit of elective CS will be achieved in HIV infected women who are on HAART.

In developing countries the benefits of breast-feeding on morbidity and mortality from common infections and malnutrition outweigh the risk of MCT through breast milk. Hence discouraging breast-feeding may not be applicable to all infected mothers. Moreover, not all infants born to HIV infected mothers are infected by vertical transmission. Thus the intervention strategies in Sri Lanka should be planned on an individual basis.

In Sri Lanka, ZDV therapy is now available at government health institutions for the prevention of MCT,

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and identification of HIV positive women during early pregnancy to allow such intervention is clearly important. Voluntary counselling and testing thus become cornerstones of intervention with ZDV therapy, undertaken with the patient's informed consent and maintaining of confidentiality.

If women know their HIV status during pregnancy, avoidance of breast-feeding, use of the short course antiretroviral therapy, avoiding invasive procedures at delivery and planned elective CS, should reduce MCT significantly in Sri Lanka.

Whether such a policy could be implemented island-wide, given the resources needed for CS, the drug, antenatal testing, training staff in counselling and testing, and the disadvantages of artificial feeding, need careful consideration.

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