Preventing perinatal transmission of HIV-1 infection

Simona Fiore, Marie-Louise Newell

It is now known that with the use of antiretroviral prophylaxis with zidovudine, elective caesarean section delivery and refraining from breastfeeding the rate of mother–child transmission of HIV infection can be reduced to less than 2%.

Nearly all 600 000 or more new human immunodeficiency virus (HIV) infections in children each year are the result of mother–child transmission. Although over 90% of these infections occur in sub-Saharan countries, a number of infants are at risk of becoming congenitally infected in Europe, where the estimated prevalence of HIV infection among pregnant women ranges from 2.6 to less than 0.2 per 1000 live-births (Law et al, 1999).

VERTICAL TRANSMISSION

Mother–child transmission can occur before, during and after delivery. Before the widespread use of interventions, rates of mother–child transmission ranged from 15–20% in Europe, to 16–30% in the USA, 25–40% in Africa and 13–48% in South and South East Asia. Based on indirect evidence it is now generally accepted that, in the absence of breastfeeding, about 75% of vertically infected infants acquire their infection around the time of delivery, while in breastfeeding populations this is about 50%. Risk factors for vertical transmission include indicators of progression of maternal disease, such as viral load and clinical disease, and obstetric and neonatal factors such as prematurity, mode of delivery and breastfeeding.

Knowledge about timing and risk factors has informed interventions resulting in the reduction of the risk of vertical transmission. Prophylactic antiretroviral therapy reduces maternal viral load, and may thus prevent transmission, while an elective caesarean section delivery avoids contact of the fetus with contaminated maternal secretions. Refraining from breastfeeding reduces exposure to potentially infectious milk.

PROPHYLACTIC ANTIRETROVIRAL THERAPY

After the positive results from the American-French trial ACTG076, which showed that zidovudine administered antenatally, during labour and neonatally reduced vertical transmission risk by over two-thirds in a non-breastfeeding population (Connor et al, 1994), trials were set up to investigate shorter, easier and cheaper zidovudine regimens to be effective in both breastfeeding and non-breastfeeding populations (Dabis et al, 1999; Shaffer et al, 1999). Results from these trials confirm the substantial effect of zidovudine in reducing the risk of vertical transmission.

In 1999, preliminary results of a trial in Uganda, evaluating the effectiveness of peripartum nevirapine compared to a similar regimen of intrapartum and neonatal zidovudine, suggested a highly significant effect of nevirapine on the rate of vertical transmission at 4 months of age in breastfed children (Guay et al, 1999). Nevirapine was given orally once to the mother at the onset of labour, and once to the infant in the first 3 days of life.

A randomized, double-blinded, placebo-controlled trial of nevirapine *vs* placebo in addition to routine zidovudine prophylaxis (PACTG316) is currently underway in the USA, Europe and Brazil. The regimen involves a single oral dose of nevirapine to the mother during labour or before a caesarean section, followed by a single oral dose to the infant within 72 hours of birth. Women receive routine antiretroviral therapy during pregnancy including as a minimum the ACTG076 regimen and are asked not to breastfeed. Nearly half of the 1000 women randomized to date have received triple therapy with a protease

Dr Simona Fiore is Research Fellow and **Dr Marie-Louise Newell** is Reader in the Department of Epidemiology and Public Health, Institute of Child Health, University College London, London WC

Correspondence to: Dr M-L Newell

inhibitor during pregnancy (S Fiore, personal communication, 2000). It is expected that trial enrolment will be completed by the end of 2000.

Observational studies have confirmed the two-thirds reduction in vertical transmission risk associated with the ACTG076 regimen (Wade et al, 1998; Mandelbrot et al, 1998; European Collaborative Study, 1999). However, questions have been raised regarding the neonatal component of zidovudine prophylaxis, including the effect of a delay in its initiation, the optimum duration of neonatal prophylaxis and the practicality of the 6-week regimen of ACTG076, in particular for infants who are premature or experiencing drug withdrawal. A European survey has shown that although prophylactic zidovudine therapy is now widespread in Europe, variations exist in the implementation of the various components of the ACTG076 regimen (European Collaborative Study, 1998). Partial use of the regimen has been shown to be somewhat less efficacious, in accordance with results from trials of short-course zidovudine regimens.

Wade et al (1998), using data from New York State, reported vertical transmission rates of 6%, 10% and 9% for zidovudine prophylaxis begun antenatally, during delivery and within 48 hours of birth respectively, although numbers were small and confidence intervals therefore large. Initiation of zidovudine prophylaxis after 48 hours in neonates whose mother had not received any zidovudine was found not to be effective in reducing the risk of vertical transmission.

Guidelines for antiretroviral therapy during pregnancy emphasize the dual nature of vertical transmission prophylaxis and optimal treatment of the mother's HIV infection (Taylor et al, 1999). An additional issue is the fact that increasing numbers of HIV-infected women are becoming pregnant while on combination therapy for their own disease progression (Lorenzi et al, 1998).

Adverse effects

A mild and reversible anaemia is the major immediate toxicity associated with exposure to prophylactic zidovudine to reduce vertical transmission (Dabis et al, 1999; Sperling et al, 1998). Zidovudine can be incorporated into the DNA of leukocytes in zidovudine-exposed adults and infants with in-utero exposure, although there is a large range in the amount of incorporated zidovudine, possibly reflecting differences in zidovudine metabolism (Olivero et al, 1999).

This issue raises the possibility that uninfected children exposed to zidovudine to reduce vertical transmission may also be at risk of mutagenic and carcinogenic effects at a later age. Following the cessation of ACTG076, 234 uninfected infants born to mothers enrolled in the trial were followed up for an average of 4 years. No adverse effects were observed in the zidovudine exposed group and during this time there have been no deaths or malignancies reported in either zidovudine or placebo groups (Culnane et al, 1999). Furthermore, there have been no significant differences between zidovudine- and placebo-exposed children with regard to growth, lymphocyte subsets and development. However, owing to the relatively small number of children still in follow-up, these studies had limited power to detect very rare adverse events.

Of concern are the recent reports of a small number of serious adverse effects possibly associated with exposure to antiretroviral therapy in the form of mitochondrial dysfunction. In France, analysis of 1754 mother–child pairs who were exposed to antiretroviral therapy, either as part of a large phase II trial of combined zidovudine and lamivudine to reduce vertical transmission or as a result of maternal treatment, identified eight children (all uninfected) with mitochondrial dysfunction (Blanche et al, 1999). Two children presented clinically and died, and the mitochondrial dysfunction was diagnosed later. The remaining six children were diagnosed in a retrospective assessment of available data in the French perinatal study. Four of the eight children had been exposed to zidovudine alone, and four to both zidovudine and lamivudine. Five children had neurological symptoms including seizures, myopathy and cognitive impairment (including the two who died at 11 and 13 months of age), while the remaining three were without clinical symptoms but had biochemical abnormalities.

Estimates of prevalence of mitochondrial disease in the general child population suggest that this is an extremely rare condition and adds weight to the hypothesis that mitochondrial dysfunction and fetal and neonatal exposure to nucleoside analogues could be linked. Investigation of the large American trials' databases have not shown any evidence of unexpected deaths in exposed uninfected children. It is fundamental to investigate more fully the occurrence of serious adverse events on an international scale, using prospective studies, which follow up large numbers of both infected and uninfected children. Systems need

to be set up to monitor the possible long-term consequences of early exposure to antiretroviral therapy.

MODE OF DELIVERY

A consistent body of evidence from observational studies, a meta-analysis and a randomized trial indicate that elective caesarean section before onset of labour and rupture of membranes significantly reduces the risk of transmission compared to both vaginal and emergency caesarean section deliveries (The European Mode of Delivery Collaboration, 1999; International Perinatal HIV Group, 1999; European Collaborative Study, 1999; Mandelbrot et al, 1998). In the European mode of delivery trial (1999) a total of 436 women were randomized to either vaginal or caesarean section delivery. The trial results confirm findings from observational studies that vaginal delivery is associated with a more than two-fold increased risk of vertical transmission of HIV infection, independent of the use of prophylactic antiretroviral therapy. The transmission rate was 1.8% in women allocated to caesarean section compared with 10.5% in those randomized to vaginal delivery. There was no significantly increased risk of complications for the mother in the caesarean section group.

Results from a large meta-analysis (International Perinatal HIV Group, 1999) involving more than 8500 mother–child pairs from 10 American and 5 European observational studies were consistent with the above trial. The effect was again independent of the use of prophylactic zidovudine during pregnancy, intrapartum or neonatally. A recent analysis of data from the European Collaborative Study (1999) evaluated the effect of elective caesarean section allowing for maternal viral load, which had not been possible in the above meta-analysis. Results showed the beneficial effect of caesarean section to be similar both for women with a viral load above and below the median.

With increasing numbers of pregnant HIV-infected women receiving antiretroviral prophylaxis and having an elective caesarean section delivery, more information has become available on the interaction between these interventions. In the French Perinatal Cohort Study, multivariate analysis of 902 mother–child pairs receiving zidovudine prophylaxis indicated a five-fold reduction in transmission risk following elective caesarean section compared with vaginal delivery, with a vertical transmission rate in women exposed to both interventions of less than 1% (Mandelbrot et al, 1998).

European guidelines recommend that all HIV infected women should be offered an elective caesarean section delivery, as well as prophylactic antiretroviral therapy and be advised to refrain from breastfeeding (Tovo et al, 1999). Similarly, the American College of Obstetricians and Gynecologists has reached a consensus that all HIV-infected women should be offered an elective caesarean section delivery, with appropriate counselling of the benefits associated with receiving both zidovudine prophylaxis and caesarean delivery. It is recommended that elective caesarean sections should be scheduled at 38 completed weeks of gestation, with intravenous zidovudine prophylaxis given before the procedure according to the dosing schedule recommended in the ACTG076 protocol. Prophylactic antibiotics should be administered if deemed necessary (American College of Obstetricians and Gynecologists, 1999).

OTHER INTERVENTIONS

Results of randomized trials which investigated the efficacy of zidovudine with or without HIV hyperimmune immunoglobulin in reducing the risk of vertical transmission have recently been published, but this trial was discontinued early because of the low rate of vertical transmission in both arms.

Results from trials evaluating the effect of vitamin A supplementation on mother–child transmission are now becoming available, suggesting a lack of effect on vertical transmission rate (Coutsoudis et al, 1999).

Vaginal cleansing with chlorhexidine was found to reduce vertical transmission only in the subset of women with duration of rupture of membranes longer than 4 hours (Taha et al, 1997).

INFANT FEEDING

Further to the recommendation developed collaboratively by UNAIDS, UNICEF and WHO that where safe, affordable, feasible and acceptable, HIV-infected women should be advised to refrain from breastfeeding, there is now increasing interest in finding ways to optimize breastfeeding while minimizing the risks of transmission. This would be particularly important in settings where alternative infant feeding methods are not an option (Newell, 1999).

CONCLUSION

There is now sufficient information to recommend a concerted effort to identify HIV-infected women during pregnancy and to offer them pro-

phylactic antiretroviral therapy, elective caesarean section delivery and advice on refraining from breastfeeding. With this advice vertical transmission risk can be reduced significantly.

However, the optimum antiretroviral therapy regimen for prophylactic purposes has not yet been determined, and it is not known what the consequences will be of the increasing use of pre-pregnancy antiretroviral therapy combinations in adults to delay progression of disease. Possible adverse effects on the large majority of uninfected children exposed to antiretroviral drugs during intrauterine or early life need careful and prolonged monitoring to ensure early recognition of what are likely to be very rare effects. **HM**

Conflict of interest: none.

American College of Obstetricians and Gynecologists (1999) *Scheduled Cesarean Delivery and the Prevention of Vertical Transmission of HIV Infection.* American College of Obstetricians and Gynecologists Committee Opinion, American College of Obstetricians and Gynecologists, USA

Blanche S, Tardieu M, Rustin P et al (1999) Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* **354:** 1084–9

Connor EM, Sperling RS, Gelber R et al (1994) Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* **331:** 1173–80

Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia H, for the South African Vitamin A Study Group (1999) Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. *AIDS* **13:** 1517–24

Culnane M, Fowler MG, Lee SS et al (1999) Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA* **13:** 151–7

Dabis F, Msellati P, Meda N et al (1999) 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo controlled multicentre trial. *Lancet* **353:** 786–92

European Collaborative Study (1998) Therapeutic and other interventions to reduce the risk of mother-to-child transmission of HIV-1 in Europe. *Br J Obstet Gynaecol* **105:** 704–9

European Collaborative Study (1999) Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS* **13:** 1377–85

European Mode of Delivery Collaboration (1999) Elective caesarean section *vs* vaginal delivery in preventing vertical HIV-1 transmission: a randomised clinical trial. *Lancet* **353:** 1035–9

Guay L, Musoke P, Fleming T et al (1999) Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* **354:** 795

International Perinatal HIV group (1999) Mode of delivery and vertical transmission of HIV-1: a meta-analysis from fifteen prospective cohort studies. *N Engl J Med* **340:** 977–87

Law MG, Downs AM, Brunet JB, Kaldor JM (1999) Time trends in HIV infection among pregnant women in Europe. *AIDS* **12:** 211–6

Lorenzi P, Spicher VM, Laubereau B et al (1998) Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. *AIDS* **12:** F241–7

Mandelbrot L, Le Chenadec J, Berrebi A et al (1998) Perinatal HIV-1 transmission — interaction between zidovudine prophylaxis and mode of delivery in the French Perinatal Cohort. *JAMA* **280:** 55–60

Newell ML (1999) Breastfeeding and HIV infection: a global perspective. *Hosp Med* **60**(11): 778–9

Olivero OA, Shearer GM, Chougnet CA et al (1999) Incorporation of zidovudine into leukocyte DNA from HIV-1 positive adults and pregnant women and cord blood from infants exposed in utero. *AIDS* **13:** 919–25

Shaffer N, Chuachoowong R, Mock PA et al (1999) Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet* **353:** 773–80

Sperling RS, Shapiro DE, McSherry GD et al (1998) Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 study. *AIDS* **12:** 1805–13

Taha TE, Biggar RJ, Broadhead RL et al (1997) Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *Br Med J* **315**: 216–9

Taylor GP, Lyall EGH, Mercey D et al (1999) British HIV Association guidelines for prescribing antiretroviral therapy in pregnancy 1998. *Sexually Transmitted Infections* **75:** 90–7

Tovo P-A, Newell ML, Mandelbrot L, Semprini A, Giaquinto C (1999) *Recommendations for the Management of HIV Infected Women and their Infants — A European Consensus.* European Commission, Brussels: 1–37

Wade NA, Birkhead GS, Warren BL et al (1998) Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* **339:** 1409–14

KEY POINTS

- About 75% of vertically infected non-breastfed infants acquire human immunodeficiency virus (HIV) infection around the time of delivery, while in breastfeeding populations this proportion is about 50%.
- Prophylactic antiretroviral therapy reduces maternal viral load in the mother, and may thus prevent transmission, while an elective caesarean section delivery avoids contact of the fetus with contaminated maternal secretions. Refraining from breastfeeding reduces exposure to potentially infectious milk.
- Of concern are the recent reports of a small number of serious adverse effects possibly associated with exposure to antiretroviral therapy. It is fundamental to investigate more fully the occurrence of serious adverse events in both infected and uninfected children. Systems need to be set up to monitor the possible long-term consequences of early exposure to antiretroviral therapy.
- European guidelines recommend that all HIV-infected women should be offered an elective caesarean section delivery, as well as prophylactic antiretroviral therapy, and be advised to refrain from breastfeeding.