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SOCIETY MEETING PAPER

Current issues in the prevention of mother-to-child transmission of HIV-1 infection[☆]

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Summary Worldwide every year approximately 750 000 children become infected with HIV, mostly through mother-to-child transmission (MTCT). Without specific interventions, the rate of MTCT is approximately 15–20%, with prolonged breastfeeding doubling the rate to 35–40%. Current approaches to intervention to reduce the risk of MTCT focus mainly on antiretroviral prophylaxis during pregnancy, labour and in the early neonatal period, but in some settings also on delivery procedures and avoidance of breastfeeding. To reduce the risk of breastfeeding transmission, shortening the breastfeeding period and/or encouraging exclusive breastfeeding has been suggested. MTCT rates of less than 2% are now reported from countries where antiretroviral prophylaxis, elective Caesarean section and refraining from breastfeeding can be applied, whilst in settings where refraining from breastfeeding is not feasible or safe and where elective Caesarean section is also not a safe option, peripartum antiretroviral therapy can halve the risk to levels of approximately 10% at 6 weeks, although further acquisition of infection through breastfeeding substantially increases the overall rate to 20% or more. In light of the high mortality in all children of HIV-infected women, programmes for prevention of MTCT should be monitored not only in terms of HIV transmission avoided but also in terms of child survival.

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1. Background

By the end of 2003, an estimated 40 million people were living with HIV/AIDS; 19.2 million women and 2.5 million children aged less than 15 years (UNAIDS, 2004). Each year, at least 2 million women become infected with HIV, mainly as a result of heterosexual transmission, and approximately 750 000 children acquire HIV infection, mostly through

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mother-to-child transmission (MTCT) (UNAIDS, 2004). The United Nations General Assembly incorporated a Declaration of Commitment on HIV/AIDS within their Millennium Goals in 2000. The targets within this declaration include a 25% reduction by 2010 in the percentage of 15–24-year-old pregnant women who are HIV infected and a 20% reduction by 2005 in infant HIV infection and 50% by 2010.

2. MTCT

In the absence of specific interventions, the rates of transmission from infected mothers to their offspring have been estimated to be approximately between 15% and 35% (Newell et al., 1996; Working Group on Mother-to-Child Transmission of HIV, 1995), with differences between studies owing to population characteristics. The risk of vertical transmission is associated with maternal factors such as HIV RNA viral load, and clinical and immunological disease progression measured as AIDS or CD4 cell counts (Table 1). Increased transmission has also been associated with prematurity, prolonged duration of rupture of membranes, and vaginal delivery. Maternal plasma viral load is the strongest independent predictor of MTCT. However, intrapartum transmission of HIV may occur through direct contact of the infant with the virus present in the genital tract.

Breastfeeding approximately doubles the risk of vertical transmission; in women with established HIV infection and in populations where breastfeeding continues into the second year, the additional risk of transmission through breastfeeding is approximately 15–20%, with about one-third of this accounted for by late postnatal transmission after 3 months of age. It is unclear whether infection takes place through cell-free virus in breast milk or through HIV-1 infected cells. The risk of trans-

mission through breast milk also depends on age at complete cessation of breastfeeding, the stage of maternal disease, breast health and feeding modality. Breast milk RNA viral load is associated with plasma viral load, although it is generally lower: in the Nairobi trial, for every 1 log₁₀ copies/ml increase in plasma viral load there was an estimated 0.58 log₁₀ copies/ml increase in breast milk viral load (Rousseau et al., 2003).

In the Breastfeeding and HIV International Transmission Study (BHITS) meta-analysis using individual patient data from clinical trials in breastfeeding populations (Breastfeeding and HIV International Transmission Study, 2004), of 4343 singleton breastfed children with HIV-1 test results, 999 (23%) were definitively infected, of whom 545 could be categorised by timing of infection: 314 children (58%) were infected before 4 weeks of age and the remaining 231 (42%) were classified as late postnatal transmission (LPT), acquiring infection after 4 weeks of age. LPT occurred throughout the period of breastfeeding; interestingly, girls had a lower risk of LPT than boys (relative risk for girls vs. boys=0.7, 95% CI 0.5–0.9), which was not explained by differences in duration of breastfeeding (Breastfeeding and HIV International Transmission Study, 2004). Using the same data set, the risk of mortality in women postpartum was estimated to be 32.2 per 1000 years of follow-up at 18 months, with mortality in ever breastfeeding women significantly lower than in those who never breastfed. Mortality was lower in women who breastfed for longer, and higher in those with low CD4 counts around the time of delivery.

3. Prevention of MTCT

Current approaches to intervention to reduce the risk of MTCT include antiretroviral prophylaxis during pregnancy, labour and in the early neonatal period, Caesarean section delivery before labour and rupture of membranes, and avoidance of breastfeeding, shortening the breastfeeding period and/or encouraging exclusive breastfeeding.

An elective Caesarean section before onset of labour and rupture of membranes significantly reduces the risk of transmission compared with both vaginal and emergency Caesarean section deliveries (The European Mode of Delivery Collaboration, 1999). Disinfection of the birth canal during labour with microbicides is an intervention aimed at preventing MTCT of HIV infection through reducing exposure of the infant to infective cervicovaginal secretions. In a trial in Malawi, there was no statistically significant difference overall in vertical

Table 1 Potential risk factors for mother-to-child transmission of HIV infection (Thorne and Newell, 2004)

Risk factor
Maternal plasma RNA viral load
Viral characteristics
Maternal immune status, CD4 cell counts
Cervicovaginal infections and sexually transmitted diseases
Mode of delivery
Time from rupture of membranes to delivery
Prematurity
Infant birth weight

Table 2 Prophylactic antiretroviral therapy in the prevention of mother-to-child transmission of HIV: results from selected relevant trials (WHO, 2004)

Trial	Antenatal/intrapartum	Postnatal	Infant feeding	Efficacy
Bangkok ZDV trial, Thailand	ZDV from 36 weeks; oral intrapartum	None	Formula	VTR 9.4% with ZDV vs. 18.9% in placebo at 6 months (50.1% efficacy)
Ivory Coast CDC trial, Ivory Coast	ZDV from 36 weeks	None	Breast	VTR 15.7% with ZDV vs. 24.9% in placebo at 3 months (37% efficacy)
DITRAME Trial, Ivory Coast/Burkina Faso	ZDV from 36 weeks	1 week	Breast	VTR 22.5% vs. 30.2% (26% efficacy) in pooled analysis with CDC at 24 months
Thai Perinatal HIV Prevention Trial	ZDV; long (from 28 weeks), short (from 36 weeks)	Long (6 weeks), short (3 d)	Formula	VTR 6.5% in long–long arm vs. 4.7% in long–short arm and 8.6% in short–long arm at 6 months
PETRA, South Africa, Tanzania and Uganda	ZDV + 3TC; from 36 weeks gestation	7 d mother and infant	Breast	VTR 14.9% for antenatal/intrapartum/neonatal ZDV + 3TC vs. 18.1% for intrapartum/neonatal ZDV + 3TC
Thai ZDV&3TC trial, Thailand	ZDV + 3TC; from 34 weeks gestation	Infant ZDV 4 weeks	Formula	VTR 2.8% at 18 months
HIVNET 012 trial, Uganda	NVP; no antenatal ART. Intrapartum: single-dose NVP vs. oral ZDV	Infant: single-dose NVP <72 h vs. ZDV (7 d)	Breast	VTR 15.7% in NVP arm vs. 25.8% in ZDV arm (41% efficacy) at 18 months
SAINT trial, South Africa	No antenatal ART. Intrapartum: single-dose NVP vs. ZDV + 3TC	Single NVP dose <48 h vs. ZDV + 3TC (7 d) (mother and infant)	Breast and formula	VTR 12.3% in NVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (statistically equivalent)

ZDV: zidovudine; VTR: vertical transmission rate; 3TC: lamivudine; NVP: nevirapine; ART: antiretroviral therapy.

transmission rates between the lavage and non-lavage groups, however the intervention was associated with a significant reduction of transmission in the subgroup of women with duration of rupture of membranes exceeding 4h before delivery, with 25% transmission in the intervention group versus 39% in the control group (Biggar et al., 1996). Furthermore, the use of chlorhexidine was associated with significant improvements in maternal and neonatal morbidity and mortality from other infections. Results from a more recent clinical trial in Mombassa, Kenya (Gaillard et al., 2001), similarly showed no effect of the chlorhexidine intervention on MTCT overall; however, there was a trend towards decreased risk of vertical transmission with the higher concentration of chlorhexidine assessed (0.4% vs. 0.2%).

Following the 1994 PACTG 076 trial of a three-part regimen of zidovudine monotherapy consisting of antenatal oral zidovudine started at between 14 weeks and 34 weeks gestation, intravenous zidovudine during labour and neonatal oral zidovudine for 6 weeks after delivery, which was shown to reduce vertical transmission risk by over two-thirds in a non-breastfeeding population, subsequent trials in developed and less developed countries among breastfeeding and non-breastfeeding women include those investigating shorter and cheaper regimens of zidovudine, trials of zidovudine and lamivudine (3TC) combinations, and the non-nucleoside reverse transcriptase inhibitor, nevirapine, on its own and in combination with nucleoside reverse transcriptase inhibitors (Table 2).

The most recent clinical trials published include the PHPT2 trial in Thailand (Lallemant et al., 2004) evaluating the efficacy of a single dose of nevirapine added to a standard short-course zidovudine regimen in a non-breastfeeding population: a 1.9% (95% CI 0.9–3.0%) transmission rate was reported in the arm where both the mother and the infant received single-dose nevirapine in addition to the zidovudine prophylaxis, and 2.8% (95% CI 1.5–4.1%) where only the mother received nevirapine. In the NVAZ trial in Malawi (Taha et al., 2003), the efficacy of short post-exposure prophylaxis was assessed among infants born to women presenting late for delivery who did not receive any antenatal or intrapartum antiretroviral therapy (ART).

In countries where antiretroviral prophylaxis, elective Caesarean section and refraining from breastfeeding can be applied, vertical transmission rates of less than 2% have now been reported (European Collaborative Study, 2005). In settings where refraining from breastfeeding is not feasible or safe, and where elective Caesarean section

is also not a safe option, peripartum ART can halve the risk to levels of approximately 10% at 6 weeks, although further acquisition of infection through breastfeeding can substantially increase the overall rate (Dabis et al., 2005; Leroy et al., 2002); current research initiatives therefore concentrate on the first 6 months after delivery and address the prevention of transmission by breastfeeding (Gaillard et al., 2004).

4. Possible adverse effects of ART exposure

Concern has been expressed about the possibility of adverse effects associated with exposure to short-term antiretroviral prophylaxis for the infected mother, the pregnancy and her infected and uninfected children. For example, it has been shown that the rate of premature delivery is increased where combination therapy with protein inhibitors was received in early pregnancy (Thorne et al., 2004). There is no evidence of an increase in congenital abnormalities.

Mortality among children born to HIV-infected mothers in sub-Saharan Africa is substantially higher than among children born to HIV-uninfected mothers in the same environment, and deaths of HIV-infected mothers have been associated with increased child mortality. In a meta-analysis of data from African trials, mortality was estimated for nearly 3500 children of HIV-infected mothers, approximately 700 of whom were HIV infected themselves. An estimated 35% of infected children will die by 1 year of age, and 53% by 2 years, compared with 5% and 7.5% of uninfected children. Survival of the mother was associated with a 2–3-fold increased mortality in the infected and uninfected children, suggesting that even when infection in the child is prevented there would still be a high risk of dying for these children of HIV-infected mothers (Newell et al., 2004).

5. Conclusion

Even if interventions late in pregnancy or around the time of delivery are highly effective in preventing perinatal infection, as a public health policy they are only of interest if alternatives to breastfeeding are feasible, affordable, safe and available. Pilot intervention programmes have been put in place in several African countries. The effect of such programmes should be monitored not only in terms of HIV transmission avoided but also in terms

of child survival. Experience to date suggests that only a minority of HIV-infected women are tested during pregnancy and benefit from the peripartum antiretroviral prophylaxis. Locally appropriate ways will have to be developed to increase the numbers of pregnant women tested for HIV and the numbers able to accept the available interventions.

Conflicts of interest statement

The author has no conflicts of interest concerning the work reported in this paper.

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