

EDITORIAL

CURTAILING MATERNAL TO CHILD TRANSMISSION OF HIV

The overall risk of transmission of HIV from mother to child is around 15-25% for non-breast feeding mothers, and doubles to 25-45% for breast-feeding mothers(1,2). Thus, in a country like Uganda where mother to child transmission (MTCT) accounts for about 10% of total cases, the MTCT rate is estimated at 26% (3). It has been suggested that 60-70% of transmissions occur around the time of delivery, with the remainder mostly late in the third trimester (30%) and the rest, postnatally (10%) through breastfeeding(4). In general, a healthy placenta appears to protect the foetus *in utero* from HIV in maternal blood for most of the gestation. The integrity of the placental protection against HIV may, though rarely, be breached by infections or drugs which can damage the vasculature and allow mixing of the two circulations(5,6). For the majority of women with HIV, it means then that interventions to reduce the risk of transmission should be focused on the last trimester of pregnancy and the risk factors that increase the chances of MTCT, giving women and clinicians time to plan ahead.

The most important determinant of risk is the maternal plasma viral load. However, other risk factors which have been identified, independent of the maternal viral load, include genital tract infections and ulcers, HIV content of maternal cervicovaginal secretions and breast infections(7,8). It has been reported by Kenyan researchers that mother-child class I HLA concordance increases perinatal HIV-1 transmission(9). No clear cut differences in transmission has been found among the various HIV-1 subtypes or clades(10-12). A study from Kenya reports a strong association between decreased HIV-1 infection risk in perinatally exposed infants and possession of a cluster of closely related class I HLA alleles (A2/6802 supertype)(13). Maternal viral load is related to CD4 count and the progression of HIV disease – a low CD4 count and more advanced HIV also increase the risk of vertical transmission. Primary infection with HIV in a pregnant or lactating woman also increases the risk of transmission, as in the first weeks of infection the plasma viral load is very high, before the immune response to HIV brings the level of the virus down(2). It is, thus, relevant that in this issue of the journal, Makokha *et al*(14) found that HIV infected pregnant women who responded to monotherapy with zidovudine with a rise in absolute CD4 counts were less likely to transmit the infection to their newborns.

To take up an intervention to reduce the risk of MTCT of HIV, a woman needs to know that she is seropositive. An HIV test should, therefore, be recommended to all pregnant women as part of normal antenatal care. An HIV test in pregnancy requires an infrastructure which can deliver counseling, testing and reliable serological results. In as much as such voluntary

counseling and testing has been acceptable in principle in some countries, like Uganda(15), much needs to be done to ensure confidentiality and allay women's fears of stigmatisation and discrimination during delivery. Such an infrastructure of antenatal care should not be devoted to HIV, but makes an opportunity to improve the overall management of women's health in pregnancy. Interventions to reduce HIV transmission should go along with a package of best antenatal care for all pregnant women, both positive and negative.

The World Health Organisation strategy includes simple measures for all-vitamins (including folate) and iron supplements; anti-malarials (where appropriate); and improved obstetric care as part of the Making Pregnancy Safer Initiative(16). Better health for all women, is undoubtedly related to status in society and the political will for change. To carry through effective programmes for pregnant women, including those with HIV, governments need to demonstrate real financial commitment to women and their children – a difficult task in resource poor countries.

From the known risks of transmission described above, the interventions to reduce transmission can be considered under four categories:

- (i) reduction of maternal viral load,
- (ii) avoidance of labour and the birth canal,
- (iii) keeping the birth canal free of infections and ulcers and
- (iv) avoidance of breast milk. Currently different approaches are taken according to the resources available.

Monotherapy with zidovudine was the first treatment demonstrated to reduce MTCT by nearly 70% to a rate of around 6-8% in a randomised controlled trial(17). Pre-labour Caesarean section has been shown to reduce the risk of transmission of HIV in women with all levels of viral load by up to 70% in a randomised controlled trial and 50% in a large meta-analysis(18,19). Zidovudine and a pre-labour Caesarean section reduced the risk of transmission to less than 2% for women at any level of viraemia, so this can still be considered as an option for a woman who wishes to restrict antiretroviral therapy exposure during pregnancy(18,19). Dual therapy with zidovudine and lamivudine reduced the late of transmission to around 2%, but is not adequate treatment for the mother, with rapid development of resistance to lamivudine(20). There have been no randomised controlled trials of triple therapy in pregnancy, but delivery at below detectable viral load is associated with a very low rate of transmission(21). Thus women who require combination therapy for treatment of their HIV will concomitantly greatly reduce the risk of transmission when their viral load is suppressed. Whether a pre-labour Caesarean section has any additive effect at

undetectable viral load is not known. Last minute treatment, in labour or even after delivery within the first 48 hours for the infant will also reduce transmission, and should be considered for women who present late(22). Women are being treated with many antiretroviral therapy combinations, exposure to these drugs in pregnancy has not been associated with any specific or an increased rate of teratogenic effects(23). However, an increased risk of premature delivery has been suggested for women on combinations with protease inhibitors(24).

In the original zidovudine monotherapy study, treatment was started as soon as possible after 14 weeks gestation, continued throughout pregnancy, administered intravenously during delivery and to the infant for six-weeks after birth(17). This regime was long and expensive and not appropriate for countries where mothers may not present early in pregnancy and where there is a dearth of resources. Short-course zidovudine commenced at 36 weeks gestation, continued orally during delivery, with none to the infant, has been associated with a 50% reduction in HIV transmission to a rate of 9.4% (25). A further study of different time courses of zidovudine monotherapy demonstrated further reduced transmission if treatment was started at 28 weeks (transmission rate 6.7%) rather than 35 weeks (transmission rate 10.6%) gestation, but little effect of the length of treatment of the infant whether 3 days or 6 weeks(26). Where women can be supplied with formula feed, short course zidovudine with or without Caesarean section will reduce the vertical transmission rate of HIV to less than 10%.

In countries with limited resources interventions should as far as possible benefit all women, both HIV positive and negative, and efforts need to be directed at general improvements in antenatal and perinatal care. Genital tract infections, use of medroxyprogesterone or oral contraceptives and vitamin A deficiency have been associated with increased risk of MTCT of HIV (27, 28). It is conceivable that treating these infections with antibiotics and other agents could reduce MTCT of HIV (29), as might avoiding the above means of contraception. Cleansing of the birth canal with chlorhexidine in labour(30, 31) and antenatal and postnatal maternal supplementation with vitamins(28,32,33) are some of the other modalities which have been tried in Kenya and Tanzania, with varying results.

Caesarean section is not an affordable or necessarily safe option for many poor women, but short course, or even in labour only antiretroviral therapy may be possible as has been demonstrated in some studies(34, 35). A very simple regime of single dose nevirapine in labour and to the infant at 48-72 hours compared to only a week of zidovudine reduces transmission by about one-half(36, 37). A 35% reduction in transmission was subsequently maintained up to one year in this breast feeding cohort(38). This intervention is very cheap and can also be given to women who present late, as is the case in many resource poor settings, although to be maximally effective the drug must be taken in early labour(39,40). The main drawback

of this intervention is that resistance to nevirapine develops in up to 20% of the women after the single dose and although this may not be relevant for subsequent delivery use, it is likely to reduce the effectiveness of the non-nucleoside class of drugs for any future combination antiretroviral therapy regime. It had been suggested that this regime could be offered to all women in labour, without knowing their HIV status, however in one study it was demonstrated that women were more likely to remember to take the drug if they were HIV infected(41).

In a resource poor setting in Kenya, it has been noted that where mothers have access to clean water, formula feeding is safe and reduces the risk of MTCT of HIV compared to breast-feeding by 44% without any increase in infant mortality by two years of age(42). Additionally, an observational study from South Africa suggests that the rate of breast-milk transmission may be less if women exclusively breast-feed, giving absolutely no other substances to their infants compared to mixed feeding where infants are exposed to other oral antigens in the first months of life(43). However, in Uganda, no correlation was found between the detection of HIV-1 in breast milk or the duration of breastfeeding and transmission of HIV-1 infection(44). Further, a study in Tanzania has revealed that knowledge of HIV transmission through breastfeeding is not associated with breastfeeding practices(45).

From the foregoing, it is evident that vertical transmission of HIV can be significantly reduced using various measures, either singly or in combination. The ongoing studies on the molecular aspects of the HIV and the host that influence MTCT are welcome. However, more studies are required to shed more light on the cost-effectiveness and safety of the modalities of intervention currently available and their applicability in resource poor countries. Ultimately, the ideal goal would be for all mothers to go into pregnancy uninfected and remain so throughout the pregnancy, a gigantic task indeed for the moment.

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