PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HIV

African Solutions for an African Crisis

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'I am convinced that our urgent task is to respond to the specific threat that faces us as Africans.'
President Thabo Mbeki[1]

The issue of mother-to-child transmission (MTCT) of HIV has become increasingly politicised in South Africa, with accusations and counter-accusations from all sides. Clinicians and activists, unable to comprehend the government's decisions not to provide inexpensive treatment to prevent MTCT, accuse it of child murder, while the President and Minister of Health claim concern about the safety of the drugs and make sweeping statements about mothers being killed. Amid all the political noise, scientific findings seem to be forgotten. The South African President has called for a 'search for specific and targeted responses to the specifically African incidence of HIV-AIDS',[1] but it appears that some of the evidence already collected by African scientists and their collaborators, with the participation of African women and children, has been ignored.

HIV seroprevalence in pregnant women in South Africa averages 23%, rising to 33% in the worst-hit provinces. Some South African studies[2] have reported MTCT rates of over 35% in the absence of any intervention and where breast-feeding is practised. With a conservative estimate of 800 000 births per year in South Africa, this suggests 70 000 infants are affected annually. The head of the Medical Research Council, Professor Malegapuru Makgoba, wrote in a recent *Science* editorial[3] that the decision not to use antiretrovirals for the prevention of MTCT 'poses serious moral and ethical dilemmas in a nation where maternal-fetal transmission of HIV accounts annually for 10% of the total HIV disease burden'. The need for an effective and affordable strategy to reduce MTCT of HIV is a matter of urgency.

ANTIRETROVIRAL THERAPY

The use of antiretroviral treatment during pregnancy has resulted in a dramatic decline in the number of perinatal HIV infections in the USA and Europe. Transmission rates in Los Angeles have dropped from 30% to 10%, and in North Carolina from 21% to 8.5%.[4] Reported transmission rates in the USA and France declined by between one-half and two-thirds within the first 3 years of routine use of zidovudine (ZDV) in pregnancy.[5,6] Further reductions have been seen, with transmission rates of less than 5% now recorded.[7] A study in France[8] showed that HIV-positive women who received this ZDV regimen and who had an elective caesarean section had a transmission rate of 0.8%.

When the results of the PACTG 076 trial became available in 1994,[9] it was obvious that the expensive regimen would not be feasible in most developing countries in the short term. African and Asian scientists, with international collaborators, commenced a series of trials to investigate the efficacy of short-course antiretroviral therapy in late pregnancy.

The first trial results, from Thailand, demonstrated that 4 weeks of ZDV given in late pregnancy produced a 50% reduction in MTCT.[10] A second random-ised trial of the ZDV regimen was conducted in 260 women in Côte d'Ivoire. This resulted in a 37% reduction in transmission in the treatment group by the time the infants were 3 months of age.[11] In contrast to the Thai study, over 95% of the infants in the Côte d'Ivoire trial were breast-fed.

Another trial of short-course ZDV was conducted among 350 women in Burkina Faso and Côte d'Ivoire. The trial com-pared placebo with oral ZDV started at between 36 and 38 weeks' gestation at 300 mg twice daily. This was followed by a single loading dose of 600 mg at the onset of labour and oral ZDV 300 mg administered to mothers twice daily for 7 days after delivery. In this trial over 85% of infants were breast-fed for longer than 3 months. The efficacy of ZDV was estimated at 38% (95% confidence intervals (CI) 5% - 60%) when infants were 6 months of age,[12] and at 30% when they were 15 months old.[13]

The PETRA study,[14] conducted in five African sites in South Africa, Tanzania and Uganda, investigated different regimens of a combination of ZDV and 3TC (lamivudine) in over 1 700 women. This trial compared the effectiveness of three different drug regimens with placebo. Arm A received ZDV and 3TC from 36 weeks' gestation, during labour and for 1 week postpartum (mother and child). Arm B received ZDV and 3TC from the onset of labour and for 1 week postpartum (mother and child). Arm C received ZDV and 3TC during labour only. Interim early efficacy results have been reported, showing that the risk of transmission by 6 weeks of age was 8.6% in arm A , 10.8% in arm B, 17.7% in arm C and 17.2% in the placebo group.[14]

Nevirapine is a fast-acting and potent antiretroviral, with a long half-life. The HIVNET 012 trial in Uganda[15] investigated the use of a single 200 mg dose of nevirapine administered orally to women at the onset of labour and a single dose of 2 mg/kg administered to infants within 72 hours of birth, compared with intrapartum ZDV and 1 week of infant ZDV treatment. Almost all babies were breast-fed. In the nevirapine treatment group the transmission rate at 14 - 16 weeks was 13.1% compared with 25.1% in the comparison group. The efficacy of nevirapine was 47% (95% CI 20 - 64). Side-effects were similar for the two regimens, both of which were well tolerated.[15] The South African Intrapartum Nevirapine Trial (SAINT) is investigating intrapartum and postpartum

nevirapine compared with the arm B regimen from the PETRA study, with results expected in mid-2000.

These trials of antiretroviral interventions have included several thousand African mother-infant pairs. To date, none of these trials has demonstrated significant toxicity or serious side-effects in mothers or infants. A small study in Uganda[16] has demonstrated the development of a nevirapine-resistant virus in 3 of 14 women who received only one intrapartum dose of nevirapine. Further studies on the development of resistance are in progress.

INFANT FEEDING

Concern remains about the effect of infant feeding choice on transmission, infant survival and the efficacy of antiretroviral interventions. While breast-feeding may be the major determinant for the difference in transmission rates between developed and developing countries, safe replacement feeding options are not always available. The additional risk of transmission via breast-feeding is estimated at between 7% and 22%, and the additional risk of transmission for women who become infected during the breast-feeding period is close to 30%. International guidelines recommend that HIV-positive women should be given the information to make an informed choice about the risks and benefits of breast and replacement feeding, and that they should be supported in their choice.

In Malawi, Miotti *et al.*[17] showed a 0.7% per month incidence of breast-feeding transmission in infants from 2 to 6 months of age, and a 0.3% incidence from 12 to 24 months, equivalent to about 3% additional risk from 12 to 24 months. A randomised controlled trial comparing breast-feeding and replacement feeding in Nairobi showed that at 24 months of age infants had a 36.7% cumulative probability of HIV infection in the breast-feeding arm and a 20.5% probability in the formula-feeding arm.[18] Forty-four per cent of HIV infection in breast-fed infants was attributable to breast-milk. Although the 2-year mortality rates were similar in the two groups, HIV-free survival was significantly lower in the breast-feeding arm (58% v. 70%, $P = 0.02$).

In work from Durban, Coutsoudis *et al.*[19] proposed an influence of infant feeding pattern on the rate of transmission. In this subanalysis of mother-infant pairs enrolled into a vitamin A supplementation study, transmission rates in exclusively breast and formula-fed infants were similar, while infants who received mixed feeding had higher rates of infection. These findings are interesting and require further investigation in a larger trial.

ONGOING RESEARCH

Several ongoing studies in Africa will add to our knowledge of prevention strategies. In Malawi, a trial of treatment for chorioamnionitis and sexually transmitted infections in pregnancy is underway. A study in Soweto is assessing escalating concentrations of Chlorhexidine for birth canal cleansing during labour, in the hope that a safe higher concentration will improve on the results from Malawi.[20] In Durban and Zimbabwe, an initial study of nevirapine administered to breast-fed infants will lead the investigation into ways to make breast-feeding safer, while in Pretoria a low-technology pasteurisation method for breast-milk is being studied. Several trials in South Africa, Uganda and other centres aim to fine-tune the antiretroviral interventions to make them more cost-effective. Pilot studies underway in eight African countries under the auspices of UNICEF, UNAIDS and the WHO will take the research findings into practice and provide invaluable information on implementation issues. Botswana, Cote d'Ivoire, Rwanda and Zimbabwe are taking the lead in this regard. In South Africa, pilot projects in Soweto, the Western Cape and three other provinces will add to this experience.

THE WAY FORWARD

There is no doubt that African solutions to the African crisis of MTCT of HIV have been found and are starting to be implemented. These are 'specific and targeted responses', which have not tried to implement Western approaches blindly, but have been tailored to meet the needs and challenges of the continent. They come from the dedication and commitment of African research teams and of African women prepared to contribute to the research efforts. Several years back, at the height of the controversy about placebo-controlled trials, a participant in a trial at Chris Hani Baragwanath Hospital was asked why she would risk participation in a study. She replied 'I am not only doing this for myself, I am doing it for my sisters who also face this terrible epidemic.' It will be an ongoing tragedy if policy makers across the continent ignore these solutions and the needs of HIV-positive women and their families.

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