

## NEVIRAPINE (Commentary)

**Reducing HIV transmission from mother to infant in resource poor settings**

Nearly two million babies are now born to HIV-infected women every year, and world inaction results in the infection and ultimate death of about 800,000 children a year.

Sustained zidovudine use during late pregnancy has long been the main strategy used to stop the baby developing infection during delivery. Combined treatment with several drugs or “highly active antiretroviral therapy” (HART) is now widely used both to control overt HIV infection, and to prevent mother-to-child transmission, in countries where such a policy is affordable. Monotherapy with zidovudine or with nevirapine has, until now, been the mainstay of management in resource-poor countries. Studies published within the last year have started to evaluate other strategies. Adherence to the current policy which calls for voluntary counselling and testing before initiating even brief peri-partum treatment is a counsel of perfection that means that, in many communities, it will be years before this growing scourge is checked.

**Starting treatment on admission in labour:** A pivotal trial in Uganda, reported in the *Lancet* in September 1999, showed that giving nevirapine during and after delivery reduced mother-to-child transmission in a breast-feeding population more than giving zidovudine. Treatment with oral nevirapine involved a single 200 mg dose by mouth to the mother in early labour and one 2 mg/kg dose to the baby within 72 hours of birth. Treatment with zidovudine involved giving the mother 600 mg by mouth in early labour and a further 300 mg every 3 hours until delivery. The baby then received 4 mg/kg by mouth twice a day for 7 days. The final outcome of this study, reported in the *Lancet* in September 2003, showed that 15.7% of the 313 babies born after treatment with nevirapine had become HIV positive by 18 months, and 25.8% of the 313 babies treated with zidovudine.

In another South African trial involving 1319 women, reported in the *Journal of Infectious Diseases* in March 2003, 12.3% and 9.3% of babies were found to be HIV positive 8 weeks after intrapartum treatment with nevirapine, and with a combination of zidovudine and lamivudine, respectively. This difference was not statistically significant. In a further trial from Thailand involving 1844 women who did not breast feed treatment with zidovudine alone during pregnancy reduced the proportion of babies becoming infected to 6.3%. However giving just two doses of nevirapine as well as zidovudine resulted in only 1.1% of babies becoming infected (Lallemant, *et al.* 2004).

The SWEN trial, reported in the *Lancet* in 2008, found that giving not only 200 mg to the mother in labour and 2 mg/kg to the baby at birth, but also a further 5 mg daily to the baby by mouth for six weeks starting on the eighth day of life, only produced a small further decrease in the number of babies with evidence of infection at 6 months. In the babies who were PCR negative for HIV at birth 87/1047 (8.3%) in the single-dose group, and 62/977 (6.3%) in the extended-dose group, were HIV positive at 6 months (RR 0.80; 95% CI 0.58–1.10).

**Starting treatment after birth:** A trial in Malawi, reported in the *Lancet* in October 2003, showed that a combination of nevirapine and zidovudine given to the babies of women who were not on any treatment when they presented in labour prevented mother-to-child transmission better than nevirapine on its own. This was a randomised open-label clinical trial in babies of late-presenting women who were HIV positive at delivery. A nurse gave 2 mg/kg of oral nevirapine using a fine-calibrated 1 ml tuberculin syringe to each baby as soon as they were able to swallow fluids after birth. They were then started on 4 mg/kg of zidovudine (or placebo) syrup twice a day for 7 days – the mother being given enough syrup to complete the course on discharge from hospital 6–48 hours after delivery. In this study 20.9% of the 468 babies who received nevirapine and 15.3% of the 484 babies who received both nevirapine and zidovudine still became HIV positive. In babies who were HIV negative at birth (the planned primary trial outcome) 12.1% of babies who had nevirapine and 7.7% of babies who had nevirapine and zidovudine became infected by 6 weeks.

**Sustained use in the breast fed babies of HIV positive mothers:** Continuing treatment with nevirapine for 14 weeks (2 mg/kg a day by mouth for the first 2 weeks and then 4 mg/kg a day for the next 12 weeks) halved the number of babies who had become HIV positive by 9 months (5.2% v. 10.6%) in a further recent trial from Malawi involving 3000 babies (Kumwenda *et al.*, 2008). However, many of those given nevirapine for 3 months still eventually became infected if breast feeding was sustained for any length of time.

Influenced by this, and by the study from Zambia (where nevirapine was not, at the time, widely available) where the abrupt termination of breast feeding at 4 months failed to improve the rate of HIV-free survival and was clearly harmful to babies who had already become infected (Kuhn *et al.*, 2008), WHO has now modified its earlier advice. It no longer says that breast feeding should cease at 6 months if the mother is HIV-positive.

It says “at 6 months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe (AFASS), continuation of breastfeeding with additional complementary foods is recommended”. Ultimately, as Gray and Saloojee say in a linked editorial, since mothers in low-resource settings will continue to select options that best suit their own cultural, economic and psychological needs, science will need to adapt and design strategies to meet their needs rather than the other way around.

## References

- Guay L, Musoke P, Fleming T, *et al.* Intrapartum and neonatal single-dose nevirapine compared to zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999;**354**:795–802. [RCT]
- Moodley D, Moodley J, Coovadia H, *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003;**187**:725–35. [RCT]
- Taha TE, Kumwenda NI, Gibbons A, *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003;**362**:1171–7. [RCT]
- Jackson JB, Musoke P, Fleming T, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003;**362**:859–68. [RCT]
- Shetty AK, Coovadia HM, Mirochnick MM, *et al.* Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months. *J Acquir Immune Defic Syndr* 2003;**34**:482–90.
- Lallemant M, Jourdain G, La Coeur S, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004;**351**:217–28. [RCT] (see also 289–92.)
- Six Week Extended-Dose Nevirapine (SWEN) Study Team. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* 2008;**372**:300–13. [RCT] (See also commentaries 267–70 and letter 287.)
- Kumwenda NI, Hoover DR, Mofenson LM, *et al.* Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med* 2008;**359**:119–29. [RCT]
- Kuhn L, Alrovandi GM, Sinkala M, *et al.* Effects of early abrupt weaning on HIV-free survival of children in Zambia. *N Engl J Med* 2008;**359**:130–41. [RCT]
- Gray GE, Saloojee H. Breast-feeding, antiretroviral prophylaxis, and HIV. [Editorial] *N Engl J Med* 2008;**359**:189–91.

First posted June 2005

Last updated August 2008