

CORRESPONDENCE



Nevirapine plus Zidovudine to Prevent Mother-to-Child Transmission of HIV

TO THE EDITOR: The articles by Lallemand et al. and Jourdain et al. (July 15 issue)^{1,2} highlight a dilemma. Should we impair the health of one patient to help another patient? Of the women receiving nevirapine, 32 percent showed resistance mutations to nonnucleoside reverse-transcriptase inhibitors (NNRTI) at 10 days post partum.² However, viral rebound may occur 21 days³ after receipt of the drug and result in an even higher rate of resistance mutations to NNRTI. Of the mothers receiving zidovudine monotherapy, 6.3 percent transmitted the human immunodeficiency virus (HIV) to their infants, as compared with 2.8 percent of mothers treated with additional nevirapine.¹ Unfortunately, no data are given on resistance mutations in infected babies. Resistance mutations might be present in 46 percent of vertically infected babies after nevirapine prophylaxis.⁴

With the use of zidovudine monotherapy in 1000 HIV-1-positive women, 63 infected babies will be delivered. If nevirapine is added to their treatment, 320 of the 1000 will have NNRTI resistance mutations, 24 infected infants will be born, and possibly 11 of them will harbor NNRTI resistance mutations. Thus, adding single-dose nevirapine to zidovudine prophylaxis will prevent 39 transmissions but may leave 11 babies and 320 mothers with NNRTI resistance mutations. These mutations may reduce their treatment options and worsen their prognosis.⁵ This risk must be considered when giving additional nevirapine during labor. Infected children should be tested for resistance mutations to allow for optimal future care.

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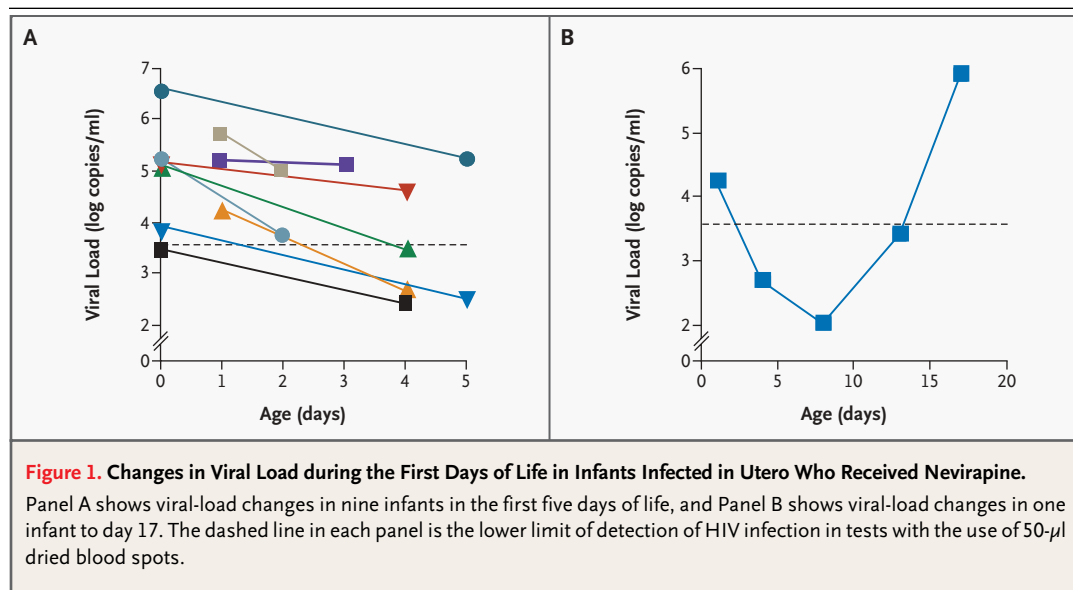
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TO THE EDITOR: The study by Lallemand and colleagues unexpectedly suggested that the rate of

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mother-to-child transmission of HIV in utero was significantly reduced by the addition of a dose of nevirapine at delivery to the antiretroviral drug therapy the pregnant women were receiving. Twenty-seven percent of the cases of HIV detected at the first interim analysis in the nevirapine groups represented in utero transmission. In contrast, in the HIV Network for Prevention Trials (HIVNET) 012 study in Uganda,¹ and in our study in Durban, South Africa, 73 to 78 percent of the infected infants had HIV at birth after perinatal administration of nevirapine. These discrepancies may relate to the method of detection of in utero infection. In the HIVNET 012 study, 50- μ l peripheral-blood samples obtained by finger prick were used; in our study, we used a quantitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay with a 500- μ l plasma sample. On the basis of our data (Fig. 1), approximately 50 percent of infections transmitted in utero would go undetected with the use of the finger-prick assay.²

Testing with the use of DNA PCR, although reportedly less sensitive than testing with RNA PCR,³ might lessen artifactual reduction in mother-to-child transmission. However, most viral DNA is unintegrated and labile. The decline in viral DNA tracks with the level of viremia.⁴ These data are important in the early diagnosis of pediatric HIV infection and in the interpretation of the action of nevirapine as a prophylactic agent against mother-to-child transmission.

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THE AUTHORS REPLY: The proportion of infants in whom HIV infection is diagnosed at birth is primarily influenced by the antiretroviral prophylaxis provided to the mother during pregnancy. In the HIVNET 012 study without zidovudine prophylaxis, the proportion of infants with HIV infec-

tion at birth was 8.2 percent, whereas in the Perinatal HIV Prevention Trial 1 (PHPT-1), which used the same diagnostic methods as those used in the Perinatal HIV Prevention Trial 2 (PHPT-2), the proportion was 5.1 percent with zidovudine prophylaxis initiated at 35 weeks of pregnancy and 1.5 percent with zidovudine prophylaxis initiated at 28 weeks.^{1,2} It is still possible, as Goulder et al. suggest, that the DNA PCR assay with 50 μ l of blood, used in PHPT-2, was less sensitive than the quantitative RT-PCR assay with 500 μ l of plasma, used in the HIVNET 012 study. However, the proportion of children with HIV infection at birth in the PHPT-2 placebo group was surprisingly high, at 3.1 percent, as compared with the overall transmission rate in the nevirapine–nevirapine group of 1.1 percent.³ This percentage cannot be explained by a lack of sensitivity of DNA PCR. Rather, it suggests that nevirapine prevented transmissions that would have occurred at the beginning of labor, and that would be detectable at birth.

Resistance mutations to nevirapine are also a concern for the children.⁴ However, we found that in mothers, the results of genotyping 10 days after exposure were very poor predictors of treatment failure, and the clinical significance of resistance mutations will be even more difficult to evaluate in the small number of children infected in our study of shortened zidovudine regimens. More generally, we feel that the dilemma posed by Herzmann and Karcher cannot be framed as impairing the health of one patient to help another. The two patients are closely related, and a mother may decide to give her unborn child the best chances of avoiding infection.

The risk for the child — HIV infection and lifelong antiretroviral therapy at best — is hardly comparable to that for the mother — a lower chance to achieve an undetectable viral load at the 50-copies threshold after six months of NNRTI-based therapy while other treatment options are available, as discussed in our report. Moreover, the risks for both mother and child associated with alternative interventions, such as triple antiretroviral combinations during pregnancy, regardless of the mother's immune status, are not yet fully documented, and no data from a comparative study are available to help balance these risks.

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Recurrent Venous Thromboembolism in Men and Women

TO THE EDITOR: Kyrle et al. (June 17 issue)¹ found that the risk of recurrent venous thromboembolism is higher among men than among women. This finding could influence the management of secondary prophylaxis against venous thromboembolism.

We analyzed the effect of sex on recurrent venous thromboembolism among patients who had had a first episode of idiopathic proximal deep-vein thrombosis or pulmonary embolism and who had been included in our previous studies.^{2,3} The comparison between our results and those presented

by Kyrle et al. is shown in Table 1. In our population of patients with proximal idiopathic deep-vein thrombosis or pulmonary embolism, we could not find a difference in the rate of recurrence between men and women. It should be noted that in the study by Kyrle et al., a substantial proportion of the patients had distal thrombosis, which was more common among the women than among the men and which is known to be associated with a lower risk of recurrence than is proximal thrombosis.^{4,5} Therefore, in the absence of further information, we do not recommend that women be treated dif-