

## EDITORIALS



## Antiretroviral Agents — How Best to Protect Infants from HIV and Save Their Mothers from AIDS

Hoosen Coovadia, M.D.

Preventing transmission of human immunodeficiency virus type 1 (HIV-1) and caring for those already infected are essential services in any comprehensive program, and enhancing the mutually beneficial effect of each is an international goal.<sup>1</sup> These reinforcing effects are clearly illustrated in the two articles from the Perinatal HIV Prevention Trial (PHPT) Group in this issue of the *Journal*. The first report, by Lallemand et al., demonstrates the considerable efficacy of a dual antiretroviral regimen in reducing mother-to-child transmission of HIV-1,<sup>2</sup> whereas the second, by Jourdain et al., evaluates the effects of subsequent provision of highly active antiretroviral therapy (HAART) to the immunocompromised mothers.<sup>3</sup>

In industrialized nations, the use of HAART in pregnant women along with an optimal package of interventions, including cesarean section and formula feeding, has reduced the rate of mother-to-child transmission of HIV-1 from about 25 percent to 1 to 2 percent. In developing countries, where HAART and complex antiretroviral regimens are unavailable and avoidance of breast-feeding is not a realistic option, short-course zidovudine, administered from weeks 32 through 36 of pregnancy, and single-dose nevirapine are the most frequently employed regimens to reduce the risk of peripartum transmission. However, owing to the breast-feeding-induced loss of efficacy of these regimens, the overall risk of transmission at 18 to 24 months remains as high as 15 to 25 percent. The risk of peripartum transmission may be further decreased by adding single-dose nevirapine or lamivudine<sup>4,5</sup> to short-course zidovudine. However, single-dose nevirapine should not be prescribed for women who are already receiving combination antiretroviral therapy during pregnancy, since in such women,

viral replication has been significantly diminished by the time of delivery and, hence, the risk of transmission is low.<sup>6</sup> This approach is consistent with the data from the PHPT,<sup>2</sup> which showed that combining single-dose nevirapine with short-course zidovudine had the highest efficacy among women with viral loads of at least 2500 HIV-1 RNA copies per milliliter and CD4 cell counts of 200 per cubic millimeter or less.

Lallemand et al. have now demonstrated in Thailand that adding single-dose nevirapine to a course of zidovudine beginning at 28 weeks of pregnancy, in women who do not breast-feed, can achieve results equivalent to the best reported from any region.<sup>2</sup> A similar short course of zidovudine had previously been established as the standard regimen in Thailand, reducing the rate of mother-to-child transmission of HIV-1 from 25 percent to 6.5 percent.<sup>7</sup> In the current study, the rate was further reduced from 6.3 percent among 348 women who, like their infants, received the standard regimen alone to 1.1 percent among 353 women who received the standard regimen plus a single intrapartum dose of nevirapine, with a single dose of nevirapine also given to their infants soon after birth. In recently updated recommendations, the World Health Organization (WHO) recommends this approach as the “most efficacious regimen” for the prevention of peripartum mother-to-child transmission of HIV-1 for women who do not require antiretroviral treatment for themselves,<sup>8</sup> and the Thai government has accepted this regimen as the standard of care. The rate of mother-to-child transmission was 2.1 percent among 333 women who received the standard regimen plus intrapartum nevirapine while their infants received placebo, and this rate did not differ significantly from the rate of

1.1 percent among the women who, with their infants, received a single dose of nevirapine.

This study showed an astonishing reduction in the rate of presumed intrauterine transmission of HIV-1 (as defined by a positive polymerase-chain-reaction [PCR] assay within 72 hours after birth) from 3.1 percent in the group of infants who, like their mothers, were given the standard regimen alone to 0.4 percent in the group of infants who received the standard regimen and whose mothers received intrapartum nevirapine. This decrease may reflect an effect of nevirapine on virus transmitted to the infant during uterine contractions in labor. These data suggest that a positive PCR assay within 72 hours after birth may reflect not only intrauterine transmission but also intrapartum transmission of actively replicating virus.

One of the chief concerns regarding the use of antiretroviral agents for the prevention of mother-to-child transmission of HIV-1 is that the drugs in these regimens could be less efficacious in subsequent pregnancies and in subsequent clinical management of the infection in the mothers or in their infants who become infected despite prophylaxis. The possibility of selection for HIV-1 variants that are resistant to antiretroviral agents has been a major worry, particularly with respect to nevirapine, because a single mutation can induce high-level resistance to nevirapine as well as to other nonnucleoside reverse-transcriptase inhibitors (NNRTIs).

In the study by Jourdain et al., resistance mutations to nucleoside reverse-transcriptase inhibitors (which include zidovudine) were detected 10 days after delivery in 5 percent of mothers, and among the women who had received intrapartum nevirapine, 32 percent had at least one mutation that conferred resistance to NNRTIs.<sup>3</sup> This rate is somewhat higher than the rates of about 17 to 19 percent reported in other studies four to eight weeks after delivery.<sup>4,9</sup> The development of nevirapine resistance after a single dose of the drug is affected by a number of factors, including maternal viral load and CD4 cell count, making comparisons between studies difficult.<sup>10</sup> New NNRTI resistance mutations have also been reported post partum in women receiving HAART who received intrapartum nevirapine, as well as in women who took nevirapine-containing HAART regimens during pregnancy that were discontinued postnatally.<sup>11,12</sup> In the HIVNET 012 study, the majority of these NNRTI mutant strains faded and were undetectable by means of standard resistance assays 12 to 24 months after delivery.<sup>9</sup>

However, whether these resistant mutations are archived in proviral DNA and, hence, have the potential to reemerge with reexposure to nevirapine requires further study.<sup>13</sup> In a Rwandan study, 1 of 10 women who received intrapartum nevirapine had an NNRTI resistance mutation identified in proviral DNA six weeks after delivery.<sup>14</sup>

A major question addressed by Jourdain et al. was whether the antiretroviral agents used to prevent mother-to-child transmission of HIV-1 might compromise the efficacy of antiretroviral agents subsequently prescribed for the treatment of HIV-1 infection in the mother. The end point of interest was virologic failure, defined by the failure to achieve maximal suppression (fewer than 50 copies of HIV-1 RNA) six months after the initiation of HAART. The study showed that at least half of the women who received intrapartum nevirapine and who subsequently had clinical indications for treatment had a good response to subsequent nevirapine-containing HAART, as indicated by rates of weight gain and increases in the CD4 cell count that were similar to those among women who had not received intrapartum nevirapine. However, among the women who received intrapartum nevirapine, those with detectable nevirapine resistance mutations 10 days post partum were less likely to have virologic suppression than were those without such mutations. Among the 221 immunosuppressed women who received intrapartum nevirapine and who later received HAART, virologic results were available for 188 (85 percent) after six months of therapy, and 96 (51 percent) had virologic failure. The rate of virologic failure was highest (62 percent) among the 61 women with NNRTI resistance mutations and among those with large viral loads at the beginning of therapy.

These findings suggest that women who receive single-dose nevirapine alone or in combination regimens for the prevention of mother-to-child transmission of HIV-1 and in whom NNRTI resistance mutations develop may be less likely than women who do not receive intrapartum nevirapine or have resistance mutations to have maximal viral suppression when NNRTI-based treatment is initiated soon after delivery. However, we need to clarify the longer-term clinical significance of these lower rates of maximal viral suppression, especially given the similar clinical improvement (weight gain) and equivalent increases in CD4 cell counts in the two groups. In addition, the success of HAART after single-dose nevirapine may be improved by delaying treatment

until resistance mutations have faded; in the study by Jourdain et al., HAART was given to about half the women within six months after delivery.

Additional studies with longer follow-up to investigate and quantify the clinical implications are urgently required, as is research into alternative antiretroviral agents for the prevention of mother-to-child transmission of HIV-1. The problem of resistance is likely to be heightened in African countries that are introducing programs for the national provision of antiretroviral agents.<sup>15</sup> The WHO has plans to develop and implement systems for measuring and monitoring resistance to HIV drugs. It is important to note that higher maternal viral loads and lower CD4 cell counts were associated with an increased risk of resistance after the intrapartum receipt of nevirapine. Thus, the very group of women most at risk for resistance are those who should be receiving HAART during pregnancy. In contrast, resistance to nevirapine is less likely to develop after single-dose nevirapine in women who do not require therapy during pregnancy than in those who do require therapy.

The group of immunosuppressed women who enrolled in the Thai PHPT follow-up study constitute a minority of those who attend antenatal clinics in developing countries. Recent trials show that between 6 percent and 16 percent of HIV-positive women attending antenatal clinics in Africa have CD4 cell counts of less than 200 per milliliter.

Improving access to antiretroviral agents in developing countries<sup>1</sup> will increase the identification of immunosuppressed women who qualify for HAART. Linkage of care, treatment, and support to programs for the prevention of mother-to-child transmission of HIV-1 should increase the rates of counseling and testing and can be used to identify those who require antiretroviral treatment. HAART will improve the mothers' health and reduce the risk of peripartum (and possibly postnatal) transmission of the virus, since women with advanced HIV-1 disease have the highest risk of transmitting the virus to their infants. For the majority of HIV-positive pregnant women without a clinical indication for HAART, alternative prophylactic regimens, including the addition of single-dose nevirapine to the short course of zidovudine described above, could be chosen by national authorities.<sup>8</sup> As Jourdain et al. themselves recognized, their results are not a reason to abandon single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1. Single-dose nevirapine is a regimen of striking sim-

ilarity, efficacy, and affordability (reminiscent of that of oral poliovirus vaccine). Implementation of even this basic regimen has been hampered by failing health systems in many countries in Africa. Overcoming these barriers and choosing optimal antiretroviral regimens are therefore simultaneous priorities.

Of the estimated 700,000 children who were infected with HIV in 2003,<sup>16</sup> about 315,000 were infected through breast-feeding. The findings of the PHPT Group do not address this massive burden, and to ensure improvement in the overall rate of survival among children, the improved regimen will have to be adapted and used by the majority of HIV-infected women in developing countries who breast-feed.

I am indebted to Lynne Mofenson and Marie-Louise Newell for their helpful suggestions.

From the Nelson Mandela School of Medicine, University of Kwazulu/Natal, Durban, South Africa.

1. World Health Organization. Accelerating HIV prevention in the context of 3 by 5. (Accessed June 7, 2004, at [http://www.who.int/3by5/publications/briefs/hiv\\_prevention/en/](http://www.who.int/3by5/publications/briefs/hiv_prevention/en/).)
2. Lallemand M, Jourdain G, Le 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.
3. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to a nevirapine-based antiretroviral therapy. *N Engl J Med* 2004;351:229-40.
4. Chalermchokcharoenkit A, Asavapiriyant S, Teeraratkul A, et al. Combination short-course zidovudine plus 2-dose nevirapine for prevention of mother-to-child transmission: safety, tolerance, transmission, and resistance results. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8–11, 2004:96. abstract.
5. Dabis F, Ekouévi DK, Rouet F, et al. Effectiveness of a short course zidovudine + lamivudine and peripartum nevirapine to prevent HIV-1 mother-to-child transmission: the ANRS 1201 ditrame-plus trial, Abidjan, Cote D'Ivoire. Presented at the Second International AIDS Society Conference on HIV Pathogenesis and Treatment, Paris, July 13–16, 2003. abstract. (Accessed June 23, 2004, at <http://www.ias2003.org/admin/images/upload/195.pdf>.)
6. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002;288:189-98.
7. Lallemand M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000;343:982-91.
8. World Health Organization. Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-limited settings: expert consultation, Geneva, 5-6 February 2004: a summary of the main points from the meeting. (Accessed June 23, 2004, at [http://www.who.int/3by5/arv\\_pmtct/en/](http://www.who.int/3by5/arv_pmtct/en/).)
9. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 2001;15:1951-7.
10. Eshleman SH, Guay LA, Mwatha A, et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1

6-8 weeks after single-dose nevirapine (HIVNET 012). *J Acquir Immune Defic Syndr* 2004;35:126-30.

11. Lyons F, Coughlan S, Byrne C, et al. Emergence of genotypic resistance in HIV-1-infected pregnant women taking HAART to reduce mother-to-child transmission of HIV-1. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004:892. abstract.

12. Cunningham CK, Chaix M-L, Rekeciewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of Pediatric AIDS Clinical Trials Group protocol 316. *J Infect Dis* 2002; 186:181-8.

13. Fowler MG, Mofenson L, McConnell M. The interface of perinatal HIV prevention, antiretroviral drug resistance, and antiretroviral therapy: what do we really know? *J Acquir Immune Defic Syndr* 2003;34:308-11.

14. Servais J, Lambert C, Karita E, et al. HIV type 1 pol gene diversity and archived nevirapine resistance mutation in pregnant women in Rwanda. *AIDS Res Hum Retroviruses* 2004;20:279-83.

15. Giaquinto C. Genotypic resistance tests for the management of the HIV-infected pregnant patient in Africa. *Scand J Infect Dis Suppl* 2003;106:88-90.

16. AIDS epidemic update. Geneva: UNAIDS, December 2003. (Accessed June 23, 2004, at <http://www.unaids.org>.)

Copyright © 2004 Massachusetts Medical Society.

## Increased Levothyroxine Requirements in Pregnancy — Why, When, and How Much?

Anthony Toft, M.D.

Those with sufficiently long memories must be somewhat bemused by the successive controversies surrounding the treatment of primary hypothyroidism, a condition viewed by many as simple, satisfying to manage, and very much within the purview of the primary care physician, rather than the specialist. The development of sensitive assays for measuring thyrotropin has led to a reduction in levothyroxine doses; in most patients, a dose of only 100 to 125  $\mu\text{g}$  daily restores serum thyrotropin levels to the reference range, thereby satisfying the 1990 recommendations of the American Thyroid Association,<sup>1</sup> which have since been reinforced.<sup>2</sup> There is no consensus, however, about whether treatment with “a little too much” levothyroxine, resulting in a low or undetectable serum thyrotropin concentration, is detrimental in the long run.<sup>3</sup> Nor is there agreement about the effectiveness of combination treatment with levothyroxine and triiodothyronine, prescribed in an attempt to reproduce normal thyroid secretion more closely.<sup>4</sup> In addition, there is now concern that even borderline maternal hypothyroxinemia early in pregnancy may compromise fetal neuropsychological development,<sup>5</sup> inevitably raising the prospect of screening for changes in thyroid function in women of reproductive age.

Early in pregnancy in normal women, as a consequence of the weak thyroid-stimulating activity of chorionic gonadotropin, serum free thyroxine concentrations may increase and thyrotropin concentrations may fall. In a small proportion of women, gestational thyrotoxicosis is the result. For reasons that are not entirely clear, free thyroid hormone concentrations then decrease as pregnancy progresses, necessitating the use of trimester-related reference

ranges. The other important change in thyroid hormone economy is the estrogen-driven increase (by 100 percent or more) in the concentration of thyroxine-binding globulin, the key thyroid hormone-binding protein. It has been determined that ordinarily some two thirds of circulating thyroxine is carried by thyroxine-binding globulin and that the proportion increases to 75 percent during pregnancy.<sup>6</sup> The increased number of binding sites for thyroxine would result in an even more marked fall in serum free thyroxine concentrations during pregnancy, unless there were a compensatory increase in thyroidal secretion and restoration of the equilibrium between the free (metabolically active) hormone and bound hormone. The raised concentration of chorionic gonadotropin may play an important role in this homeostasis. In pregnant women with primary hypothyroidism, however, the thyroid cannot respond to stimulation adequately. Consequently, there is little or no appropriate compensation for the increased availability of binding sites on thyroxine-binding globulin, which effectively “mops up” substantial amounts of free thyroxine.

In this issue of the *Journal*, Alexander et al.<sup>7</sup> elegantly demonstrate the interrelated changes in thyroid hormone, chorionic gonadotropin, and estradiol concentrations in pregnant women who are taking levothyroxine for primary hypothyroidism. The authors not only reaffirm the need for an increased dose of levothyroxine in most such women in order to restore the preconception serum thyrotropin concentration,<sup>8</sup> but they also make the important clinical observation that this increased requirement may be evident as early as the fifth week of gestation — an important time for maternal pro-