

New Options for HIV in Pregnancy Worldwide

BY DIANA MAHONEY
New England Bureau

BOSTON — Short-term treatment with one or more antiretroviral drugs starting in late pregnancy—in addition to or instead of single-dose nevirapine—may reduce the likelihood that HIV-infected women will transmit the virus to their newborns and that the women will develop nevirapine resistance, research has shown.

The practice of giving pregnant women with HIV a single dose of nevirapine (Viramune) during labor has significantly reduced maternal/child transmission rates in the developing world. It also has been heralded as an optimal approach for lowering the transmission rates among women in the United States who are identified as HIV positive very late in pregnancy or at the time of labor, and who also may be unlikely to follow extended treatment regimens because of lifestyle or health care inaccessibility.

There is growing evidence, however, that many women who receive this treatment develop mutated strains of the virus that resist future treatment with nevirapine and, potentially, other drugs, said James McIntyre, M.D., at a conference on retroviruses and opportunistic infections.

"While people have been lauding [single-dose nevirapine] as a stunning breakthrough, others have said it represents a less-than-optimal regimen" to which women in developing countries should not be subjected, said Dr. McIntyre of the perinatal HIV research unit at the University of Witwatersand, Johannesburg, South Africa. "In my country, this has been seen as a U.S. and pharmaceutical company conspiracy."

The value of nevirapine monotherapy should be reassessed, Dr. McIntyre stressed, in light of new evidence suggesting that possible alternatives to the single-dose, single-drug regimen may be as effective at preventing vertical HIV transmission minus the potential for drug resistance.

In one of the studies presented at the conference, which was sponsored by the Foundation for Retrovirology and Human Health, 329 HIV-infected pregnant women in the West African nation of Cote d'Ivoire began therapy with a combination of zidovudine (AZT) and lamivudine (3TC [EpiVir in the U.S.]) in their 32nd week of pregnancy through 3 days post partum, in addition to single-dose nevirapine during labor, reported lead investigator Francois Dabis, M.D., of Victor Segalen University in Bordeaux, France. The newborns in the study were treated with AZT for 1 week and a single dose of nevirapine.

The 6-week HIV type 1 (HIV-1) maternal/child transmission rate was 4.7%, representing "among the lowest transmission rates ever reported in Africa," said Dr. Dabis. Single-dose nevirapine alone typically reduces the transmission rate from an estimated 35% to approximately 12%, he noted. (Maternal/child HIV transmission rates in the United States, where women

have more access to antiretroviral therapy, are approximately 2%, according to CDC data.)

The drop in nevirapine resistance was even more dramatic, with a reported rate among the mothers of 1.1%. Although the exact mechanism for the reduced resistance rate has yet to be identified, the multidrug strategy "may impair the ability of the virus to mutate into a [nevirapine-] resistant strain," according to Dr. Dabis.

A second study of 1,179 live births conducted in Botswana compared the effect of giving HIV-infected mothers multiweek zidovudine alone versus giving it in combination with single-dose nevirapine. Initially, each mother in the study was given zidovudine from 34 weeks' gestation and each mother/infant pair was randomized to receive blinded maternal and infant single-dose nevirapine or maternal and infant placebo. The study protocol was changed at 17 months because the infant nevirapine placebo was deemed unethical. Under the revised protocol, all infants received nevirapine as soon as possible after birth, while half of the mothers still got placebo, explained lead investigator Roger Shapiro, M.D., of Beth Israel Deaconess Medical Center in Boston.

Before the revision, the 1-month HIV transmission rates in 485 births were 5.3% in babies given nevirapine and 6.2% in babies who received placebo. In the 694 births that occurred during the revised study period, the 1-month transmission rates were 3.7% in babies born to mothers who received nevirapine and 4.3% in babies born to mothers given a placebo. The overall transmission rate for the entire study was approximately 4%, Dr. Shapiro said.

The results suggest that maternal single-dose nevirapine may not be needed to reduce mother/child transmission rates when both mother and infant are treated with zidovudine and when the infant receives nevirapine at birth—an important possibility, given that a substudy of the investigation found that 44% of the women who received the single-dose nevirapine developed resistance mutations, Dr. Shapiro noted.

Although the findings from both studies are promising, "the translation from trials to programs is incredibly challenging," said Mary Glenn Fowler, M.D., chief of maternal-child transmission, Centers for Disease Control and Prevention, Atlanta. "It's important not to be rapidly overoptimistic. We need to see what happens when those women start therapy [after delivery]."

Advocates for AIDS research and treatment agree. A press release issued by the Elizabeth Glaser Pediatric AIDS Foundation stressed the importance of preserving single-dose nevirapine as an option: "Even simple interventions like nevirapine are still available to less than 10% of the women who need them worldwide. Therefore, we must continue to aggressively expand access to services and improve our ability to offer the most effective drug regimens in all instances." ■

Proinflammatory Cytokine Tied To Depression in Pregnancy

BY ERIK GOLDMAN
Contributing Writer

NEW YORK — Macrophage migration inhibitory factor, a newly characterized cytokine that inhibits cortisol and increases production of inflammatory cytokines, may be the key to understanding depression during pregnancy, Brad D. Pearce, Ph.D., said at a symposium sponsored by the National Alliance for Research on Schizophrenia and Depression.

Pregnant women seeking treatment for major depression have markedly higher levels of macrophage migration inhibitory factor (MIF) than do nondepressed pregnant women of similar age. In general, MIF levels are slightly elevated in pregnant vs. nonpregnant women, but the difference is insignificant compared with the difference between depressed and nondepressed pregnant women, said Dr. Pearce of the department of psychology at Emory University, Atlanta.

"We all hear that pregnancy is a time of joy, a natural high, and that pregnancy-related hormones are protective. The data, however, collide with these truisms," said Dr. Pearce, noting that roughly 7% of all American women experience episodes of major depression during their first pregnancies. The proportion increases to 12%-14% for second and third pregnancies.

The prevalence of major depression among nonpregnant women is roughly 8%. So, on a statistical basis, pregnancy is hardly protective and may actually increase the incidence of depression, particularly in multiparous women, he said.

"There are some very big changes in body chemistry during pregnancy. The shift in the balance of hormones, cytokines, cortisol, and many other things can be huge and very complex. Some women feel bliss; many others become depressed," he noted.

Depression during pregnancy can have significant complications: It is predictive of preterm labor and delivery, as well as other obstetrical complications, and is linked to an increased risk of behavioral and social problems in the children. "The physiological changes caused by depression during pregnancy result in changes in maternal-fetal interaction, which can

have adverse effects on the fetal brain," Dr. Pearce said.

Antidepressant drug therapy, however, is not a neutral, risk-free proposition during pregnancy. Although none of the major antidepressant drug classes is considered strongly teratogenic, many commonly used medications have been linked to adverse obstetrical outcomes, including preterm delivery.

Dr. Pearce and his colleagues at Emory have been looking at potential biologic mediators involved in depression during pregnancy with the hope of eventually identifying targets for novel treatment strategies.

They've focused largely on inflammatory cytokines, many of which are consistently elevated among individuals with major depression. Patients with chronic inflammatory disorders, characterized by elevated cytokine levels, often have comorbid depression. Some cytokines used as drugs in the treatment of serious illnesses like cancer can actually induce symptoms of depression if given intravenously.

MIF is a fairly recent discovery, and it has attracted considerable attention among immunologists and infectious-disease researchers. "It is a very unique protein. It is not like any of the other cytokines. It is really in its own family," Dr. Pearce said.

MIF is produced endogenously by a number of different immune cells and appears to block the action of cortisol. This results in an overall up-regulation of inflammation because cortisol normally inhibits inflammatory signaling molecules. MIF is also a modulator of catecholamine metabolism. Interestingly, MIF is also produced in large quantities by the hippocampus. "Nobody knows yet what it is doing there in the brain," he said.

If the connection between elevated MIF levels and depression in pregnancy is borne out in future studies, Dr. Pearce believes that MIF may be useful as a prognostic marker for both depression and pregnancy complications like preterm labor. Prepregnancy depression predicts depression during and after pregnancy, he said.

"It seems that MIF levels predict postpartum outcomes," Dr. Pearce commented. ■

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'Continuing to debate these early papers is like doing a thesis on the Wright brothers' first flight when you already have a 747 that flies.'

Peter Levine, CEO of Correlogic Systems Inc.

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