International HIV trial is halted

On October 27, 2010, DH pediatrician Paul Palumbo, M.D., got some surprising news. A study he'd been leading in Africa and India to identify new treatments for HIV-infected children was being halted by its data and safety monitoring board. The new regimen was working so much better than the standard therapy in treating the infants enrolled in the study that the board decided the trial should be stopped so all the subjects could benefit from the new therapy.

"We were a little surprised, anticipating the trial would run to March of 2011," Palumbo says. "We didn't expect such a superior difference."

Palumbo and his colleagues in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) found that a drug called lopinavir was far better than the standard therapy, nevirapine, at preventing transmission of HIV to infants with no previous exposure to nevirapine. The study was carried out in South Africa, Zimbabwe, Zambia, Malawi, Uganda, Tanzania, and India. The results, Palumbo says, "turned the whole treatment world on its head."

Phase: It wasn't the first time Palumbo and IMPAACT have caused a stir. In the spring of 2009, an earlier phase of the trial, involving a different group of children, was halted by the safety board. The children in this earlier phase were also given either lopinavir or nevirapine, but they had already been exposed to nevirapine. For many years, nevirapine has been the standard approach in Africa to trying to prevent the transmission of HIV from mother to child. One problem with the drug is that in many people, HIV eventually develops resistance to it, decreasing the drug's effectiveness.

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The initial phase of the first trial involved 164 HIV-infected children aged 6 to 36 months. All had previously received a single dose of nevirapine in liquid form at birth, and their mothers had taken nevirapine in pill form during labor. All of the children received the antiretroviral drugs zidovudine and lamivudine; half also received nevirapine, and the other half lopinavir. The combination including lopinavir was so effective that the World Health Organization (WHO) began to recommend that whenever possible, infants with HIV infection and exposure to nevirapine at birth start a regimen including lopinavir.

Lead: The results of that initial phase were published in the *New England Journal of Medicine* last fall. Palumbo, as lead author for IMPAACT, cited the need for wider use of lopinavir in combination with zidovudine and lamivudine "for the prevention of HIV transmission from mother to child, as well as for the treatment of HIV infection."

An accompanying editorial praised the IMPAACT results, as well as those of a related study. "These studies help equip us with strategies to deal with the current imperfections in our scale-up efforts," the editorial noted. "With the new WHO guidelines calling for increased access to therapy and prophylaxis . . . the goal of eradication of pediatric HIV is within sight."

Within distant sight, Palumbo cautions, especially in sub-Saharan Africa and India. "Nevirapine is relatively cheap to produce and distribute," he says. But the lopinavir combination "is four times more expensive and . . . doesn't do well in high-temperature environments without much refrigeration."

Maladies: Clinicians and researchers face other challenges, too. For example, breastfeeding by an HIV-positive mother can lead to infection of the infant, but the mother's milk also strengthens the baby's immune system, Palumbo says, protecting the child against many common infections. Formula feeding to prevent HIV transmission—a common practice in the developed world—leaves infants in developing countries prone to diarrhea, upper-respiratory infections, and other maladies.

In other words, AIDS is only one of a number of dangerous diseases such children face. WHO and the United Nations Children's Fund estimated in 2009 that, worldwide, over nine million children younger than five are expected to die each year—17% from pneumonia, 17% from diarrhea, and 7% from malaria, compared to only 1.5% from HIV/AIDS. And IMPAACT estimates that at least 10% of enrollees in the trial already may be suffering from tuberculosis.

Quandary: These and other difficulties underscore the quandary for clinicians and researchers who work with patients in countries with limited resources—prevention versus treatment. "We're left with what to do in the real world," Palumbo says. He adds that new treatments can take a long time to gain acceptance. The regimen including nevirapine, for example, took nearly a decade to be accepted.

"We're right in the middle of this active debate," Palumbo says. "The question is, how fast can we do it? Can scientific mandates be translated into practice?" David Corriveau

JON GILBERT FOX

Palumbo says the new HIV regimen was so "superior" that the trial was halted.