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Latest findings of Dartmouth HIV/AIDS study could turn treatment 'on its head'

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A clinical study of anti-HIV/AIDS medicines in the developing world is on the verge of turning "the whole treatment world on its head," according to Dartmouth pediatrician Paul Palumbo.

Palumbo, a professor of pediatric medicine at Dartmouth Medical School and executive director of the Dartmouth-affiliated DarDar Pediatric program in Dar-es-Salaam, Tanzania, unveiled the latest findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) during the 2011 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston from February 27-March 2.

Before making a formal, "late-breaking" presentation about IMPAACT's findings in Africa and India to fellow clinicians and researchers at CROI, Palumbo also shared, under confidentiality restrictions, the revelations with representatives of the World Health Organization (WHO) and of a working group of pharmaceutical leaders and officials of the U.S. State Department.

The IMPAACT P1060 trials – comparing the effects of different forms of treatment on infants and young mothers – began in 2006, with support from the National Institute of Allergy and Infectious Disease (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). On October 27, 2010, an independent data and safety monitoring board (DSMB), which confidentially reviews large clinical trials on an interim basis for safety and efficacy of drugs,

halted the second phase of P1060, declaring that the protease inhibitor lopinavir (LPV/r) was working so well among infants with no previous exposure to the popular anti-retroviral nevirapine (NVP) that the IMPAACT team didn't need to go further in the head-to-head trials between LPV/r and NVP to prove their point.

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

This was the second time that IMPAACT, which Palumbo serves as a vice chair, turned heads: In the spring of 2009, the DSMB halted the first phase of the P1060 trial involving 164 HIV-infected children ages 6 to 35 months, after learning that a cohort of 82 youngsters responded better to treatment with LPV/r than did a cohort of 82 children in the same age group who had received NVP.

The difference from the current study cohort was that all 164 children in the first-phase cohort had previously received a single dose of NVP in liquid form at birth, and their mothers had taken NVP in the form of a single pill during labor in an effort to prevent transmission of HIV. When these children, who were HIV-infected despite efforts to prevent mother-to-child transmission, later required HIV treatment, they were enrolled into the P1060 trial and randomly assigned to therapy with the antiretroviral drugs Zidovudine and Lamivudine, plus either NVP or LPV/r – the latter also known as Kaletra.-- The treatment with LPV/r proved superior enough for WHO to recommend that infants with HIV infection and exposure to NVP at birth start on an LPV/r-based regimen whenever possible.

The DSMB then gave IMPAACT the go-ahead to continue to enroll children who did not receive NVP at birth into the second-phase cohort. And in October of 2010, a couple of weeks before the DSMB halted the second phase, the New England Journal of Medicine (NEJM) published

IMPAACT's first-phase study results. In an editorial accompanying the NEJM study, authors Marc Lallemant, M.D., and Gonzague Jourdain, M.D., praise the IMPAACT findings and those of a trial with HIV-infected mothers that another group of researchers conducted.

"These studies help equip us with strategies to deal with the current imperfections in our scale-up efforts," the authors write. "With new WHO guidelines calling for increased access to therapy and prophylaxis … the goal of eradicating 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," Palumbo says. "Kaletra (LPV/r) is four times more expensive, and it needs a little help because it doesn't do well in high-temperature environments without much refrigeration. Much of the world is used to having access to something inexpensive. [The Kaletra findings] turned things upside-down."

Those and other facts underscore a continuing quandary for clinicians and researchers working with patients in "resource-limited countries," Palumbo says – prevention versus treatment. The NVP regimen needed nearly a decade to gain acceptance.
"We're left with what to do in the real world," Palumbo says. "We're back to the WHO. … It's been very slow getting this off the ground."

Provided by Dartmouth-Hitchcock Medical Center