# Trial in youngest group points to HIV treatment overhaul

BOSTON — By some estimates, around 1,800 children, mostly newborns, become infected with HIV each day. But even though the stakes are high, the most commonly used strategy to combat the deadly virus among infected children in resource-limited countries may need a massive overhaul. According to data presented here last month at the Conference on Retroviruses and Opportunistic Infections, babies born with HIV should immediately start receiving antiretroviral drugs known as protease inhibitors, not the reverse transcriptase inhibitor widely used throughout the developing world.

"We have created a bit of a stir at the guideline level moving forward," says Paul Palumbo, a pediatrician at Dartmouth Medical School in Hanover, New Hampshire. "We need to move into considerations of using [protease inhibitors] as a first-line therapy."

The reverse transcriptase–blocking drug nevirapine, marketed as Viramune by the German company Boehringer-Ingelheim, is the cornerstone of both preventing mother-to-child transmission of HIV and treating infections in affected infants in the third world, where the vast majority of the world's 2.1 million HIV-positive children live. But in children who become infected despite receiving nevirapine as prophylaxis, the drug often selects for resistant viruses. To avoid using the same medicine for prophylaxis and treatment, researchers have sought a different drug regimen for kids once they become infected, and a protease inhibitor called Kaletra—a formulation of ritonavir-boosted lopinavir developed by Chicago-based Abbott Laboratories—has emerged as the front-runner.

Last year, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group, for which Palumbo serves as a vice chair, showed that Kaletra repressed viral loads better than nevirapine in HIV-positive youngsters who had previously been exposed to the latter drug (*N. Engl. J. Med.* **363**, 1510–1520, 2010). In response, the World Health Organization (WHO) recommended that Kaletra should be used among nevirapine-exposed kids. But, owing to logistical concerns and a lack of data demonstrating Kaletra's general superiority, the agency stopped short of advocating Kaletra as a first-line treatment for all HIV-infected children.

Now, in the first head-to-head trial of the two drugs conducted anywhere in the world for young children not previously exposed to nevirapine, the IMPAACT team found that Kaletra led to half as many drug failures as nevirapine among close to 300 infants under the age of three at ten study sites across sub-Saharan Africa and India.

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**Newborn notions:** Experts are rethinking HIV treatments for infants.

"Kaletra is really the drug that you should use to treat young children regardless of their exposure to nevirapine," says Marc Lallemant, an epidemiologist at the Institute for Research and Development in Marseilles, France who was not involved in the trial.

Shaffiq Essajee, a medical officer with the WHO's AIDS treatment and care unit who specializes in pediatric HIV, says that agency officials are now mulling over whether to advise Kaletra for all HIV-infected infants under the age of three. "It's certainly something that we're looking at with a good deal of interest," he says. However, he notes that "it's important that those recommendations be looked at in a national context and they reflect a resource environment that's especially constrained."

## Unexpected findings

The results of the latest trial are surprising. In February, researchers reported that nevirapine- and Kaletra-based treatments were equally effective in suppressing viral load in a study of 266 previously untreated HIV-infected children aged three to 13 from Europe and the Americas (*Lancet Infect. Dis.* doi:10.1016/S1473-3099(10)70313-3, 2011). And, last October, a study of 500 African women without prior exposure to nevirapine also revealed comparable efficacy rates (*N. Engl. J. Med.* **363**, 1499–1509, 2010).

So, why did the drugs work differently in the younger cohort? "Young children are more like adults with acute infection," says Lynne Mofenson, head of the Pediatric, Adolescent & Maternal AIDS Branch at the US National Institute of Child Health & Human Development in Bethesda, Maryland and a project officer for the IMPAACT group. Mofenson notes that infants tend to have elevated viral counts and highly compromised immune systems, "so they're much less able to control the virus than adults or older children."

Doctors are now calling for new guidelines to reflect the recent findings. "There's evidence of superiority, so that stands as a push to get changes at a local level," says Jane Achan, a pediatrician at Makerere University in Kampala, Uganda who is leading a study testing the safety and efficacy of switching from a regimen of nevirapine to Kaletra among HIV-infected children in eastern Uganda.

However, logistical challenges might preclude a large rollout of Kaletra, as the drug has an unpleasant taste, must be refrigerated and costs four times as much as nevirapine. (Last year, UNITAID and the William J. Clinton Foundation negotiated a price of $53 per year for pediatric nevirapine in developing nations, compared with $220 annually for Kaletra). What's more, switching back and forth between the drugs could have drawbacks. Data presented at the meeting by Louise Kuhn, an epidemiologist at Columbia University's Mailman School of Public Health in New York, indicates that, whereas going back to the cheaper nevirapine after a few months of Kaletra lowers viral load further in most kids, in a small subset it can lead to more instances of elevated blood levels of the virus.

"So it's not just a simple 'this is better than that and so everyone should change,'" notes Mofenson. "It requires a global look based on the results of this trial and how can we best implement this."

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