Landmark study defines benefits of early HIV testing and treatment for infected infants

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Testing very young babies for HIV and giving antiretroviral therapy (ART) immediately to those found infected with the virus dramatically prevents illness and death, according to a report in the *New England Journal of Medicine*. The study found that giving ART to HIV-infected infants beginning at an average age of 7 weeks made them four times less likely to die in the next 48 weeks, compared with postponing ART until signs of illness or a weakened immune system appeared--the standard of care when the study began.

These findings come from the "Children with HIV Early Antiretroviral Therapy" (CHER) study, the first Phase III randomized clinical trial to study the best time to begin ART in infants. Launched in South Africa in July 2005, CHER is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and the departments of health of the Western Cape and Gauteng in South Africa.

"HIV devastates the nascent immune systems of infants very quickly, yet too many HIV-infected infants do not get tested for the virus, get tested too late or get tested but lack access to lifesaving antiretroviral drugs," says Anthony S. Fauci, M.D., the director of NIAID. "The results of CHER are a clarion call to scale up widespread early HIV testing of at-risk infants and to make ART immediately accessible to all infants who test positive."

Preliminary results of CHER, released in July 2007, showed that HIV-infected infants were four times less likely to die if given ART immediately after HIV diagnosis (http://www3.niaid.nih.gov/news/newsreleases/2007/cher.htm). This finding helped influence the World Health Organization (WHO) to change its guidelines for treating HIV-infected infants. The new guidelines, issued in April 2008, strongly recommend starting ART in children under age 1 immediately after HIV diagnosis, regardless of their state of health. An NIAID study to identify the best drug regimen for these highly vulnerable children is under way.

"The new WHO guidelines will profoundly improve the survival rate and quality of life of infants born with HIV," says Ed Handelsman, M.D., chief of the Pediatric Medicine Branch in NIAID's Division of AIDS. "We are excited that we know the best time to begin treating HIV-infected infants; the challenge now for the global community is to ensure that all HIV-infected infants who need ART receive it soon enough."

The CHER study team, lead by Avy Violari, FCPaed, and Mark F. Cotton, MMed PhD, recruited and enrolled 377 infants between 6 and 12 weeks of age who had confirmed HIV infection but normal immune system development. Originally, the infants were randomly assigned to one of three regimens: start ART immediately and continue for 40 weeks; start ART immediately and continue for 96 weeks; or defer ART until signs of clinical or immunological progression to AIDS appeared. The ART regimen consists of ritonavir-boosted lopinavir, zidovudine and lamivudine, provided by GlaxoSmithKline PLC of Britain and the South African Department of Health. CHER is being conducted at two locations in South Africa: the Perinatal HIV Research Unit of the University of Witwatersrand; and the Children's Infectious Diseases Clinical Research Unit of Tygerberg Children's Hospital and Stellenbosch University. These sites are collaborating with the Medical Research Council Clinical Trials Unit in London.

In June 2007, a data and safety monitoring board (DSMB) overseeing CHER found that the babies who received immediate ART were four times less likely to die than the babies whose treatment was deferred. This was true even though 66 percent of those in the deferred treatment arm had met the criteria for ART during the first 32 weeks of the trial and already had begun treatment. Consequently, the DSMB recommended, and NIAID agreed, to assess all the children in the deferred-treatment arm for potential initiation of ART.

The study measured the effectiveness of the treatment strategies by counting the number of babies who died or whose immune systems were not protected by the original ART regimen. After a median of 48 weeks, 10 of 252 infants (4 percent) in the immediate-treatment arms had died, as had 20 of 125 (16 percent) infants in the deferred-treatment arm. Thus, immediate ART reduced deaths by 75 percent. As a secondary measure of success or failure, CHER counted the number of infants who developed HIV-related disease. Such disease developed in 16 babies (6.3 percent) in the immediate-treatment arms and 32 babies (26 percent) in the deferred-treatment arm. Thus, the infants who received treatment immediately were more than four times less likely to develop HIV-related disease.

Reference: A Violari et al. Early antiretroviral therapy reduces mortality in HIV-infected infants: evidence from the CHER trial. New England Journal of Medicine DOI 10.1056/NEJMoa0800971 (2008).

Source: NIH/National Institute of Allergy and Infectious Diseases