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International HIV/AIDS Trial Finds Continuous Antiretroviral Therapy Superior to Episodic Therapy

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), today announced that enrollment into a large international HIV/AIDS trial comparing continuous antiretroviral therapy with episodic drug treatment guided by levels of CD4+ cells has been stopped. Enrollment was stopped because those patients receiving episodic therapy had twice the risk of disease progression (the development of clinical AIDS or death), the major outcome of the study.

NIAID made the decision to halt enrollment in collaboration with the study's Executive Committee and following a recommendation received from an independent Data and Safety Monitoring Board (DSMB). The DSMB, charged with regularly evaluating data and safety issues during the multi-year trial, conducted a review of the interim study data in early January.

The trial, known as Strategies for Management of Anti-Retroviral Therapy, or SMART, was designed to determine which of two different HIV treatment strategies would result in greater overall clinical benefit. HIV-positive volunteers were assigned at random to either a viral suppression strategy, in which antiretroviral therapy (ART) was taken on an ongoing basis to suppress HIV viral load; or a drug conservation strategy, in which ART was started only when the levels of key immune cells, called CD4+ cells, dropped below 250 cells per cubic millimeter (mm^3). Volunteers in the drug conservation group were taken off ART—with the aims of reducing drug side effects and preserving treatment options—whenever their CD4+ cells were above 350 cells/mm^3. (For more details see http://www.smart-trial.org).

The trial involved an international collaboration of 318 clinical sites in 33 countries. It began enrollment in January 2002 and had successfully recruited more than 90 percent of its target of 6,000 participants: as of January 11, 2006, when enrollment was stopped, 5,472 volunteers had joined the study.

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At the time of the DSMB review, the average follow-up was approximately 15 months. The analysis revealed that participants on CD4+ cell-guided episodic treatment faced more than twice the risk of disease progression relative to participants on continuous ART. Furthermore, there was an increase in major complications such as cardiovascular, kidney and liver diseases in the participants on the drug conservation arm. These complications have been associated with ART, and it was hoped that they would be seen less frequently in those patients receiving less drug.

Although the risk-to-benefit ratio of drug conservation over the longer term remains uncertain, the DSMB recommended that enrollment into the trial be halted in light of the findings to date, and the SMART Executive Committee and NIAID agreed with the recommendation. Upon reviewing the results, the Executive Committee also conveyed to local study investigators its recommendation that it would be prudent to re-initiate therapy in ART-experienced patients in the drug conservation arm. All study physicians and participants are being notified of the findings and recommendations.

Follow-up visits will continue for all participants in the SMART trial while the study team considers plans for longer follow-up.

The investigators will analyze the SMART study data in detail to gain insights into the reasons for the increased risk.

“SMART is one of the largest HIV/AIDS treatment trials ever conducted,” notes NIAID Director Anthony S. Fauci, M.D. “The study reflects an extraordinary global collaboration among hundreds of dedicated AIDS clinicians and thousands of their patients, all of whom should be commended for their exceptional achievement in contributing to this pivotal HIV/AIDS treatment study.”

“This trial was designed to help physicians and their HIV-positive patients identify the best approach to treatment management,” adds Wafaa El-Sadr, M.D., M.P.H., M.P.A., of the Harlem Hospital Center and Columbia University in New York City, one of the principal investigators for the trial. “We were surprised to learn that in the short term, episodic antiretroviral therapy carries such an increased risk without evidence of sparing patients the known side effects associated with ART.”

The University of Minnesota’s James Neaton, Ph.D., another principal investigator and chief biostatistician for the trial, notes, “The SMART trial reached a conclusion much earlier than we expected. That is the significant value and potential power of conducting such a large trial.”

The SMART study was coordinated by four international centers: the Medical Research Council Clinical Trials Unit in London; the Copenhagen HIV Program in Denmark; the National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales in Sydney, Australia; and

the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) in Washington, DC. The statistical and data management center was based at the University of Minnesota in Minneapolis.

Fred Gordin, M.D., of the VA Medical Center in Washington, DC, the CPCRA director, says, "It is gratifying when the fruits of such hard work by so many individuals and the faith put in the investigators by the volunteers results in important data concerning the use of ART."

David Cooper, M.D., D.Sc., of the National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales, the Sydney international coordinating center director, notes, "SMART is an example of how a large group of investigators around the world can work together to obtain an answer to an important HIV treatment question."

Further information concerning the study findings can be found in a Questions and Answers document (http://www.nih.gov/news/pr/jan2006/niaid-18.htm). An earlier NIAID news release describing the initiation of the SMART trial can be viewed at http://www3.niaid.nih.gov/news/newsreleases/2002/smart.htm.

NIAID is a component of the National Institutes of Health, an agency of the U.S. Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies.

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