



National Institute of Allergy and Infectious Diseases
National Institutes of Health

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QUESTIONS AND ANSWERS

**A Large International HIV/AIDS Study Comparing Two Strategies for
Management of Anti-Retroviral Therapy
(The SMART Study)**

The related SMART study news release can be found at
<http://www.nih.gov/news/pr/jan2006/niaid-18.htm>.

1. What is the SMART trial?

The Strategies for Management of Anti-Retroviral Therapy (SMART) trial is a large international trial designed to determine which of two distinct HIV treatment strategies yields a better clinical outcome over the long term. The trial enrolled HIV-positive participants with CD4+ cell counts of more than 350 cells per cubic millimeter (mm³) of blood. (CD4+ cells are a type of infection-fighting white blood cell and are a primary target of HIV.) Volunteers were randomized to receive one of two antiretroviral treatment (ART) strategies: continuous drug therapy, designed to suppress viral load as much as possible (the viral suppression, or VS, arm); or episodic ART (the drug conservation, or DC, arm). The use of ART in the DC arm was determined by the participant's CD4+ cell count: trial participants in the DC arm began ART when CD4+ cell counts fell below 250 cells/mm³, with the aim of suppressing viral load and increasing the CD4+ cell count, and discontinued ART when counts were above 350 cells/mm³.

Enrollment in SMART began in January 2002 (<http://www3.niaid.nih.gov/news/newsreleases/2002/smart.htm>). Full enrollment of 6,000 participants was expected to take 3 to 5 years. As of January 11, 2006, when enrollment was stopped, more than 90 percent of the volunteers had been enrolled.

2. What were the rationale and primary objectives of the SMART trial?

Widespread use of ART in economically developed countries has resulted in a significant decline in HIV-related illness and death. However, ART effectiveness may wane over time as the virus becomes resistant to drugs. There are also short- and long-term toxicities, as well as cost and quality-of-life issues, associated with lifelong ART. Therefore, a randomized clinical trial was implemented comparing the use of CD4+ cell-guided episodic ART (DC strategy) with continuous ART (VS strategy).

The SMART trial was designed to compare the DC strategy with the VS strategy for progression to AIDS or death over a minimum follow-up period of 6 years for each patient. It was hypothesized that the DC strategy would result in lower rates of disease progression and serious toxicities as compared to the VS strategy in the planned follow-up period ranging from 6 to 9 years.

3. Who is conducting this study and where?

The Terry Bein Community Programs for Clinical Research on AIDS (CPCRA, <http://www.cpcra.org>) was funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, to conduct the study. The CPCRA is conducting this study, known as CPCRA 065, in collaboration with the Copenhagen HIV Programme in Denmark (CHIP, <http://www.cphiv.dk>); the Medical Research Council Clinical Trials Unit in London (MRC, <http://www.ctu.mrc.ac.uk>); and the National Centre in HIV Epidemiology and Clinical Research at the University of New South Wales in Sydney, Australia (NCHECR, <http://web.med.unsw.edu.au/nchechr>). As of January 11, 2006, 5,472 volunteers had been enrolled at 318 sites in 33 countries. Sites are located in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Lithuania, Luxembourg, Morocco, New Zealand, Norway, Peru, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Thailand, United Kingdom, United States, and Uruguay.

4. What is the Data and Safety Monitoring Board, and how does it monitor this study?

The Data and Safety Monitoring Board (DSMB) is an independent committee composed of clinical research experts, statisticians, ethicists, and community representatives. The DSMB reviews data while a clinical trial is in progress to ensure the safety of participants. The DSMB may recommend that a trial, or part of a trial, be stopped if there are safety concerns or if the trial objectives have either been achieved or are unlikely to be achieved. The DSMB looks at analyses that are not available to the investigators or to anyone else. The SMART study was monitored at a minimum annually by an NIAID DSMB.

5. What were the results of the most recent DSMB review?

The DSMB for the SMART trial reviewed interim data from this study in early November 2005 and in early January 2006. At the time of their January review, the average follow-up was approximately 15 months; some patients had been followed for approximately 3.5 years. The data at the last review indicated that volunteers in the DC arm of the trial had more than twice the risk of progression to AIDS or death compared with individuals in the VS arm.

6. What actions were taken by the DSMB and the SMART Executive Committee?

On January 10, 2006, the DSMB informed the Executive Committee that there was an increased risk of disease progression in the DC group, and that it appeared very unlikely that the DC arm would be found to be superior to the VS strategy in the planned follow-up period

of the trial. The DSMB recommended that enrollment into the trial be stopped and that steps be taken to minimize risks to patients. The SMART Executive Committee decided to recommend to site investigators that treatment-experienced patients in the DC arm who were not taking ART be re-started on therapy.

On January 11, 2006, the Executive Committee informed the SMART trial investigators of 1) the increased risk of disease progression and other clinical events in the DC arm; 2) treatment recommendations for patients in the DC arm; and 3) the decision to stop enrollment.

Study participants are currently being notified of the findings and recommendations.

7. What does the SMART Executive Committee recommend for study participants?

Individuals currently enrolled in the VS arm of the study will continue to receive care from their primary care physician and will continue with the VS strategy as defined in the study.

Participants in the DC arm who are currently on ART will be advised to stay on treatment. Those participants in the DC arm who are currently off ART, but who have taken ART in the past, are being advised to review with their physicians the option to re-start ART. While the long-term risks and benefits of the DC arm remain uncertain, the short-term information indicates that it would be prudent to re-start ART.

Because the study findings do not address the question of when to start ART, it is advised that the decision to initiate ART for those participants in the DC arm who have never been on ART should be based on local treatment guidelines on when to initiate ART.

Follow-up visits will continue for all participants in the SMART trial while the study team considers plans for longer follow-up. Data collection (such as case report forms and laboratory reports) will continue for all enrollees as specified by the trial protocol.

8. How might these new findings affect the management of HIV disease?

The current U.S. Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Oct. 6, 2005) state: "Several clinical trials have been conducted to better understand the role of treatment interruption in these patients, yielding conflicting results. The Panel [the Panel on Clinical Practices for Treatment of HIV Infection convened by DHHS] notes that partial virologic suppression from combination therapy has been associated with clinical benefits, thus interruption is generally not recommended unless it is done in a clinical trial setting."

The data from the SMART trial provide evidence that episodic use of ART based on CD4+ cell levels as used in the study is inferior to use of continuous therapy for treatment-experienced patients and thus should not be routinely recommended.

9. What were some of the key baseline characteristics of the trial participants?

- The overwhelming majority (95 percent) of SMART participants have had some experience with ART (a median of six years of ART use prior to enrollment).
- Median baseline and nadir CD4+ cell counts of study participants were 598 and 253 cells/mm³, respectively.
- Seventy percent of the participants had an HIV viral load < 400 copies/milliliter at baseline.
- The average age of enrollees at study entry was 46 years.
- Twenty six percent of the participants are women.
- Thirty-one percent of participants are black, and 69 are white or of another race or ethnicity.
- Fifty-five percent of participants were enrolled by sites in the United States, 26 percent by sites in Europe, and the remainder from the other countries.

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NIAID is a component of the National Institutes of Health (NIH), 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.