



**For immediate release  
18 January 2006**

**CONTACT: Richard Jefferys  
212.253.7922**

**Treatment Action Group Statement on the  
Termination of the SMART Study**

**New York NY, January 18, 2006** – The Treatment Action Group (TAG) today expressed disappointment that SMART – a large, international study comparing CD4-guided, intermittent antiretroviral therapy to continuous treatment – has had to be stopped due to a significantly higher incidence of clinical events in the intermittent treatment arm. TAG salutes the many researchers and participants involved in this large and important trial of HIV treatment strategies. However, TAG also wishes to stress that the conclusion being promulgated by the National Institutes for Allergy & Infectious Diseases (NIAID), “International HIV/AIDS Trial Finds Continuous Antiretroviral Therapy Superior to Episodic Therapy” (see <http://www.nih.gov/news/pr/jan2006/niaid-18.htm>), could be over-interpreted. SMART has shown that, over the short term, continuous therapy is superior *to the specific strategy of episodic therapy employed in the trial.*

SMART evaluated a “drug conservation” approach that involved interrupting therapy when CD4 counts crested 350 cells and restarting when they fell below 250, and compared this to a standard “virological suppression” strategy using continuous therapy. The primary endpoints were progression to AIDS and death in the two arms, with secondary endpoints including incidence of potentially drug-related toxicities such as cardiovascular disease and liver problems. The study was addressing an important question because, while it is known that continuous therapy is beneficial in the short term, it remains unknown whether there is a point at which long term toxicities become a greater risk than events related to disease progression. It is also not known if intermittent CD4-guided therapy might be a less costly and toxic strategy for preventing disease progression. The study has reportedly been stopped by the Data Safety Monitoring Board (DSMB) due to roughly twice as many clinical events occurring in the drug conservation arm compared to the virological suppression arm. The nature and seriousness of the clinical events in question remain unknown at this time. Perhaps surprisingly, it is also reported that there was a higher incidence of events relating to drug toxicity in the drug conservation arm.

It is important to emphasize that the cessation of SMART does not necessarily mean that all treatment strategies involving interruptions of antiretroviral therapy are dangerous, just that the specific approach employed by the SMART study design was less successful at preventing clinical events than continuous treatment. There is a large body of data suggesting that individuals who initiate therapy with relatively

high CD4 counts (for whom therapy would no longer recommended based on recent guidelines) can safely interrupt therapy.

Previous treatment interruption studies have also uniformly identified the CD4 nadir (lowest ever CD4 count, usually experienced before any antiretroviral therapy was initiated, or after virologic treatment failure) as a predictor of clinical events during treatment interruption and the SMART study accepted participants without regard to their CD4 nadir.

One of the key goals of the SMART study was to answer the question of whether less exposure to antiretroviral therapy would reduce the incidence of potentially life-threatening drug-associated toxicities. Recent data has emphasized the importance of addressing this question, suggesting that such toxicities can pose a greater risk for individuals on therapy than clinical events related to disease progression (see Reisler et al, *JAIDS* 34;4:379-386, 2003). In light of this fact, TAG strongly believes that further studies of treatment interruption and intermittent therapy strategies, addressing questions different from those addressed by SMART, continue to be warranted. Data from the SMART study should be used to design potentially safer approaches to CD4-guided therapy, with particular attention paid to the impact of CD4 nadir and the CD4 threshold for restarting therapy on the outcome of SMART. Ongoing trials of treatment interruption strategies, such as the international DART trial, should be reviewed in order to establish whether the data from SMART impacts the study design, but it would be premature to cease all investigation of intermittent treatment strategies because of the results from SMART.

The early cessation of SMART also means that the long term incidence of toxicity-related events among individuals on continuous antiretroviral therapy in this study will not be quantified unless follow-up is continued. TAG urges to the study sponsors to follow-up study participants for long term outcomes.

The SMART study was designed and conducted by the Community Programs for Clinical Research on AIDS (CPCRA), an international network of clinical trial sites funded by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH). TAG has been a strong supporter of the SMART study and believes that it asked and answered a question of paramount importance in the search for optimal antiretroviral treatment strategies, balancing the need to preserve immune function with that of avoiding unnecessary toxicity and expense.

Well designed studies that ask and answer important questions in a reliable, definitive way with adequate sample size, statistical power, participant retention, and length of follow-up are all too rare in the HIV field. The NIH should be commended for supporting, and the CPCRA for designing and executing this important study, which adds to our understanding of the optimal ART standard of care.

**About TAG.** The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and health care delivery systems. We meet with researchers, pharmaceutical companies, and government officials to encourage exploration of understudied areas in AIDS research and speed up drug development, approval, and access. We work with the World Health Organization and community organizations globally, and strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

**Richard Jefferys** is the Director of the Michael Palm Basic Science, Prevention, and Vaccines Project, which seeks to accelerate research on HIV pathogenesis, immunology, immune-based therapies, vaccines, and biomedical prevention interventions. The Project is funded by The Michael Palm Foundation. Michael Palm was a philanthropist and an early and consistent supporter of TAG.

**For more information:**

Treatment Action Group  
611 Broadway, Suite 608  
New York, NY 10012 USA  
1.212.253.7922 – tel.  
1.212.253.7923 – fax  
[www.treatmentactiongroup.org](http://www.treatmentactiongroup.org)  
[tagnyc@verizon.com](mailto:tagnyc@verizon.com)

**# # #**