insight

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INSIGHT Leadership Application Approved

On 21 April 2006, the National Institute of Allergy and Infectious Diseases (NIAID) announced that INSIGHT is one of six networks that will be established under NIAID's new HIV/AIDS clinical trial network structure. NIAID, part of the National Institutes of Health (NIH), supports the world's largest portfolio of clinical HIV/AIDS research. The new networks will lead the search for safe and effective treatments and prevention strategies, including HIV vaccines. In addition to INSIGHT, the other five networks are: the AIDS Clinical Trials Group, the HIV Prevention Trials Network, the HIV Vaccine Trials Network, the International Maternal Pediatric Adolescent AIDS Clinical Trials, and the Microbicide Trials Network.

The announcement was followed on 29 June by an initial award to the University of Minnesota to facilitate the establishment of INSIGHT coordinating and operations, laboratory, and statistical and data management infrastructure. A second award is expected in August to provide the remaining funds for the first budget year.

These leadership awards represent the first step of the two-part NIAID restructuring process. Awards for the Clinical Trials Units, which will carry out the clinical research at numerous sites throughout the world, are expected to be announced later this year.

> "The new network structure expands our clinical research capacity and strengthens our ability to take advantage of emerging scientific opportunities," said NIAID director Anthony S. Fauci, M.D. "By creating a more integrated, collaborative and flexible structure, we will be better equipped to meet evolving global AIDS research priorities."

SMART: A Brief Recent History

The Data and Safety Monitoring Board (DSMB) met on 1 November 2005 for a regular review of interim SMART data and requested additional analyses. On 6 January 2006, the DSMB reviewed the additional analyses by teleconference. On 10 January, the DSMB transmitted a summary of its review to the SMART Executive Committee, noting that the current data indicated an early safety risk in the form of an increased risk of progression of disease (AIDS or death) during the first 2 years of the trial for the Drug Conservation (DC) group compared to the Viral Suppression (VS) group. The DSMB also noted that, in its opinion, there was substantial uncertainty about the long-term benefit-to-risk profile of the DC to VS strategy. Therefore, the DSMB recommended stopping further enrollment to the trial.

After careful consideration of the DSMB's summary and review of the interim data, the Executive Committee agreed with the recommendation to stop enrollment. On 11 January, sites and investigators were informed that 1) enrollment was stopped at 5472 patients, just short of the projected enrollment of 6000 patients, 2) there was an increased short-term risk of HIV progression or death in the DC group compared to the VS group, and 3) the Executive Committee believed it prudent to re-initiate antiretroviral therapy (ART) for treatment-experienced DC patients currently off ART.

Following this decision, patients were informed of the study findings. The Executive Committee initiated work on a protocol amendment to follow patients further to collect additional data and to assess long-term outcomes. They informed investigators that follow-up data collection should continue according to the current protocol while the protocol amendment was considered. Initial study findings were presented at the 13th Conference on Retroviruses and Opportunistic Infections (February 2006, Denver, Colorado) by Wafaa El-Sadr on behalf of the SMART Study Team.

SMART Letter of Amendment Update

The SMART Letter of Amendment (LoA), version 2.0, received final approval by the Division of AIDS (DAIDS) on 20 July 2006. The LoA, including a cover letter outlining procedures for submitting institutional review board/ethics committee (IRB/EC) approval materials to the DAIDS Protocol Registration Office at the Regulatory Compliance Center (RCC), was submitted to INSIGHT International Coordinating Centers (ICCs) on 3 August 2006. The INSIGHT Executive Committee expects that each ICC

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SMART Letter of Amendment (continued from page 1)

will work with its site investigators to process the LoA through IRBs/ECs as quickly as possible. The LoA provides the rational for continued study follow-up of SMART patients with a common closing date of 11 July 2007.

There are numerous new objectives for SMART. The primary objective is to compare the DC group with the VS group for opportunistic disease or death after 11 January 2006, the date on which enrollment to SMART was stopped. Secondary objectives include, for example, comparing the DC and VS groups for risk of opportunistic disease/death by subgroups defined by calendar date of enrollment, determining the extent to which the hazard ratio of opportunistic disease/death is explained by CD4+ cell count and HIV RNA levels during follow-up, and investigating predictors (e.g., demographic characteristics, duration of initial ART interruption) of opportunistic disease/death in the DC group.

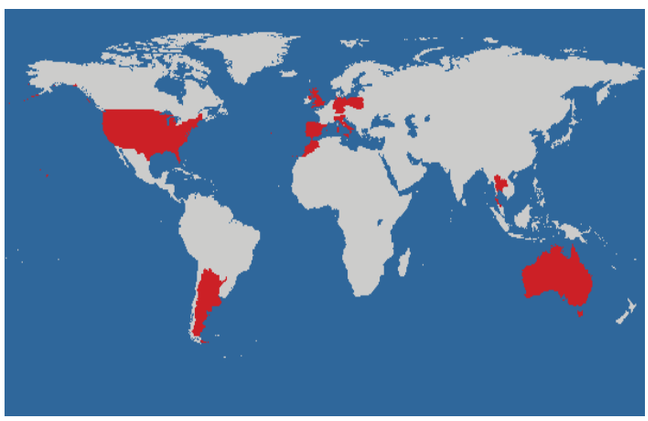
The LoA also provides for the collection and reporting of additional laboratory data needed to answer the new objectives. The following labs will be reported retrospectively and prospectively at each follow-up visit on new case report forms: CD8+ cell count and percentage, WBC and differential, platelet count, hemoglobin, serum creatinine, ALT/AST, and albumin. These follow-up laboratory tests will not require additional blood collection. Investigators will receive the new data collection forms shortly.

STALWART Sites Open Worldwide

STALWART, also known as ESPRIT 002, officially opened in September 2005. Congratulations go out to the 18 sites in two countries that have received full site registration approval. Eight sites have already recruited 27 patients. When fully operational, the STALWART infrastructure will recruit 480 patients at over 67 sites in 11 countries. A number of obstacles to opening sites to recruitment have been overcome in the last few months – protocol and informed consent documents have been translated, documentation of indemnification has been received, local regulations regarding stored specimens and genetic testing have been addressed, and new requirements of the European Union Clinical Trials Directive have been met. All sites and their respective Site Coordinating Centers (SCCs) and ICCs are working hard to finalize their IRB/EC approvals and other site registration materials. It is estimated that all sites should be enrolling patients into the study by the fourth quarter of this year.

Countries Participating in STALWART

Argentina
Australia
Germany
Italy
Morocco
Poland
Portugal
Spain
Thailand
United Kingdom
United States



Although the current priority is opening enrollment at all 67 sites, increasing enrollment at open sites is also essential. Any open site that has not yet commenced recruitment should do so, and all STALWART sites should remember to keep their SCC informed of any change in their enrollment projections. The STALWART protocol places considerable demands on our sites as well as our study participants. Study enrollment criteria are stringent, and visit schedules and data collection are more aggressive than those of ESPRIT 001. The STALWART protocol team is committed to supporting sites in any way possible, so please contact your SCC for assistance or if you have any suggestions.

Investigators are encouraged to review the results of the United Kingdom Vanguard Study, which were recently published (Youle M, Emery S, Fisher M, Nelson M, Fosdick L, et al. A randomised trial of subcutaneous intermittent interleukin-2 without antiretroviral therapy in HIV-infected patients: The UK-Vanguard study. PLoS Clin Trials 2006; 1(1): e3. DOI: 10.1371/journal.pctr.0010003; http://clinicaltrials.plosjournals.org). This study concluded that, in participants with HIV infection and baseline CD4+ T-lymphocyte counts of at least 350 cells/mm^3, intermittent subcutaneous IL-2 without concomitant ART was well tolerated, produced significant increases in CD4+ T-lymphocyte counts, and did not adversely affect plasma HIV RNA levels. The results of STALWART will be important to confirm the findings of this small pilot study and to investigate the impact of peri-IL-2-cycle HAART on immunologic and virologic outcomes.

At the request of the STALWART protocol team, the DSMB for the study will perform an early safety review across the three study arms in November of this year. All sites will receive the DSMB recommendations and will be asked to forward these to their respective IRBs/ECs.

FEATURED SCC: ESPRIT in Scandinavia

by Jesper Grarup, Karoline B. Jensen, and Daniela C. Gey

The Copenhagen ICC also serves as the Scandinavian SCC for Austria, Denmark, Norway, Poland, and Sweden. Initially, only Scandinavian countries were part of this geographically diverse SCC, but Poland joined in 2001 and Austria in 2002. Both countries have contributed to the ESPRIT study with great success; however, independent SCCs were not established due to the limited number of ESPRIT sites in both Poland and Austria. Poland was featured in the July 2005 edition of the *ESPRIT Update;* therefore, the following description of the Scandinavian SCC will cover all countries listed above except for Poland.

Among Danish nationals, HIV transmission is primarily between men who have sex with men (MSM), whereas for immigrants transmission is primarily heterosexual. Out of 303 new HIV infections in 2004, 194 were among Danish nationals, of whom 176 were male (70% MSM). The number of new cases among MSM in 2004 was the highest since 1991. In Norway, 252 new cases of HIV were reported in 2004. This is the highest incidence in recent years and is primarily caused by an increase of cases among MSM. Heterosexual transmission is the most common (47%), of which 74% were among non-Norwegian immigrants. Among the new infections, 40% were female. Of the 426 new HIV cases in Sweden in 2004, 59% were transmitted heterosexually and most cases of heterosexual transmission were found among non-Swedish immigrants, mainly those from sub-Saharan Africa. People who have been infected outside Sweden constitute two thirds of the reported cases in recent years.

In Austria, 453 new cases of HIV were reported in 2005. Compared to the previous three years (442 cases in 2002, 422 in 2003, and 470 in 2004), the number of new HIV infections remains at a low and fairly constant level. Of the 453 newly diagnosed HIV-infected persons, 244 were seen by one of the five major treatment centers in Austria. Among these 244 new infections, 29% were female. MSM still constituted the dominant risk group (43%), and the relative percentage of MSM as compared to recent years was approximately stable. However, the percentage of non-Austrians (27%) almost doubled compared to the year 2000.

In total, the Scandinavian SCC has randomized 121 patients to ESPRIT: 72 in the Danish sites Hvidovre and Rigshospitalet (Copenhagen), Skejby (Aarhus), Odense, and Aalborg; 34 in Austrian sites SMZ Baumgartner Hoehe and Vienna General Hospital (both in Vienna); 8 in Oslo, Norway; and 7 in Venhalsan and Karolinska Hospitals in Sweden. Of the ESPRIT patients in our region, 58 were randomized to IL-2. The number of IL-2 patients with CD4+ at goal shows a wide range from 0-44.4% with an average of 34.5%. Worldwide, the average is 26.3%. Still, IL-2 cycling continues to be a challenge.

The Scandinavian sites are very motivated and perform very well in maintaining participants in active follow-up, which is reflected in the low lost-to-follow-up number of three patients in total (2.5%). We look forward to continuing our enjoyable collaboration with our clinical sites in a combined effort to contribute to the successful conclusion of ESPRIT. We would like to take this opportunity to acknowledge our clinical staff and patients for their continued and much appreciated support of the study.

SMART Highlighted at NIH Structured Treatment Workshop

The NIH, in collaboration with the Treatment Action Group, sponsored a workshop in London on structured treatment interruptions/intermittent therapy (STI/IT) clinical trials on 17-19 July 2006. The goals of this workshop were: 1) to discuss the results from previous STI/IT studies and recent findings from SMART and the lessons learned; 2) to determine the impact the findings from SMART and other recent studies may have on ongoing and planned STI/IT protocols; and 3) to recommend future directions for this important area of clinical research. Approximately 70 persons attended the workshop, representing investigators and community members from all the major groups conducting trials in this area. Attendees from INSIGHT included the two co-chairs, Jintanat Ananworanich and Janet Darbyshire, and ten other persons from all four of the INSIGHT ICCs.

During the meeting, SMART was discussed as the pivotal trial in the field, based on its sample size and reliance on clinical endpoints. Many participants voiced their hope that the stored specimens in SMART will help reveal the reasons that some patients developed clinical events – with a special interest in understanding why the cardiovascular events were higher in the DC arm – possibly by evaluating immune activation, inflammation, and thrombogenic factors. There was also interest in better

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SMART at NIH Workshop (continued from page 3)

understanding what happened to persons with high CD4+ cell counts at nadir and at entry to appreciate better the absolute risk of stopping therapy in persons perceived by some to be at lowest risk.

Information from SMART and the other trials that were discussed was summarized on the last day by five breakout groups. The summary conclusions were that interest and research in STIs is "not dead" and that studies should be pursued in STIs and treatment interruptions in both adults and children. In addition, the attendees emphasized that work from the completed studies makes the question of when to start ART more timely and appropriate than it has ever been.

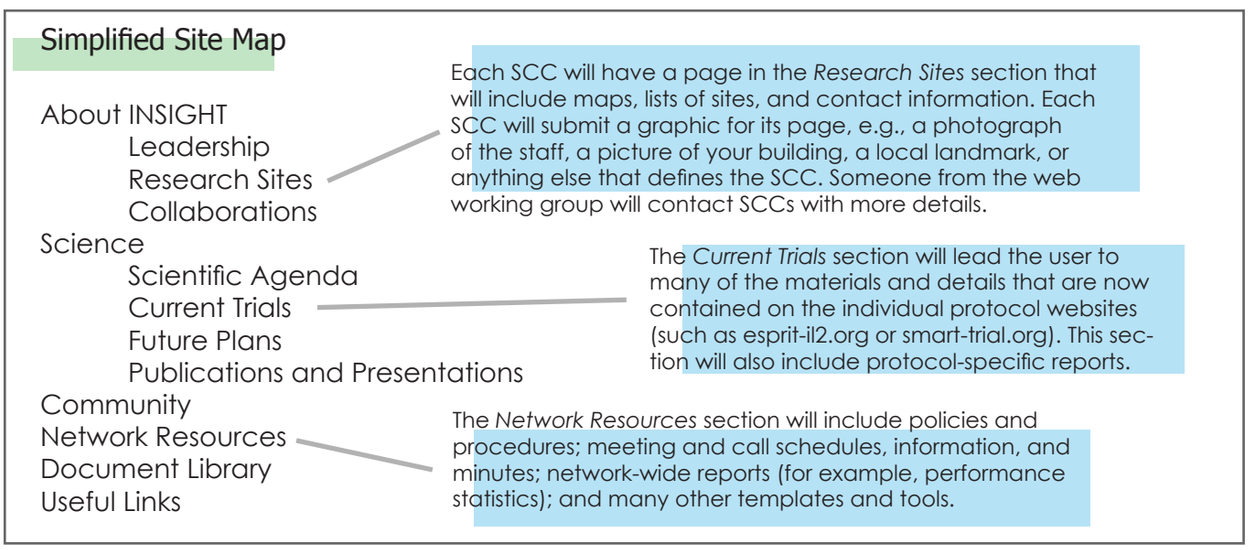
SMART Presentations at Toronto AIDS Conference

The SMART study will have a strong presence at the XVI International AIDS Conference, 13-18 August 2006, in Toronto, Canada. Wafaa El-Sadr will present comparisons of the episodic versus continuous ART strategies in subgroups and Jens Lundgren will explore how differences in CD4+ and HIV RNA levels through follow-up influenced the risk of opportunistic disease and death in the two treatment strategies (both oral presentations). Three posters will also be presented. One will address the effect of episodic versus continuous ART on health-related quality of life, a second will describe the clinical events that occurred in SMART, and a third will describe the initial CD4+ decline after stopping ART. At the INSIGHT/SILCAAT Joint Scientific Session for investigators on Sunday, 13 August, Andrew Phillips will present results on cardiovascular disease in SMART.

Several abstracts on SMART results are being developed for upcoming conferences. Writing groups are working on presentations on the influence of episodic ART on the risk of cardiovascular disease and on first results of the body composition substudy of SMART.

Coming Soon: www.insight-trials.org

We are in the process of building the new INSIGHT website at www.insight-trials.org. One big change at the new site will be more accessibility as most of the site will be viewable without having to sign in. Features will include more tools, better graphics, a greatly expanded community section, and a more comprehensive directory.



The website will continue to be a major communications tool and, as in the past, will include many reports and reminders. We hope that everyone will find the new site helpful and easy to navigate. We are estimating a launch in the fourth quarter of 2006 at which time the current study-specific websites will be disabled. More details will be provided in the future.

Upcoming Meetings

INSIGHT investigators will meet in conjunction with the Conference on Retroviruses and Opportunistic Infections in Los Angeles, California, in February 2007. Details will be announced later.

Note from the Editor

This is the first issue of the INSIGHT newsletter. It will be published approximately four times a year. Send your ideas, thoughts, and suggestions to Sue Meger (sue@ccbr.umn.edu). Please note that the *ESPRIT Update* will no longer be published.