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START Protocol Nearing Final Approval

INSIGHT's new protocol for the Strategic Timing of AntiRetroviral Treatment (START) trial is nearing final approval by the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH). START is a randomized, international multicenter trial that will determine whether the immediate initiation of antiretroviral treatment in HIV-infected, treatment-naïve persons with CD4+ counts >500 cells/mm^3 is superior, in terms of morbidity and mortality, to deferral of treatment until the CD4+ count declines to <350 cells/mm^3.

The START protocol received its second set of DAIDS Clinical Science Review Committee comments in late December. The protocol team is now preparing responses. Approval by the Medical Officer and the Regulatory Affairs Branch at DAIDS will complete the protocol review process.

START Initial Phase Sites

ICC	Country	Number of Sites
Copenhagen	Total	**16**
	Belgium	2
	Denmark	2
	Finland	1
	Germany	5
	Poland	1
	Spain	5
London	Total	**13**
	Greece	3
	Italy	1
	Morocco	1
	Switzerland	3
	United Kingdom	5
Sydney	Total	**16**
	Argentina	8
	Australia	3
	Chile	1
	Israel	1
	Singapore	1
	Thailand	2
Washington	Total	**15**
	Brazil	2
	Peru	2
	South Africa	1
	United States	10
	United States (CPCRA CTU)	**10**
Total		**70**

Upcoming work will focus on START clinical site establishment. In mid-January, DAIDS approved 60 sites from INSIGHT's Copenhagen, London, Sydney, and Washington International Coordinating Centers (ICCs), plus ten sites that comprise the DAIDS-funded CPCRA Clinical Trials Unit (CTU). These 70 DAIDS-funded sites, distributed among 21 countries, will open the initial phase of the study with a goal of accruing 900 participants within the first year. Site selection criteria emphasized past performance in INSIGHT studies and the ability to accrue treatment-naïve participants quickly. Sites with alternative support will also participate. These include sites sponsored by the French national agency on AIDS research (ANRS), the US Department of Defense, and the NIH Clinical Center; the German Federal Ministry of Education and Research will support additional sites later in 2008. Upon achievement of the first phase accrual goal, additional sites and countries will be added in a second phase that will bring accrual to a total of 4000 participants within the overall 3-year enrollment period. Three years of follow-up are planned after the last participant is randomized.

Four substudies that will enroll main study participants from all or selected sites are moving forward. In the **Genomics Substudy**, whole blood specimens will be obtained from participants who consent to archive their specimens for future genetic analyses. The **Neurology Substudy** will enroll about 600 participants at a subset of sites. Participants will be equally divided between the early and deferred treatment arms of START and compared for changes in neurocognitive function. Funding for this substudy has been requested from the National Institutes of Mental Health and Neurological Disorders and Stroke at NIH. The **Informed Consent Substudy** will enroll about 1000 participants at approximately 40 sites. Sites will be randomized to use either a standard or concise consent. Participant responses will be compared regarding comprehension of START protocol requirements. In the **Arterial Stiffness Substudy**, about 300 participants will be enrolled at a subset of sites. An equal number of participants in the early and deferred treatment arms of START will be compared for changes in large and small artery elasticity.

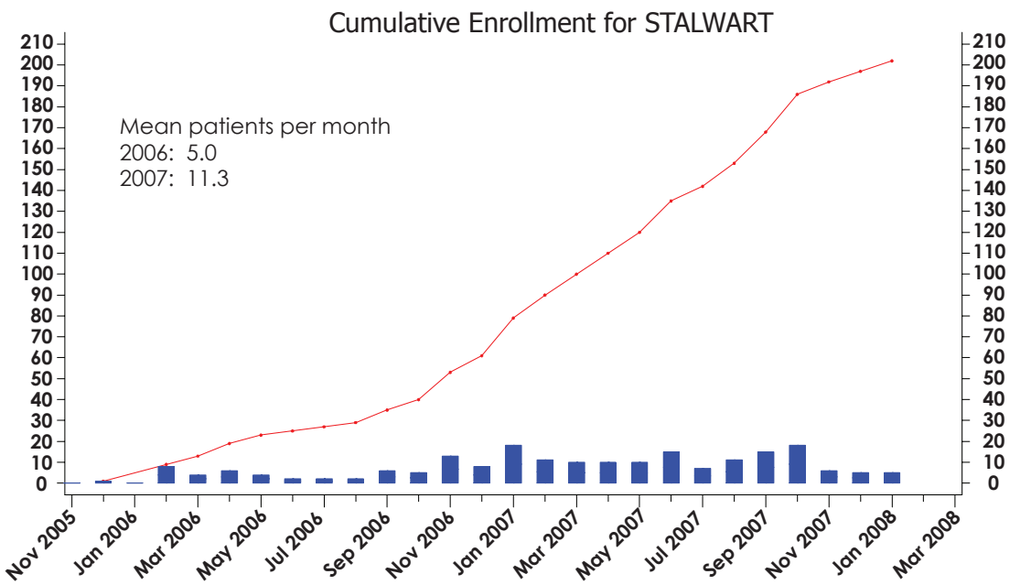
INSIGHT Renal Interest Group investigators have prepared a grant proposal for the National Institute of Diabetes and Digestive and Kidney Diseases to study predictors of renal disease progression in START. A grant proposal also will be submitted to the National Heart, Lung, and Blood Institute to fund the Arterial Stiffness Substudy and collection of ECGs and blood for biomarker analyses.

DSMB Conducts Final Scheduled Review of ESPRIT

ESPRIT's ninth Data and Safety Monitoring Board (DSMB) review took place on 27 November 2007. After carefully reviewing interim safety and efficacy data from all participating sites, the DSMB concluded that it had no concerns arising at the present time to warrant a change in the conduct of ESPRIT. Because the trial is expected to close to follow-up no later than 31 December 2008, the DSMB suggested that no further review of ESPRIT is necessary. The DSMB recommended that the ESPRIT team continue to encourage re-cycling and reducing the number of participants lost to follow-up.

STALWART Update - Enrollment Climbs

STALWART enrolled its 200th participant on 2 January 2008 — congratulations to the 29 STALWART sites that have enrolled patients so far. Compliments are particularly in order for Australia's St. Vincent's Hospital (612-002) and Gladstone Road Medical Centre (612-023), Thailand's Khon Kaen University (613-003), and the Washington DC VA Medical Center (642-001) for exceeding their enrollment projections. Because of a number of hurdles, some sites have not yet opened to recruitment. The protocol team is working to bring all sites on board by the end of March 2008 and to maximize enrollment rates.



The DSMB for STALWART met on 27 November 2007. At that time, mean baseline age was 38 years, median CD4+ count was 415 cells/mm^3 and median HIV RNA was approximately 22,000 copies. Approximately three quarters of patients were antiretroviral-naïve at the time of randomization. Median time since last use of antiretroviral treatment (ART) was 32 months among ART-experienced participants.

The DSMB concluded that there are no concerns arising from either efficacy or safety data that warrant a change in the conduct of STALWART. The DSMB also agreed with the following proposals from the STALWART protocol team: STALWART enrollment will end in conjunction with the planned end of the ESPRIT and SILCAAT trials; the protocol team will focus efforts on sites that are likely to open during the first quarter of 2008; and a letter of amendment will be written to allow genotyping beyond cycle 3 in participants randomized to peri-cycle antiretrovirals plus IL-2. The next DSMB review of STALWART safety data will occur approximately 6 months from the November review.

Interest Groups Develop Research Proposals

Eight interest groups are forming to promote INSIGHT research opportunities, especially for junior investigators. The groups are CVD, Genomics, Immunology, Liver, Malignancies, Neurology, Renal, and Virology. The interest groups are designed to be inclusive; membership is open and investigators, community members, INSIGHT staff, and outside experts are encouraged to participate.

Each interest group will meet one or two times a year via teleconference. The interest groups will appoint working groups to pursue specific research projects, such as biomarker analyses using INSIGHT repository specimens; plan substudies for new trials; and prepare grants, abstracts, and papers. The interest groups also will provide input on data collection tools and specimen collection protocols and will work with the INSIGHT Executive Committee to establish liaisons with funding agencies.

Information on the interest groups, including membership details, meeting and teleconference schedules and minutes, specimen repository information, and other documents related to the work of the various groups, is available on the INSIGHT website.

Upcoming Meetings

The next INSIGHT/SILCAAT Joint Scientific Session for investigators will be held in Mexico City, Mexico on 3 August 2008 in conjunction with the XVII International AIDS Conference. Details on the venue are forthcoming.