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START Study Progress

INSIGHT's early treatment pilot study continues to advance. Following the INSIGHT investigators meeting in Los Angeles in February 2007 and additional meetings with Division of AIDS (DAIDS) staff, the Executive Committee initiated work on a draft START (Strategic Timing of AntiRetroviral Therapy) protocol. The DAIDS Clinical Site Review Committee (CSRC) reviewed the proposed protocol and informed consent on 21 June. Following receipt of comments from the CSRC and others, the protocol will be revised and submitted for final review by the CSRC. At the same time, INSIGHT International Coordinating Centers (ICCs) have started work on site selection, reviewing performance measures, enrollment potential, and investigator interest.

START

As currently proposed, START would begin enrolling 1200 participants in early 2008. Another 600 participants would be enrolled in 2009 if funding permits. Treatment-naïve participants with CD4+ counts > 450 cells/mm^3 would be randomized to either immediate treatment or deferred treatment in a 1:1 ratio. Participants in the immediate-treatment arm would initiate potent antiretroviral therapy (ART) soon after randomization, and participants in the deferred-treatment arm would initiate such therapy if their CD4+ counts fall below 325 cells/mm^3. Preferred ART regimens that are consistent with national guidelines will be used. Data collection visits will occur at 1 and 4 months, and every 4 months thereafter.

START study endpoints will include fatal AIDS or nonfatal serious AIDS events, nonfatal serious non-AIDS events (cardiovascular, renal, liver, and cancer), and deaths not attributable to AIDS. The total duration of the study will be determined after Data and Safety Monitoring Board review and re-estimation of sample size at approximately 18-24 months after the first randomization.

Specimen Repository Think Tank Meeting

On 1-2 June 2007, more than 40 people met in Washington DC to discuss the role of biomarkers in HIV research in general, as well as specific research conducted by INSIGHT. The INSIGHT Specimen Repository Think Tank included national and international experts in nephrology, cardiology, cancer, and liver disease. Several National Institutes of Health (NIH) also were represented. The meeting was co-chaired by Dr. Cliff Lane, National Institute of Allergy and Infectious Diseases, Dr. Stephen Deeks, University of California at San Francisco, and Dr. John Baxter, Cooper University Hospital.

The meeting included presentations by experts on biomarkers of cardiovascular, renal, and hepatic disease, and cancer, and immunologic markers of disease progression. Additional analyses of SMART specimens were discussed. The meeting ended with a discussion of the collection of specimens in START and future clinical trials.

Workshop on Serious Non-AIDS Conditions

Over 100 people representing INSIGHT, DAIDS, the HIV community, and pharmaceutical companies, as well as outside experts in various medical specialties, met on 9-10 July 2007 in Washington DC, for a workshop on serious non-AIDS conditions in HIV. The workshop was originally proposed by the DAIDS Strategic Working Group (SWG) in January 2007, following the SWG review of early treatment proposals, to examine cohort data on non-AIDS morbidity. Dr. Henry Masur, chief of the Critical Care Medicine Department at the NIH Clinical Center, chaired the workshop.

In anticipation of the meeting, Dr. Bruno Ledergerber, University Hospital Zurich, Switzerland, surveyed over 90 cohorts to determine whether the cohorts collect data on serious non-AIDS conditions, such as cardiovascular, hepatic, and renal conditions, malignancies, dementia, and others. The workshop opened with the results of Dr. Ledergerber's survey. Other topics covered included the pathogenesis of serious non-AIDS conditions, the risks and benefits of early ART use, and the reliable quantification of those risks and benefits. The workshop concluded with a discussion of how to move forward with a research agenda that addresses serious non-AIDS conditions in HIV disease, the effect of ART on those conditions, and what types of clinical trials are needed.

SMART Study Closeout

The SMART study closed to follow-up on 11 July 2007. The study opened to enrollment on 9 January 2002 and closed to enrollment on 11 January 2006 with 5472 participants. SMART is the largest international randomized HIV clinical trial ever conducted, with more than 14,621 person-years of follow-up.

To ensure successful completion of SMART, a Closeout Status Verification case report form needs to be completed for each participant between 12 July and 13 October 2007. The form verifies each participant's event status (regarding AIDS-related illnesses, supplemental diagnoses, and grade 4 events) and ART regimen history between the date of randomization through 11 July 2007. Also, each participant's vital status as of 11 July will be captured on the form. Payment for completion of this case report form will be made on the same basis as payment for SMART follow-up forms.

SMART Closeout Timeline

11 July 2007	Last day of study follow-up Last day for enrollment into Genomics 065H
12 July 2007	First day to complete and submit Closeout Status Verification CRFs
1 August 2007	Deadline for all ECGs to be received by EPICARE
13 October 2007	Deadline for all specimens to be received by ABML Last day to submit all CRFs to SDMC
31 December 2007	Last day to resolve all data queries

Administrative funding for SMART will end 31 December 2007. To ensure that all SMART-related research activities are completed by the end of the calendar year, a memo regarding SMART closeout procedures was distributed to ICCs on 8 May 2007. Research materials (i.e., Closeout Status Verification case report form and instructions, participant-specific clinical profiles, last required study visit listings, outstanding specimen reports, and missing ECG reports) are available on the INSIGHT website.

Genomics Accrual Closure Dates

The SMART Genomics 065H protocol requires enrollment to close on 11 July 2007. This substudy accrued 504 participants who enrolled into SMART at international sites and non-CPCRA sites in the Washington ICC and consented to the one-time collection of whole blood for future research.

Although the SMART Genomics substudy 065H requires enrollment to end on 11 July, the Genomics 066 protocol does not specify a closure date. Genomics 066 is only open to former CPCRA sites in the United States who previously enrolled participants into the CPCRA FIRST, LTM Naïve cohort, MDR-HIV, PIP, or SMART studies. Currently, more than 2400 participants have been enrolled in Genomics 066. It was originally decided that enrollment to Genomics 066 would also cease on 11 July, but at the request of investigators in the Washington ICC, the study will remain open until 30 September 2007.

STALWART Enrollment Climbs

In the last 6 months, STALWART accrual has more than doubled as new sites have completed registration and opened for enrollment. Enrollment now stands at 136 participants, 28% of the goal of 480 participants. The Sydney ICC leads with 68% of participants, followed by the London ICC with 17%. The Argentina SCC is the largest single enroller with 49 participants. Twenty-four of 56 sites have not opened to enrollment yet due to changes in regulatory requirements and delays in obtaining national and local ethics committee approvals.

ESPRIT Investigators Urged to Cycle Participants

The ESPRIT protocol team has sent a letter to investigators urging them to cycle all eligible participants assigned to IL-2 who are not currently at goal at least once in 2007. At the midpoint of 2007, only 9% of the 1263 participants not at goal and eligible for cycling (i.e., no contraindication) have cycled.

The importance of cycling participants was underlined in the most recent DSMB recommendations. The DSMB stressed the need for participants assigned to the IL-2 arm to actually receive the treatment per the protocol instructions. Given the many years and effort expended to complete the study, it is essential that ESPRIT end with an answer to the study question. To accurately test the hypothesis that the CD4+ increases induced by IL-2 are of clinical value, it is critically important that we do all that we can to make sure that the IL-2 group is treated per the protocol guidelines.

Upcoming Meetings

The next INSIGHT/SILCAAT Joint Scientific Session for investigators will be held in Boston, Massachusetts, on 3 February 2008 in conjunction with the 15th Conference on Retroviruses and Opportunistic Infections.