Study examines best time for healthy HIV-infected people to begin antiretrovirals

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A major new clinical trial seeks to determine whether HIV-infected asymptomatic individuals have less risk of developing AIDS or other serious illness if they begin taking antiretrovirals sooner rather than later, based on their level of CD4+ T-cells. An HIV-infected individual's level of CD4+ T-cells—commonly referred to as their CD4 count—is a key measure of immune system health. The study is co-funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

While data from randomized clinical trials exist to support starting antiretroviral treatment when CD4 counts fall below 350 cells per cubic millimeter (mm^3), well-designed clinical trials have not been conducted to guide decisions to support starting treatment above that threshold. As a consequence, guidelines differ with regard to if and when to begin antiretroviral treatment in asymptomatic HIV-infected individuals with CD4 counts above 350 cells/mm^3. Current U.S. guidelines recommend that these individuals should begin antiretrovirals when their CD4 counts fall below 500 cells/ mm^3, whereas the World Health Organization recommends this group start treatment only when their CD4 count falls to or below the 350 cells/mm^3 cutoff.

The new Phase IV study, known as the Strategic Timing of Antiretroviral Treatment (START) clinical trial, is a randomized clinical trial designed to provide definitive evidence of the risks and benefits of early antiretroviral treatment to more clearly define the optimal time to begin medication. It seeks to determine if immediate antiretroviral

therapy among HIV-infected individuals with CD4 levels above 500 cells/mm^3 is better than deferring treatment until CD4 counts fall below 350 in terms of potential benefits and risks, such as developing AIDS and other serious illnesses, including cardiovascular disease, cancer, kidney failure, and liver disease, or death. The launch of the START trial follows the successful completion of a pilot study involving more than 1,000 participants.

"Some epidemiological evidence suggests that HIV-infected patients remain healthier when they begin treatment at higher CD4 counts. However, there are also concerns about the health complications and side effects associated with lifelong antiretroviral use and the possibility that the virus may become resistant to medication," says NIAID Director Anthony S. Fauci, M.D. "The START trial will provide a more clear-cut answer as to the best time for HIV patients to begin treatment, taking into account both the risks and benefits associated with early versus deferred treatment."

START will be conducted in 30 countries. It will enroll 4,000 HIV-infected men and women 18 years of age and older who have CD4 counts above 500 cells/mm^3 and who have never taken antiretroviral therapy. Once entered into the study, half of the participants will be assigned randomly to receive immediate antiretroviral therapy. The other half of the study group will not receive antiretroviral therapy until their CD4 counts fall below 350 cells/mm^3 or an AIDS-related event occurs.

Study clinicians will select the appropriate antiretroviral regimen for each participant from a pre-approved list based on U.S. Department of Health and Human Services treatment guidelines. The HIV medicines being used in the trial are approved medications donated by Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck & Co. and Tibotec Pharmaceuticals.

Participants will be followed for up to five years. Once enrolled, they will return to the clinic to be seen by study staff at one month, four months and then every four months thereafter. At each visit, participants will provide a medical update and undergo a brief medical exam, and CD4 cell counts and viral load (the amount of HIV in the blood) will be recorded.

The study is being conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), an HIV/AIDS clinical trial network funded by NIAID. The University of Minnesota in Minneapolis is the trial sponsor with primary funding from NIAID and additional funding provided by other NIH entities, including the National Cancer Institute, the National Heart, Lung and Blood Institute, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Additional support comes from four government organizations based in Australia, France, Germany, and the United Kingdom.

Although START will primarily look at major health outcomes associated with immediate and deferred antiretroviral therapy, the study will also examine HIV transmission risk behaviors, treatment adherence, drug resistance, health care utilization and the cost of care. "The intent is to fully evaluate the individual and the broader public health implications of earlier antiretroviral treatment," according to James D. Neaton, Ph.D., of the University of Minnesota, principal investigator for INSIGHT.

START will also feature several sub-studies to be conducted across some of the 200 study sites. These sub-studies include examining the effect of genetic variants of the virus on the progression of untreated HIV, as well as the response of patients to antiretroviral therapy; comparing the early and deferred antiretroviral groups for neurocognitive function and

measures of vascular function, pulmonary function, and bone mineral density; and evaluating participant understanding of study information and satisfaction with the consent process to better inform future research guidelines.

More information: START is identified on www.clinicaltrials.gov as NCT00867048.

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