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Early antiretroviral therapy prevents non-AIDS outcomes in HIV-infected people, study

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Starting antiretroviral therapy early not only prevents serious AIDS-related diseases, but also prevents the onset of cancer, cardiovascular disease, and other non-AIDS-related diseases in HIV-infected people, according to a new analysis of data from the Strategic Timing of AntiRetroviral Treatment (START) study, the first large-scale randomized clinical trial to establish that earlier antiretroviral treatment benefits all HIV-infected individuals. Rates of both serious AIDS-related events and serious non-AIDS-related events were significantly reduced with early therapy.

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, provided primary funding for the START trial. New results appear today in the *New England Journal of Medicine* and are being presented at the 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Vancouver, Canada.

The study's composite endpoint had two components: serious AIDS events or death from AIDS, and serious non-AIDS events or non AIDS-related death. In May 2015, the START trial investigators released their initial groundbreaking findings that starting antiretroviral therapy early when immune systems are healthier, without waiting for CD4+ cell counts to decline, prevented the composite of serious AIDS events (such as AIDS-related cancers), serious non-AIDS-related events and death among HIV-infected individuals. Today's findings, which draw on more than two months of additional data since that announcement, show that

starting treatment early significantly reduces the risk of both major components of this combined outcome: serious AIDS events and serious non-AIDS events. Non-AIDS-related events tracked by the study included cardiovascular disease, end-stage renal disease, liver disease, non-AIDS defining cancer or causes of death not attributable to AIDS. Serious AIDS events were reduced by 72 percent and serious non-AIDS events were reduced by 39 percent.

Based on the new data and analysis, the study now reports the overall risk of developing serious AIDS events, serious non-AIDS events, or death, was reduced by 57 percent among those in the early treatment group, compared to those in the deferred group. This reduction was seen regardless of age, sex, baseline CD4+ cell counts, geographic region or country income level. Other potentially life-threatening events and unscheduled hospitalizations for reasons other than AIDS were also assessed, and results did not differ between the immediate and deferred therapy groups, demonstrating the safety of early antiretroviral therapy.

"This study conclusively shows that the benefits of early therapy far outweigh any adverse outcomes, and reinforces recommendations to offer immediate antiretroviral therapy to all patients," said NIAID Director Anthony S. Fauci, M.D. "Today's findings show that early antiretroviral treatment presents no additional risk of serious, non-AIDS-related disease to people taking treatment, but actually confers valuable protection against these illnesses, helping keep HIV-infected people healthier longer."

The START study, which opened widely in March 2011, was conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). It enrolled 4,685 HIV-infected men and women ages 18 and older in 35 countries. Participants had never taken antiretroviral therapy and were enrolled with CD4+ cell counts in the normal range—above 500 cells per cubic millimeter (cells/mm3).

Approximately half of the study participants were randomized to initiate antiretroviral treatment immediately (early treatment), and the other half were randomized to defer treatment until their CD4+ cell count declined to 350 cells/mm3. On average, participants in the study were followed for three years.

Although the median age of study participants was 36 - a relatively young group of participants - the most common events observed in the study were serious non-AIDS events, including many that typically affect older individuals. The two most common individual serious non-AIDS events in the immediate and deferred groups were cardiovascular disease (12 and 14 participants with events, respectively) and non-AIDS-defining cancer (9 and 18 participants with events, respectively).

To evaluate the safety of early treatment, potentially life-threatening symptomatic events not attributable to AIDS and unscheduled hospitalizations for reasons other than AIDS were assessed in both treatment groups. Rates for these events were similar in the two groups. When these events were combined with the serious AIDS and serious non-AIDS events, as an overall measure of clinical benefit for early treatment, the rate was 18 percent lower in the early treatment group, compared to the deferred treatment group.

"The comprehensive evaluation of the risks and benefits of early treatment in START provides policy makers, clinicians and HIV-positive individuals a strong set of data to inform antiretroviral therapy initiation policies," said INSIGHT principal investigator James D. Neaton, Ph.D., a professor of biostatistics at the University of Minnesota, Minneapolis.

The study was conducted in 215 sites across 35 countries, representing a diverse population of HIV-positive individuals. Specific outcomes differed by geographic region, though the benefits of immediate antiretroviral therapy were consistent. Most of the cancers and

cardiovascular disease events occurred among participants from higher-income countries in Europe, and Australia, Israel and the United States (22 of 27 cancer diagnoses and 19 of 26 cardiovascular events, respectively). Most of the tuberculosis occurred among participants at study sites in Africa (16 of 26 events), where both TB and HIV/AIDS are endemic.

"The results show that early treatment not only reduces opportunistic infections, which offers a bigger benefit in lower-income countries, but it also prevents a significant amount of illness in higher-income countries as well by reducing the risk of serious non-AIDS events that consisted largely of cancer and cardiovascular disease," said Jens Lundgren, M.D., of the University of Copenhagen and one of the co-chairs of the START study.

According to the study team, these findings are subject to some limitations. The patient population enrolled in START was younger than projected and experienced fewer overall events than were originally projected in the study's design. This limited the ability to determine the effect of immediate antiretroviral therapy on specific serious non-AIDS conditions, such as the risk of cardiovascular disease. "Further follow-up of this relatively young study population may help us better understand how early antiretroviral therapy impacts the cardiovascular system," said study co-chair Fred M. Gordin, M.D., Chief of Infectious Diseases at the Washington, D.C., Veterans Affairs Medical Center and professor at the George Washington University, "While this study was long enough for us to gather important evidence on starting therapy early, three years is a relatively short time period compared to lifelong antiretroviral therapy."

More information: Lundgren J., et al. Initiation of antiretroviral therapy in early asymptomatic HIV Infection. *New England Journal of Medicine* DOI: 10.1056/NEJMoa1506816 (2015).