An Exciting Act II for the Study That Proved Treating HIV Early Is Best

With a grant to follow their large study population through 2021, researchers hope to gain vital new insights about HIV infection.

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Three years ago, one of the most important studies in the history of HIV science proved, at long last, that starting antiretroviral (ARV) treatment for the virus earlier in the course of infection is preferable to delaying until the immune system has deteriorated to a certain point. Numerous previous studies had indicated that earlier treatment of HIV offered a net health benefit. But those studies were not randomized controlled trials, considered the gold-standard basis of scientific proof, so their findings were less reliable.

The May 2015 release of the results of the randomized controlled START trial and the publication of the study three months later in The New England Journal of Medicine marked a watershed moment in the global effort to control the HIV pandemic. The World Health Organization (WHO) promptly revised its guidance on when people with HIV should be offered ARVs, recommending immediate access to treatment for all. (Since 2013, the agency had stated that all those with a CD4 count below 500 should be offered treatment.)

For the team of researchers behind the START trial—collectively they're known as the INSIGHT network—making such a substantial impact on the pandemic was only an opening act. These scientists recently won a new funding stream from the National Institute for Allergy and Infectious Diseases (NIAID), a division of the National Institutes for Health (NIH), to continue following START's large population of study participants for another four years, through 2021. By the end of that period, the investigators will have gathered a decade or more of follow-up data on most participants, provided they can keep these individuals engaged in the study.

The researchers' main goal is to understand how delaying HIV treatment, compared with starting immediately, affects long-term health. They're looking at differences in health outcomes between those treated immediately and those treated on a delayed basis according to factors such as cardiovascular disease (CVD), cancer, AIDS and the risk of death as well as key markers such as CD4 count and viral load.

"I'm ecstatic about it," says James D. Neaton, PhD, a professor of biostatistics at the University of Minnesota and the lead researcher of the INSIGHT network, referring to the promise of

accumulating such a treasure trove of long-term follow-up data. “I think it will have a tremendous impact on our knowledge about the effects of treatment on these major outcomes.”

The new NIAID funding phase began January 1, 2018, and will provide an average of $4 million to $5 million per year going forward—which is a considerably scaled-back budget given the original phase of the study received a total of $167 million from the federal agency.

While the INSIGHT network members will certainly study the information they gather from the START participants along the way and likely publish new findings in the coming years, they plan to conduct their main analysis of the data in 2022 and 2023.

START recruited a highly diverse population of HIV-positive participants from around the world between 2009 and 2013 and ultimately enrolled 4,685 individuals, all of whom had recently contracted the virus, had a relatively healthy CD4 count of greater than 500 and no experience with ARV treatment. The participants were randomized into two even groups. One group was offered HIV treatment immediately. The other was offered ARVs on a deferred basis: after their CD4s dropped below 350, after they received an AIDS diagnosis or after they were indicated for treatment according to local guidelines, such as by becoming pregnant.

The trial was meant to run according to this initial treatment protocol through 2016. But after reviewing study data through March 2015, the study’s independent data safety monitoring board concluded that it was already clear that those in the immediate treatment group were significantly better off health-wise than the members of the deferred treatment group. Consequently, the safety board recommended that the investigators immediately offer treatment to the deferred group. Today, 90 percent of those in the deferred arm are on ARVs.

According to Neaton, the upside of this earlier-than-expected shift in protocol was that more people got treatment from which they clearly stood to benefit. The downside was that less follow-up time under the original protocol meant fewer health outcomes, such as heart attacks or cancer diagnoses, for the research team to factor into their statistical analysis to estimate how treating HIV earlier affects the risk of such outcomes.

During an average of three years of follow-up, 42 of those in the immediate treatment group and 96 of those in the deferred treatment arm experienced any health outcomes that fell under a pre-established umbrella that included an AIDS diagnosis, serious non-AIDS illnesses (including a major cardiovascular health event, kidney and liver disease, and cancer) or death from any cause. The study authors calculated that compared with delaying treatment, treating the virus immediately among those with a high CD4 count was associated with an estimated 57 percent reduction in the composite risk of such outcomes.

Most commonly, these health outcomes included cardiovascular disease, non-AIDS-defining cancer and tuberculosis. (TB is endemic in Africa, where 21 percent of participants lived. Meanwhile, 11 percent of the study population was in North America.)

The START study authors’ analysis also indicated that immediate treatment compared with

deferred treatment was associated with an estimated 72 percent reduced risk of serious AIDS-related health events, a 39 percent reduced risk for serious non-AIDS-related health events and a 42 percent reduced risk of death from any cause.

While these shifts in relative risk were considerable, the absolute risk of the study's key negative health outcomes was actually quite small, with just a respective 1.8 percent and 4.1 percent of participants in the immediate and deferred treatment groups experiencing such an outcome. Such small figures are only logical given the relative youth (a median age of 36) and good health (high CD4s) of the study members upon enrollment. The pressing question now is how their health will fare as they live with HIV for a few more years and the typical participant progresses through middle age.

Importantly, given the concerns about how toxicities associated with ARVs may at least in theory counterbalance HIV treatment's beneficial effects, the initial phase of the START study found that treating HIV earlier was not associated with an increased rate of serious adverse health events or unscheduled hospital admissions.

Researchers have already published numerous follow-up papers about the participants in START. These studies have investigated matters such as early versus deferred treatment's effect over the study's three-year follow-up on: cardiovascular risk factors such as cholesterol (an essentially insignificant effect); the risk of severe bacterial infections (a decreased risk, in part due to a boost in CD4 count); the risk of bone mineral density decline (the decline was greatest during the first year of treatment, what with most people taking tenofovir disoproxil fumarate, an ARV associated with bone loss); the elasticity of major arteries (no substantial influence); lung function (no major short-term effect); kidney function (a modest benefit, but more follow-up is needed to determine whether this translates to lower chronic kidney disease risk); the rates of infection-related versus non-infection-related cancers (based on the information available thus far, the investigators could only determine for certain that early treatment reduced the risk of the former type of cancer).

As for the INSIGHT network's goals for the coming years of analysis of the START participants, Neaton says, "We want to follow people to determine if those in the deferred group in START ever catch up" health-wise to those in the immediate treatment group. "And if they don't catch up, understanding why could be very important."

Steven Deeks, MD, a professor of medicine at the University of California, San Francisco, and a member of the INSIGHT network, says, "One of the great unanswered questions in the field is whether the initiation of ART [antiretroviral treatment] very early in the disease process truly normalizes health. You have a fair amount of data about how a delay in ART does not in many people lead to complete immune reconstitution and overall normal prognosis. But it remains completely unknown whether ART during the first several months to couple years [of infection] does so, and if so, in which patients and why."

In recent years, much research has delved into how HIV harms the body not just by killing off CD4 cells and suppressing the body's ability to combat infections but by prompting a chronic

inflammatory state that likely influences the progression of conditions like cardiovascular disease and cognitive decline. The virus is also known to cause an immediate assault on the gut, home to more than half of the body's CD4 cells, which even very early treatment can't seem to reverse. This is likely why people with HIV experience gastrointestinal problems at a high rate.

So to Neaton's point about playing catch up, what are the long-term implications of permitting a few years of such unabated viral replication and its associated high level of chronic inflammation early on in the course of infection compared with promptly reducing the virus to an undetectable level? (Fully suppressing the virus does not, however, totally rid the body of HIV-associated chronic inflammation.) Answers may surface in the coming years thanks to the continuation of START.

Deeks hopes he and his research collaborators will eventually compare the trial's participants who received immediate treatment to an outside group of controls who don't have the virus in order to find ways to address residual health problems associated with well-treated HIV.

Additionally, by observing patterns in the study participants' individual disease trajectories—not to mention studying information gleaned from sequencing the full genome of certain participants' viruses—the investigators may gain knowledge that will likely translate into real-world means of individualizing the care and treatment of people with HIV. For example, if the scientists find a particular biomarker that helps predict a certain negative outcome in people taking HIV treatment, then perhaps clinicians could conduct a test for that that biomarker, the result of which would indicate that a specific treatment would reduce the risk of such a negative health outcome.

Jens Lundgren, PhD, who is a professor of infectious diseases at the University of Copenhagen, the chair of the INSIGHT network scientific steering committee and a cochair of the START study, says such knowledge will hopefully help researchers develop "preventive interventions that will guide HIV medicine for people who are on HIV treatment in a much more personalized way."

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