# At Last, Gold-Standard Evidence Backs Early Treatment of HIV

The hotly anticipated START trial, designed to answer whether starting HIV treatment at a high CD4 count is preferable to delaying, has been halted more than a year early due to powerful evidence supporting early treatment.

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For the first time, a major clinical trial has found that beginning antiretrovirals (ARVs) soon after HIV diagnosis reduces the risk of sickness and death when compared with delaying treatment until CD4 levels drop considerably. Until now, only substandard research has supported U.S. health officials' recommendation for immediate and universal HIV treatment.

Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), which was the primary backer of the study, told reporters in a May 27 teleconference that the study findings mean that people with HIV will benefit from ARVs regardless of their CD4 level.

These health benefits, Fauci said, "are another reason why we should be more aggressive seeking out voluntary [HIV] testing, linking to care and putting people on treatment."

James D. Neaton, PhD, a professor of biostatistics at the University of Minnesota and the lead investigator of the trial, said in the teleconference that he and his colleagues' research offers a "comprehensive assessment of benefits and risk" that is not limited simply to AIDS diagnoses. "Early treatment essentially wins on almost every assessment we looked at," he said.

The study's findings finally sync up the dual role that antiretrovirals (ARV) have come to play in the fight against HIV: as lifesaving medications for people living with the virus, and as prevention against its transmission. In 2011, data from the HPTN 052 trial demonstrated that treatment lowers HIV-positive people's chances of passing on the virus by 96 percent. That study was a randomized controlled trial (RCT), considered the gold standard of scientific research. No such high level of proof has existed to support starting HIV treatment early, specifically with CD4s higher than 500; RCT data has only backed starting ARVs once CD4s drop below 350. This deficit of scientific evidence has left some in the HIV community wary that the medical autonomy of people with HIV may be harmfully subverted to the larger public health goal of reducing transmission.

Fauci noted that “there is at least a portion” of HIV medical providers who have been hesitant to prescribe early treatment to their patients because of their concerns over lacking proof that doing so was both beneficial and not harmful. “Those two important questions are answered now,” he said. “I think this will sway a considerable number of people to start [treatment] at any CD4 count.”

A fresh START

Known as the Strategic Timing of AntiRetroviral Treatment, or START, this new, landmark RCT included 4,685 treatment-naive HIV-positive men and women who began the trial with a CD4 count above 500, no symptoms of the virus, and who were not pregnant or breastfeeding. About half were randomly assigned to begin treatment immediately; the other half were assigned to wait until their CD4s dropped to 350 or below, until they developed AIDS other serious illnesses, or until they met qualifications for starting treatment according to local guidelines, such as by becoming pregnant.

START was conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) and primarily supported by $167 million in funding from the U.S. National Institutes of Health and the NIAID, which is a division of the NIH. The trial began enrollment in 2011 and operated at 215 sites in 35 countries. It was intended to run under its initial protocol until the end of 2016. But the study’s independent data safety monitoring board conducted an interim analysis based on March 2015 data and found that evidence supporting the benefits of early treatment was already very strong. Consequently, the board recommended that everyone in the trial be informed of the results and offered immediate treatment. The participants will still be monitored through 2016.

Twenty-seven percent of the study participants were women. Fifty-five percent of the participants were men who contracted HIV from sex with another man, 38 percent acquired the virus from heterosexual sex, and 1 percent did so from injection drug use. The median age of the study members was 36.

Public health experts believe the study findings are widely applicable to HIV-positive people worldwide, thanks to the international distribution of the study sites. Thirty-three percent of the participants lived in Europe, 25 percent in South America, 21 percent in Africa, 11 percent in North America, 8 percent in Asia and 2 percent in Australia.

The participants began the trial a median of one year after being diagnosed with HIV and with a median CD4 count of 650. The members of the immediate treatment arm went on ARVs at that point. Almost half of the deferred group eventually started treatment, with an average of about 400 CD4s.

The main reason those in the deferred group started treatment was because they fell below the 350 CD4 threshold. Some developed AIDS-defining illnesses, others became pregnant, and some became nervous when their viral load rose or their CD4 level dropped considerably, although not

yet to 350, and asked to start treatment.

The study design did allow for those in the deferred group to go on ARVs whenever they chose, regardless of the reason. Emailing POZ/AIDSmeds, Neaton said that, in an effort to minimize such "deviations from protocol," the INSIGHT team "encouraged site investigators to adhere to the protocol," providing them with data on the importance of answering the outstanding question about whether early treatment is ideal. "The investigators in turn routinely discussed this with their study participants," Neaton said.

The participants were followed for an average of around three years, contributing about 7,000 person-years of follow-up in each group. (Person-years represent the cumulative number of years participants spend in a study. So if 10 people each spend five years in a study and one person spends six, that amounts to 56 person-years.) Those in the immediate treatment arm spent about 95 percent of those person-years taking ARVs, while the deferred group spent a cumulative 25 to 30 percent of the study's follow-up time on treatment.

Those in the immediate treatment arm experienced 41 instances of AIDS diagnoses, serious non-AIDS illnesses (including a major cardiovascular problem, kidney and liver disease, and cancer) or death by any cause, compared with 86 instances in the deferred group. This meant that immediately starting treatment reduced the risk of such negative outcomes by 53 percent. The risk reduction was even greater for AIDS diagnoses.

The benefits of early HIV treatment were consistent across the regions of the study and similar between those in low- and middle-income nations when compared to those in high-income nations.

At this time there is no information available detailing any differences in the development of resistance to ARVs between the two study arms. The START trial investigators are aiming to present more comprehensive information on their findings at the International AIDS Conference in Vancouver, Canada, in late July.

In the START teleconference, James Neaton did disclose that the rate of what are known as grade 4 serious adverse events—severe physical symptoms or conditions that are potentially life-threatening—was similar in the two study groups. (These health matters are separate from the AIDS-defining illnesses the researchers took into account when calculating the 53 percent risk reduction. However, there is some overlap with the non-AIDS health problems, such as heart attack, included in that equation.) Clinical trials of medications examine the incidence of grade 4 events in an attempt to determine if the drugs are causing such harmful effects. This was apparently not the case in START, especially given that those in the immediate treatment group cumulatively spent about four times longer on treatment than those in the deferred arm.

One major point that is likely to get lost beneath the enthusiastic global response to the START trial findings is the fact that the health benefits of early treatment, while substantial in terms of the 53 percent reduction of risk, was quite small in terms of absolute numbers, at least during the three-year follow-up period. Three to four percent of the members of the delayed group and about

1.5 percent of those in the immediate treatment arm developed AIDS, a serious non-AIDS illness, or died.

The study also does not answer skeptics' questions about the cumulative lifetime effect of taking ARVs, and whether those who go on the medications earlier in the course of HIV disease may suffer negative consequences down the road. Such skepticism is clouded, however, by the fact that early treatment with ARVs may amount to only a few extra years tacked onto potential decades on treatment. On the other hand, if treatment protocols change significantly in the relatively near future, or if a cure for HIV is finally developed, those additional years spent on today's standard treatments may ultimately prove more significant.

Translating exciting findings into reality

World Health Organization (WHO) officials will take START into account when they meet in June to consider a revision to the agency's HIV treatment guidelines, with the intention of issuing new recommendations later in the year. Since 2013, WHO has advised starting HIV treatment once CD4s drop below 500, while major European guidelines in particular still put the cut-off at 350. The U.S. Department of Health and Human Services recommends beginning ARVs immediately after diagnosis, regardless of CD4 count. However, the U.S. recommendation to start treatment with CD4s above 500 has only been based on "expert opinion." START will likely alter that critical nuance.

"The question is, how quickly can we translate guidelines into clinical practice and into public health impact?" Mitchell Warren, executive director of the global HIV advocacy group AVAC, said in an interview.

Data indicates that, among HIV-positive Americans, there is a steady trend toward earlier treatment. In 2006, the median CD4 count upon beginning ARVs was about 300, and today it is the low-to-mid-400 range.

Median CD4 counts upon treatment initiation are also apparently rising in sub-Saharan Africa, although unevenly. When ARVs were first introduced in that part of the world in the early 2000s, the median CD4 at treatment start was just 50, and rose to about 150 by 2006 to 2007. In Rwanda, the figure went up from about 180 in 2009 to nearly 300 in 2011 to 2012. In 19 sub-Saharan African nations, the CD4 median for those going on ARVs was greater than 200 in 17 countries and more than 250 in 9 nations, while in two others it topped 300.

A major question in the developing world is whether there are enough resources to offer universal treatment. At this time, the answer appears to be a resounding "no." Of the estimated 31.8 million adults living with HIV worldwide, only about 38 percent are receiving treatment. The United Nations Joint Programme on HIV/AIDS (UNAIDS) estimates that reaching targets from rapid HIV treatment scale-up—more than doubling the number of people treated—in low- and lower-middle-income nations will require $18.4 billion in forgeign investment in 2020. Current international funding stands at about $8 billion. Both the Global Fund and the United States' efforts to provide

HIV treatment in poorer nations have seen relative flat funding throughout the decade.

Treatment figures are similarly grim domestically: Out of an estimated 1.2 million HIV-positive Americans, 37 percent are taking ARVs and 30 percent have a fully suppressed viral load.

Tim Horn, HIV project director at Treatment Action Group, noted in an interview that, in the United States, “issues like undiagnosed and untreated mental illness, active substance use, unstable housing, and poor access to support services are frequently cited barriers to both HIV care and treatment.”

Some HIV advocates have expressed concern that enthusiasm over the START trial results could wind up effectively steamrolling some HIV-positive people’s right to choose when to start treatment, and that eager prescribers and public health officials may overlook the byzantine structural challenges standing in the way of universal treatment.

Warren, for one, was quick to stress that people with HIV should be “offered” as opposed to “put on” treatment.

START, according to longtime treatment activist David Barr, “tells us about the biological effects of treatment. But it doesn’t tell us anything about patient readiness. Foisting treatment upon people who are not ready to commit to it is likely to result in poor adherence.”

Joel Gallant, MD, medical director of specialty services at Southwest CARE Center in Santa Fe, New Mexico, argued that concerns about overzealous HIV physicians prescribing immediate HIV treatment regardless of patient readiness are “far-fetched.” At least according to his observations of his colleagues’ attitudes and prescribing patterns, the U.S. guidelines’ recommendation of universal treatment has not had such an effect.

“Most HIV clinicians know that [ARV treatment] is rarely an emergency and that treatment can usually be deferred until the patient is ready,” Gallant said.

Editor’s note: a previous version of this article misstated the current amount of international funding for HIV treatment in lower- and lower-middle-income nations. The correct figure is an approxmiate $8 billion, rather than $6.3 billion as previously stated. Also, Joel Gallant’s title is now medical director, rather than associate medical director.

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