Evaluating the Costs of Earlier HIV Treatment

Emerging data suggest that starting antiretroviral therapy earlier than is currently recommended provides even greater protection against illness and death. But starting treatment when CD4s fall below 500, as opposed to the current 350 cutoff, may not be as easy as some imagine.

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Earlier this year, U.S. treatment guidelines adjusted the official CD4 cutoff used to determine when antiretroviral (ARV) therapy should be started—from below 200 to below 350 cells—when studies suggested that the benefits of earlier treatment, including fewer AIDS and non-AIDS health problems, outweighed the risks. Now research says that a starting point of 350 CD4s may not be high enough.

In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study, reported last month at a conference in Washington, DC, people who waited to start ARV treatment until their CD4 count dropped below 350 had a 71 percent higher chance of dying during the course of the study than those starting treatment with CD4s between 351 and 500.

Experts agree that additional research is needed to confirm the NA-ACCORD results before treatment guidelines are changed. Nevertheless, at a gathering of experts in October hosted by the San Francisco advocacy group Project Inform, many researchers and activists predicted that it's only a matter of time before earlier treatment becomes the official recommendation. Some, however, remained cautious about jumping on the early treatment bandwagon—at least at this stage of the game.

"I think that one can mount arguments for not starting treatment earlier," explains Daniel Kuritzkes, MD, a longtime AIDS researcher from Harvard Medical School in Boston. As an example, he says, "We don't know if the benefit you might achieve in terms of reducing AIDS- and non-AIDS-related complications will be better or greater than the harm you might do from the long-term toxicity of therapy."

Arguments in favor of earlier treatment stem from the widely held assumption that ARV therapy is both more potent and tolerable than it was 10, or even five, years ago. While this may be true, treatment is not without its challenges—side effects, adherence problems and drug interactions remain very real issues. Starting treatment earlier also means having to contend with these

challenges earlier—and for an even longer period of time—than is currently necessary. And in a country already struggling to fund HIV therapy, the science of early treatment won't necessarily dictate what is economically possible.

Perhaps the greatest obstacles will be the willingness and readiness of patients themselves. Many people living with HIV enter care with fewer than 500 CD4 cells, with concerns far greater than ARV therapy on their minds—stigma, fear of disclosure, ignorance about HIV/AIDS, limited support and stability, drug abuse and depression are pervasive among newly diagnosed HIV-positive people and, as countless studies have documented, major barriers to the effective use of HIV treatment.

Clinical trials may ultimately change treatment guidelines and lead to earlier treatment recommendations, but it's going to take a lot more than data to change the minds and hearts of people with HIV.

Earlier May Be Better

A handful of studies now suggest that early treatment effectively reduces the risk of illnesses and deaths. Untreated HIV, for reasons scientists haven't entirely figured out, is associated with a higher risk of non-AIDS-related problems, including cardiovascular disease and a variety of cancers—even in people with high CD4 counts. What have been missing from this growing body of research, however, are conclusive results from a clinical trial designed to specifically test the value of early treatment.

An international trial, called the START study, is set to begin enrolling next year. It will be the first large head-to-head comparison of starting treatment at 500 versus waiting until CD4 counts drop to 350. Dr. Kuritzkes, however, questions whether such a study will be able to get off the ground or provide a meaningful answer. "It's very hard to find people with more than 500 CD4s. If you need 4,000 people [with] over 500 [CD4s] to do a randomized trial like this, it's going to be quite a challenge to find them."

Even if the study manages to recruit enough volunteers, Kuritzkes points out, by the time START produces an answer, "the field will have once again moved on to newer drugs and newer regimens. This will leave a question mark whether the findings, whatever they are, were specific to the regimens tested."

In the absence of START or another clinical trial, the experts are left having to make recommendations based on cohort studies. These studies—which include NA-ACCORD—come with weaknesses. For example, they don't proactively randomize people to different treatment groups, thus making it difficult for researchers to ensure that study participants receiving early treatment are similar to those delaying treatment.

This doesn't worry Kuritzkes, however, as cohorts form the bulk of studies supporting the current recommendation for starting treatment when the CD4 count hits 350 cells. "There's no

randomized trial about 350, and I think [that the argument for doing a controlled trial has] sort of come and gone because the cohort studies have now all convincingly shown as that 350 is an appropriate place [to start treatment]."

Igho Ofotokun, MD, an Assistant Professor of Medicine who also treats many inner-city HIV patients in Atlanta at Emory University, agrees with Kuritzkes: "That is probably where the science is going to go, and we just need more data."

Start Early? Not So Fast!

While researchers have been optimistic about further preventing complications and deaths using earlier treatment, few seem to be publicly pondering its possible downsides. Changing guidelines to treat earlier, Kuritzkes says, "would have enormous cost implications and would potentially affect tens or hundreds of thousands of people in the United States and millions of people worldwide."

AIDS Drug Assistance Program (ADAP) waiting lists, even for those who require treatment immediately, are not a thing of the past. Kuritzkes says some researchers are beginning to do cost projections to determine what earlier treatment might mean financially.

There are also adherence challenges and, with them, the risk of treatment failure due to drug resistance. "There's always concern that the sooner you start therapy the longer you have to adhere to it, and so over time problems with adherence and therefore with treatment failure and drug resistance could mount and potentially negate some of the benefits of earlier initiation of therapy," Kuritzkes says.

Changing treatment guidelines to initiate therapy at 500 CD4s would mean that most people would find themselves in the position of many of Dr. Ofotokun's patients, who find out they need treatment during their first visit. "One of the big issues in our clinic is that the average CD4 cell count when people present is around 50," he says. "We almost always have to start people on treatment as soon as they show up."

Fear and stigma already keep many people, as with Ofotokun's patients, from finding out their status until they have AIDS. "There are two groups of people," Ofotokun explains. "There are people who are resigned and say, 'No matter what I do, this is a bad disease and I'm just going to die.' So we have to educate them. Then there's the other group of people who say, 'I've had this for many years, and I've never been sick, and I don't care what you say. I'm not going to take any drugs!'"

Middle of the Road

Ultimately, Kuritzkes says, the best road may be a middle path between where we are now and simply starting everyone at 500. Such moderation will likely rest on the role that inflammation and over-activation of the immune system play in disease progression. Concerns about inflammation

are part of the rationale for using ARV treatment earlier. Many experts believe that too much inflammation, which occurs when people are not on treatment and HIV is actively reproducing, may be a factor in many of the health complications seen in studies such as SMART and NA-ACCORD.

Kuritzkes hopes that the big cohort studies will not only tell us whether starting earlier is a good idea, but also help us identify the specific individuals at highest risk for health complications. “What we really need to understand [are the factors that] place individuals at risk for having these non-AIDS events at high CD4s,” Kuritzkes says. “Can we also find markers—whether they’re traditional serum markers that are easy to measure in the lab or genetic markers or biomarkers—that will help us identify which patients to treat [earlier]?”

Identifying those at greatest risk would not only keep us from needlessly treating thousands of people, it may also provide the motivation some people need to go on treatment in the first place. It’s one thing to tell people they’ve got a one in 200 chance of getting sick—it’s another to tell them that most people with their specific health profile are at risk. Kuritzkes says getting this kind of data is vital “so that we know how to use antiretroviral therapy and our dollars most effectively.”
