Treatment for Everyone With HIV?

New guidelines from the U.S. Department of Health and Human Services recommend starting HIV meds even earlier than before—but the updates are not without controversy.

December 15, 2009 By David Evans

On December 1, 2009, the rotating committee of researchers, clinicians and community activists responsible for writing HIV treatment guidelines for the United States issued what was fated to be a controversial new set of recommendations about when to start HIV treatment. The document—the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents*—now recommends that people with HIV start antiretroviral (ARV) therapy much sooner than had previously been recommended.

"You know the when-to-start question has been an open one in our field since AZT [Retrovir] was first released in 1987, and it continues to be a source of controversy," says Paul Sax, MD, the director of the HIV program at Brigham and Women's Hospital in Boston and a member of the guidelines panel. Sax also stresses that he speaks for himself, and not for the guidelines panel.

The new recommendations continue in that contentious tradition, and will likely spark further debate. While many activists and community physicians agree that earlier antiretroviral (ARV) treatment is probably a good idea for many people with HIV, others are decidedly unconvinced that there's enough data from studies to justify recommending treating nearly everyone living with HIV.

Though Paul Bellman, MD, an HIV-specialist in New York City, thinks the new guidelines "are an excellent reflection of the hard work, scholarship and commitment to good patient care on the part of the panel members," he also wishes that they offered a fuller discussion of the risks and unknowns of starting treatment earlier.

The panel now recommends people with CD4 cell counts of 500 or below start HIV treatment right away. Previously, the guidelines recommended waiting until CD4s fell to below 350. The panel was split 50/50 about whether people with over 500 CD4s should start; half of the panelists essentially recommended treatment for everyone with HIV. Aside from the personal health benefits of being on ARV treatment, the panelists in favor of very early treatment also cited a public health benefit—suppressing viral loads in a large number of people to slow the ongoing spread of HIV.

In contrast, the more skeptical activists and providers contend that while very savvy and

experienced physicians and patients know enough about the data—or the lack thereof—to assess the risks and benefits of earlier treatment, most providers and patients don't. Paul Dalton, a longtime activist who is an HIV-positive member of the DHHS panel, stresses that these caveats are discussed in the heavily annotated discussion sections of the guidelines. "My belief is that many users of the guidelines look at our tables and look at our bullet points, but don't look at the discussion sections," he says.

The guidelines state clearly their purpose is merely to distill the best HIV science and make recommendations to help guide clinicians and patients as they make individual treatment decisions. Some activists say the panel underestimates the guidelines' strength and scope, arguing the published recommendations now carry so much weight that they have become the de facto standard of care for the United States—turned to by health insurance companies and government programs and institutions to make coverage decisions.

Ironically, this power could actually undermine researchers' abilities to collect solid data needed to conclude, beyond doubt, that starting treatment as early as possible is in the best interest of people living with HIV. The current extension of treatment to people earlier in the course of disease was based mostly on retrospective studies—a look back at the real-world experiences of people living with HIV participating in clinic cohort studies. The best evidence comes from randomized clinical trials that follow patients over time and are designed specifically to answer key treatment questions. In fact, one such trial is just getting off the ground and is comparing people who start treatment at CD4 counts above 500 with those who wait until their counts drop to below 350.

Simon Collins, a British activist from HIV i-Base in London, worries that the U.S. groups responsible for ensuring that studies are run ethically and safely, called institutional review boards (IRBs), might decide that it would be unethical to make people enrolled in the START study wait until their CD4s drop to 350—unethical because the new guidelines recommend treatment for those with CD4s of 500 or below and even suggest that people consider treatment for those with CD4s above 500. The consequence would be the derailment of our best hope for a rigorous study answering the when to start question.

"[START] is a seven year trial," counters guidelines panelist Renslow Sherer, MD, a professor of medicine at the University of Chicago. Waiting seven years for the results of the START study and ignoring the available cohort data, he says, wasn't a feasible option for the panel.

In the end, the fate of the new guidelines—they're now official and can't be put back in the box—will rest in the hands of the doctors who treat HIV on the ground and the people with HIV who must decide whether to fill that prescription.

Tony Urbina, MD, medical director of HIV education and training at St. Vincent's Catholic Medical Center in New York City, says that the new guidelines are similar to his treatment philosophy, but acknowledges how challenging individualized patient care can be. "It's kind of easy to be in an ivory tower and say, 'From the data and the evidence I think it's best to start patients with a

higher CD4 count,'" he says, "and then you have that patient sitting in front of you and there are really so many factors that go into the decision of when to start therapy."

Why Start Earlier?

The previous guidelines, issued in November 2008, stated that people with CD4 counts under 350 should take ARV therapy. Several studies were cited that showed a significant increase in the risk of illness and death for people who waited to start HIV treatment until their CD4 counts dropped below 200 compared with people who started treatment between 200 and 350. Those guidelines also stated that there was rationale, though only limited data, to start treatment even sooner. They left those decisions, however, to the individual clinician to discuss with people living with HIV.

The new guidelines still strongly recommend that people with less than 350 CD4 cells be on ARVs. They now also recommend that people with between 350 and 500 CD4s start therapy. However, the guidelines' panelists didn't universally agree on the strength of that recommendation. Typically two thirds of the 30 panelists must agree on the strength of a recommendation to merit a bona fide change in the guidelines. This time 55 percent voted that the recommendation for treating between 350 and 500 be strong, and 45 percent voted that it be moderate. Based on the votes, though, the recommendation to start treatment earlier was unanimous.

"I'd say the evidence [to recommend starting before 350] is strong, in my opinion," Sax says, "and some of the panelists think the evidence is moderate, but you can see by the way it was phrased there was very little disagreement about that."

The rationale behind recommending treatment for those with up to 500 CD4s comes primarily from two large cohort studies. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study and the ART Cohort Collaboration (ART-CC) study strongly suggested that people who waited to start treatment until CD4s dropped below 350 faced a higher risk of premature death, from any cause, than people who start treatment at a CD4 count above 350.

"For patients with CD4 counts above 500, there was less agreement," Sax acknowledges, ultimately because far less data unanimously support very early treatment. That said, emerging data—again from cohort studies—suggest that uncontrolled HIV replication might be associated with a number of illnesses not traditionally associated with AIDS. These include non-HIV-related cancers, cardiovascular disease, liver disease, kidney disease and immune inflammation.

Collins thinks, though, that the panel might have reached too far in using these data to guide their recommendations. "I am an advocate for early treatment," he says. "I think ongoing viral load probably explains many of the higher risks we see for many other complications. I just want this to be based on evidence. The guideline panel has been wrong many times before—they could be wrong again now."

Collins is referring to the significant shifts in the guidelines since protease inhibitors were introduced in the late 1990s. The first set of guidelines, published in 1998, recommended hitting HIV "hard and early" and treating anyone who has a CD4 count under 500. Within four years, it

became clear that ARVs couldn't easily clear HIV from the body and that the available meds caused significant side effects. As a result, the next version of the guidelines recommended holding off on treatment until the CD4 count falls below 200.

With emerging data suggesting that ARV therapy has protective effects when started earlier, along with today's better crop of drugs, early therapy is once again the recommendation. This, Dalton believes, is where the guidelines will remain, though he stresses that this is his own opinion and not those of the panel at large. "I personally want to retire the idea of the swinging pendulum metaphor," he says, "because it accepts the idea that we're going to keep going back and forth in this almost mechanical, fatalistic kind of [debate]…and I don't think that reflects what's really going on."

A Balancing Act

Bellman believes the data are not as strong as the panel feels they are, and he suggests ARV treatment is not necessarily the best answer to some of the problems noted. "The theoretical arguments in terms of inflammation/immune activation and neurocognitive decline are just that: theoretical," he says, asserting that cardiovascular disease, in particular, is something that can be dealt with successfully through lifestyle modification.

Sax points out that non-HIV-related illnesses are not the only risk if treatment is delayed. One aspect not highlighted much in the guidelines is the finding that many people who wait to start treatment until their CD4 count gets low never experience the robust CD4 increases we've come to expect with ARV therapy. "If we knew that everyone could wait safely until 200 and then they went on therapy and they would normalize their CD4 count, that would be great," says Sax, but unfortunately there's no tool in the hands of clinicians to make that prediction.

The panelists also point out that the risk-benefit balance of ARV treatment has invariably shifted in recent years. "In earlier versions of these treatment guidelines," the panelists write, "concerns about long-term toxicity, reduced quality of life and the potential for drug resistance served as key reasons to defer HIV therapy for as long as possible. Inherent in this argument was the assumption that the harm associated with viral replication was less than the harm associated with the toxicities of antiretroviral drugs in patients with higher CD4 count. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the drug combinations now available are better tolerated than previous regimens, leading to greater efficacy and improved adherence. The current guidelines therefore emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity."

The guidelines go on to praise the relatively low number and intensity of side effects of the newest ARVs. But there are downsides, and Bellman believes more should be said in the guidelines about the risks and shortcomings of treatment. "We should be cautious about presuming their long-term toxicity is minimal," he cautions. "My general impression is that the newer drugs are a lot better, but we've been humbled so many times before—about what we thought we knew, and what we thought was okay and wasn't."

Moreover, says Collins, “None of these studies [upon which the new guidelines are based] collect data on resistance and how it limits future treatment options, or on quality of life from non-life-threatening side effects.”

How providers in the field interpret the guidelines will certainly influence where and whether they are adopted. “I’d say that it depends not only on the conviction of the patients, but also the provider as well,” Urbina adds. “How strongly do you feel that a patient should start with a CD4 count of 900 or 550, because that’s going to factor into how you influence the patient’s decision.”

Between Doctor and Patient

The guidelines “can be dehumanizing” if the CD4 count is overemphasized when making the important decision of when to start, says Bellman, and “if each patient’s specific needs, concerns and life situation are not taken into account.”

It’s the dynamic of that relationship that is ultimately going to prove one of the greatest challenges to the guidelines’ adoption. A significant percentage of people are so frightened of HIV that they don’t even get tested until their CD4 count is well below 350, frequently less than 200. Others do get tested, but disappear from care until they get sick.

Sax agrees: “For many people who are diagnosed, the guidelines are obviously irrelevant, because their CD4 counts are already too low.”

Bellman worries that a tendency to minimize the reality of side effects, both within the guidelines and among some providers, worsens the fear and stigma that keep people from care in the first place. “If the patients don’t feel that their concerns about side effects are heard,” he stresses, “then that’s going to cause them to lose trust.”

A recent study funded by Bristol-Myers Squibb seems to bear this out. The No. 1 reason people with HIV they surveyed gave for delaying ARV treatment was fear of side effects.

Sax says the panel agrees with the importance of the patient and provider relationship and individual decision making. He says they strive to provide the tools providers need to maximize this communication. The relationship is discussed in a number of places in the guidelines, but as Dalton says, “What the guidelines can’t possibly do is bridge the divide that plagues the entire health care system, the difference between the haves and the have-nots.”
