Changing the HIV Treatment Paradigm

What will HIV treatment look like in the immediate future? Some of the brightest scientists and activists recently gathered to develop an agenda to answer that question and explain how to keep us on track.

November 4, 2008 By David Evans

Project Inform, the HIV treatment information and advocacy group, explored the future of HIV treatment during HAART 2.0 (H20), a think-tank style conference it hosted in October. Thirty-five of the country's leading HIV treatment activists, scientists, pharmaceutical representatives and Food and Drug Administration (FDA) staff spent nearly two days assessing where we are with HIV treatment, where we ought to be going—and how to get us there with speed and confidence.

Conference participants explored three primary themes: how to help people who are already developing resistance to the most recently approved drugs; what to do about immune system over-activation; and what will be needed to change the treatment paradigm for first-line HIV therapy. In each area, there were differences of opinion regarding the directions to take. Nevertheless, some consensus emerged that may help people with HIV make better treatment decisions in the near future and beyond.

Scientists in attendance discussed new tests—notably levels of key proteins, or biomarkers, in the blood—that, if confirmed, may help predict who might benefit from earlier treatment and how likely a person is to suffer cardiovascular disease and non-AIDS-related cancers. Though participants differed in their thoughts about which research will best determine whether starting antiretroviral (ARV) therapy earlier is a good idea, most felt we are clearly headed in that direction.

Encouragingly, data from many sources confirm that while current ARV treatment continues to be problematic for some, it is working far better and for far longer than most would have predicted—even in people who are heavily treatment experienced.

Ultimately, H20 attendees concluded that the priorities of HIV treatment research going forward will be heavily influenced directly by the needs of people living with HIV and the activists who advocate on their behalf.

When to Start

When to start ARV therapy—and what drugs to use as first-line treatment—dominated much of the conference discussion. Late last year, the U.S. Department of Health and Human Services (DHHS) issued new HIV treatment guidelines, recommending that all HIV-positive individuals with CD4 counts below 350 be started on treatment. Before December 2007, DHHS recommended treatment for those with 200 or fewer CD4s. But with the arrival of new data from the large SMART clinical trial and other studies suggesting that people with HIV are at a higher risk of death—notably from non-AIDS-related health problems, such as cardiovascular disease and cancer—if they're not on treatment with a CD4 count between 200 and 350, the official start recommendation was revised.

The conference participants rigorously debated the meaningfulness of the newest data and the plans for another large clinical trial, called the START study, beginning early next year to determine whether starting HIV treatment at 500 CD4 cells will lead to even less cardiovascular disease and cancer and fewer deaths. Just days after the HAART 2.0 conference concluded, a study was debuted at the 2008 joint meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Disease Society of America (IDSA) in Washington, DC, lending further weight to the notion of starting treatment earlier.

While it will likely be several years before the results of START and other when-to-start studies provide meaningful information, all of the H20 participants conceded that much work will be needed to prepare people with HIV for the possibility of starting treatment sooner. As it is, more than a quarter of people learn they have HIV when their CD4s are already below 350 and thus face an immediate decision whether to begin ARV therapy. Studies have found that people adhere best when they are well prepared and committed to treatment—a rather optimistic expectation for people who have just learned that they are infected with the virus.

Changing guidelines to recommend treatment at 500 CD4 cells ultimately means that many more patients will be encouraged to start treatment soon after testing positive. Many newly diagnosed people struggle with mental health, substance use and societal issues—factors that can greatly impair adherence—so H20 participants agreed that now is the time to address these significant concerns.

(The early treatment debate, including the research that speaks for and against it, will be reviewed in much greater detail in the next AIDSmeds exclusive, to be published November 18.)

What to Start With

It is also critical to define what combinations of the 20-plus approved ARVs work best together and in what order. For instance, Prezista (darunavir) was recently approved for people who've never taken treatment before, and several participants indicated that they expect Isentress (raltegravir) to be approved for first-time treatment takers in the not too distant future. Are these drugs, with their unique resistance profiles, best preserved for treatment-experienced patients? Or should treatment-naïve patients benefit from their potency and apparent tolerability early on?

As excited as some were about this possibility, others expressed caution, reminding their colleagues that we've got nearly a decade of experience with many current first-line therapies and that unknown side effects could eventually appear with the newer therapies.

Another drug that may get a second chance at approval for treatment first-timers is the entry inhibitor Selzentry (maraviroc), due to a reanalysis of data involving treatment naïve patients using new, more sensitive tropism tests.

The original study concluded that Selzentry was somewhat inferior to Sustiva, with both combined with nucleoside analogues, in treatment-naïve patients. The new analysis, using highly sensitive tropism tests, allowed the researchers to exclude people with virus that used the CXCR4 coreceptor on CD4 cells to infect them. Such individuals were originally missed using a less sensitive test at the beginning of the study and, thus, shouldn't have been enrolled.

Scientists have also been pleasantly puzzled by the fact that in nearly every study, people taking Selzentry seem to gain significantly more CD4 cells than people on other regimens. It has been noted in recent years that people who are genetically unable to make CCR5 seem to have less severe progression of rheumatoid arthritis and possibly lupus, two diseases characterized by immune system inflammation—itself a growing concern of researchers in HIV disease.

This doesn't mean that blocking CCR5 with drugs like Selzentry will necessarily have anti-inflammatory effects, but it could. Further studies of Selzentry and CD4 gains and inflammatory proteins are ongoing or planned according to several participants at the conference.

Inflammation and HIV

The role of inflammation in HIV disease was another topic of much discussion. Data from the SMART study, published by one of the conference participants, found that the risk of a heart attack among those not on treatment was linked to elevated levels of at least two inflammatory proteins, D-dimer and Interleukin-6 (IL-6). Moreover, the higher a person's viral load, the more likely he or she was to have D-dimer and IL-6 elevations.

There is growing accord that persistent immune inflammation occurs in HIV disease, which may increase the risk of cardiovascular disease and some non-AIDS cancers. But there are a number of inflammatory biomarkers to look for and it's not yet clear which are associated with these health problems in people with HIV.

While most of the conference participants agreed that further research is needed to identify and prove the possible causes of inflammation, along with the biomarkers associated with it, nearly all agreed that the evolving science will influence treatment decisions during the coming years. Several participants believe that such inflammation is what makes HIV deadly in humans and, as a result, are looking to research to prove this and to test immune-based therapies to curtail inflammation and treat HIV.

Multidrug Resistance

Drug-resistant HIV—including virus that has become resistant to the handful of more recently approved ARVs—is a constant threat. Yet, according to information presented at H20, the number of people at the end of their HIV treatment rope is much lower than had been anticipated.

According to Roy M. Gulick, MD, MPH, a professor of medicine at Weill Medical College of Cornell University in New York and a conference organizer, the more immediate questions are: How many people are becoming resistant to the most recently approved drugs, and what are we going to do about such individuals. One of the hopeful pieces of information coming out of the conference was the small number of people who now have one or fewer treatment options left. Though doctors, scientists and activists were all aware of a few individuals in this dire situation, the number is still very small and doesn't appear to be growing quickly. In fact, data presented by Dr. Gulick showed that the majority of treatment-experienced people in studies testing combinations of the newest ARVs—including Prezista (darunavir), Intelence (etravirine), Isentress (raltegravir) and Selzentry (maraviroc)—are able to achieve and maintain undetectable viral loads for significant lengths of time.

However, clinical trials don't necessarily reflect what's happening in the real world, and activists at the conference were urged to call on labs conducting drug resistance testing to share information regarding the number of people living with HIV without effective treatment options, both now and in the foreseeable future.

The numerous drug approvals over the past two years have been extraordinary and ultimately allowed treatment-experienced patients to piece together entirely new ARV combinations to suppress their highly drug-resistant HIV. As one conference participant put it, however, this kind of happy coincidence happens rarely, and the pipeline of experimental drugs is now awfully empty by comparison.

This is not necessarily a grim situation. One researcher who has done extensive studies of heavily treatment-experienced individuals reported that, before the advent of the newer therapies, studies showed that as long as patients were able to maintain a viral load of less than 10,000 they continued to do well clinically, though they did continue to develop further resistance to the drugs they took.

Project Inform will produce an extensive report from the H20 conference that will include the action steps outlined for each area of research. While the scientists at the meeting will be responsible for making sure such action is taken, they universally expressed how important the voices of people with HIV and their advocates will be to ensure that priority is given to the science and treatments with the greatest promise of improving HIV treatment.

Keep an eye on projectinform.org *for a more in-depth report coming soon.*