More on ’When to Start"

June 10, 2009 By Paul Dalton

Yet more evidence supports earlier treatment

A clinical trial looking at when to start anti-retroviral (ARV) treatment in Haiti was halted early when unacceptably large differences were seen between those who started earlier compared to later. The study’s DSMB- an independent group charged with ensuring the safety of the study participants- looked at preliminary results from CIPRA HT001 and found that people who waited to start HIV treatment until their CD4 counts fell to below 200 (or they were diagnosed with AIDS), were 4 times more likely to die than those who started sooner. The DSMB stopped the study, determining that these results made it unethical to continue the study, and recommended that everyone in the study whose CD4 count was less than 350 be offered treatment immediately.

The most immediate impact of this finding might be on the developing world, where many guidelines recommend delaying initiation of ARV therapy until CD4 counts fall to 200. The limited availability of ARVs in less wealthy countries is the main driver for these kinds of recommendations, along with insufficient medical infrastructures and other issues. This finding might help to tip the balance and help to push for the expansion of ARV therapy in the developing world.

It also adds to the growing body of evidence supporting earlier treatment. In the US current guidelines (disclosure: I am a community member on the Departement of Health and Human Services (DHHS) Adult and Adolescent HIV Treatment Guidelines Panel), recommend treatment when CD4 counts fall to 350- so this study does not directly add to the ongoing debate over whether to recommend treatment *earlier* than 350. It does however stack up well alongside a growing list of studies (one I wrote about recently here is the NA-ACCORD study) that are consistently finding better outcomes for people who start treatment earlier.

For my part, I am growing more and more convinced that the time to start treatment is as soon as you ready. In addition to HIV’s impact on CD4 counts and HIV viral loads, there is more and more evidence that untreated HIV damages our hearts, kidneys, brains and maybe more. This, along with more tolerable drugs and more collected experience using them makes the argument for starting treatment early stronger and stronger.

At the risk of oversimplification here is how I see the pro/con argument for earlier versus later treatment. On the earlier treatment side it goes something like this:

"In medicine the basic rule is that earlier treatment l

eads to better outcomes. This is particularly true with infectious diseases like HIV. There is abundant evidence that HIV drives ongoing immune dysregulation, including both immune suppression and inflammation. The SMART study and others have shown definitively that people who delay starting treatment are more likely to get sick and/or die, from all causes- including AIDS defining conditions and non-AIDS related illnesses like heart and kidney disease. Moreover, there are enough treatment options available now, allowing most people enough available combinations to ensure decades of successful therapy. Lastly, in addition to its beneficial effects on the person with HIV, decreasing HIV levels through treatment is likely to reduce the transmission of HIV, thereby improving community health."

The argument against might sound something like this:

“There are simply not enough data. The first principle in medicine is to do no harm, and we know that HIV drugs can cause harm. Unless and until we have conclusive evidence from a prospective, randomized clinical trial demonstrating that earlier treatment leads to longer, healthier lives the only clear beneficiaries of earlier treatment are the pharmaceutical companies that sell them. We mad the mistake of ’hit hard, hit early’ and many people suffered unnecessarily- from disfigurement to heart disease, from persistent diarrhea to peripheral neuropathy. And, let us not forget that while these new drugs look good today, there is no guarantee they will look half this good in the long term. At best we have two or three years worth of data on any drug when it comes to market, yet we treat people with HIV for the rest of their lives. Lastly, it has never been proven that HIV treatment reduces HIV transmission- and some think it might increase risk-taking behavior, possibly leading to higher rates of new infections.”

I really see both side of this argument, but I find myself more and more convinced that earlier treatment is better- especially when we expand our thinking to include long term health outcomes- looking at things like heart disease and dementia. I know full well how crappy the drugs can be- I have taken most of them at one point or another. I also think that untreated HIV is more toxic than any of the drugs widely used today- the damage it does might be harder to feel than the side effects of drugs, but it is no less real.

More and more the question for me is not so much when to start, but how to get people ready to start. The demands of ARV therapy are real and they are challenging. Mixing in issues of mental health (especially depression, and also- to a lesser extend substance abuse), uneven access to treatment, HIV associated stigma and so on- makes it even more of a challenge.

Challenges are just challenges- and increasingly I think it is the job of HIV docs, researchers, activist and people living with HIV to pay attention to non-traditional factors affecting HIV treatment decisions- not just viral load and CD4, but also psycho-social support, HIV prevention, inflammation and so on.

Below is the full text of the National Institutes of Health statement on this study. If you have any questions about this study, or any other, please ask me- this is what I do.

Starting Antiretroviral Therapy Earlier Yields Better Clinical Outcomes

Interim Review Leads to Early End of Clinical Trial in Haiti

A clinical trial has demonstrated that HIV-infected adults in a resource-limited setting are more likely to survive if they start antiretroviral therapy (ART) before their

immune systems are severely compromised.

On May 28, 2009, an independent data and safety monitoring board (DSMB) met to conduct an interim review of an ongoing clinical study known as CIPRA HT 001, which is being conducted in Haiti. The DSMB found overwhelming evidence that starting ART at CD4+ T cell counts--a measure of immune health--between 200 and 350 cells per cubic millimeter (mm3) improves survival compared with deferring treatment until CD4+ T cells drop below 200 cells/mm3. In light of these results, the DSMB recommended that the trial sponsor--the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health--end the trial immediately, before its scheduled conclusion. NIAID agreed with the DSMB recommendation, and all study participants who have fewer than 350 CD4+ T cells/mm3 will be offered ART.

The study investigators say this new finding has the potential to change the standard of care for HIV

infection in dozens of countries around the world where ART is initiated only when CD4+ T cell counts drop below 200 cells/mm3. Like the results of several recent epidemiologic studies in developed countries that examined the optimal time to begin ART, the new finding underscores the importance of identifying people who are HIV-infected earlier in the course of their infection and starting ART earlier.

“The public health community now has evidence from a randomized, controlled clinical trial--the gold standard--that starting ART at CD4+ T cell counts between 200 and 350 cells/mm3 in resource-limited settings yields better health outcomes than deferring treatment until CD4+ T cell counts drop below 200 cells/mm3,” says NIAID Director Anthony S. Fauci, M.D.

“The number of people who meet the medical criteria for receiving ART likely will grow as treatment guidelines are revised as a consequence of this finding, challenging the global community to supply

antiretroviral drugs to all who need them," adds Carl Dieffenbach, Ph.D., director of the NIAID Division of AIDS. "Today, only 30 percent of HIV-infected individuals in low- and middle-income countries who need ART are receiving it."

The clinical trial CIPRA HT 001 began in 2005. It is funded by NIAID through the Comprehensive International Program of Research on AIDS (CIPRA) and is being carried out by the Haitian Group for the Study of Kaposi's Sarcoma and Immune Deficiency Disorders (GHESKIO) Centers in Port-au-Prince, Haiti. The principal investigator is Jean William Pape, M.D., the director of the GHESKIO Centers and a professor of medicine at Weill Medical College of Cornell University.

The trial enrolled 816 HIV-infected adults ages 18 and older with early HIV disease and CD4+ T cell counts between 200 and 350 cells/mm3. Half of the participants were assigned at random to begin ART within two weeks of enrollment, and the other half were

assigned to defer treatment until their CD4+ T cell counts dropped below 200 cells/mm3 or they were diagnosed with AIDS. This deferred treatment is in keeping with the standard of care in Haiti and the current guidelines of the World Health Organization (WHO). The first-line treatment regimen consisted of the anti-HIV drugs zidovudine, lamivudine and efavirenz.

At the time of the DSMB interim review, six participants in the early treatment group had died, while 23 participants in the standard-of-care group had died--nearly four times as many. The DSMB also found that, among participants who began the study without tuberculosis (TB) infection, 18 people in the early treatment had developed TB, while 36 people--twice as many--in the standard-of-care group had developed TB. These results were statistically significant.

In light of these results, the DSMB recommended that NIAID end the trial immediately and that the study team offer ART to all participants in the standard-of-care

group who have fewer than 350 CD4+ T cells/mm3. The DSMB also recommended that the study team continue to follow all participants for another year and make every effort to ensure that participants receiving ART continue their therapy. NIAID concurred with these recommendations.

The study investigators are notifying all participants and have notified institutional review boards and national ethics committees involved with CIPRA HT 001 as well as the Haitian Ministry of Health about the findings of the DSMB. Investigators also have shared the information with WHO, the U.S. President's Emergency Plan for AIDS Relief, and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

For more information about CIPRA HT 001, see Questions and Answers: The CIPRA HT 001 Clinical Trial.
