Start HIV Treatment Early—But When?

February 10, 2009 By Tim Horn

There are now multiple lines of evidence supporting the earlier initiation of antiretroviral (ARV) therapy than is currently recommended. But if guidelines experts are to commit a new recommendation to paper, they will require research consistently illustrating when treatment should be started based on CD4 cell counts. While two presentations reported Monday, February 9th, at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) confirm that earlier treatment yields life-saving benefits, they did not agree on the best time to begin taking ARVs.

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study reported at CROI by Mari Kitahata, MD, of the University of Washington in Seattle found that HIV-positive people who deferred treatment until their CD4 cell counts fell below 500 faced a 60 percent greater risk of death, compared with those who started ARVs above this CD4 cutoff.

A second study, involving data from 15 North American and European cohorts, produced much more conservative results. Patients starting therapy with CD4 counts between 250 and 350—reflective of the current standard-of-care—had a 28 percent higher risk of AIDS or death compared with those starting treatment with CD4s between 350 and 450. Among those starting ARVs with CD4s above 450, no additional AIDS-free or survival benefit was discernable.

The first solid evidence supporting early HIV treatment, also from the NA-ACCORD study, was presented by Dr. Kitahata at the 2008 joint meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Disease Society of America (IDSA), held in October in Washington, DC. Dr. Kitahata's group reported a 71 percent higher risk of death for patients who deferred treatment until their CD4s fell below 350, compared with those who started ARVs when their CD4s were between 350 and 500.

At the time of her original ICAAC/IDSA presentation, the NA-ACCORD researchers did not have the data necessary to determine if starting therapy even earlier—with a CD4 count above 500—confers further survival benefits. For her CROI presentation, Dr. Kitahata's group included 2616 HIV-positive people who began treatment when their CD4s were above 500—or, more specifically, within a year and a half of a documented CD4 count above 500—compared with 945 people who started treatment within a year and a half of their CD4 cell counts falling between 350 and 500.

Most of the patients who started treatment with CD4s above 500 did so in 1997 and 1998, when the “hit hard, hit early” approach to treatment—when viral load, not CD4 cell counts, was a chief determinant of starting ARVs—was at its apex. Approximately 16 percent of HIV-positive patients started treatment with high CD4s ten years ago, a rate that fell to below 10 percent by 2003.

Among those who deferred treatment until their CD4s fell below 500 (with an average CD4 count of 390 cells), the relative hazard of death was 1.60—a 60 percent increase—compared with those starting therapy with CD4s above 500 (with an average CD4 count of 674 cells). Approximately 10 percent of patients who deferred therapy were dead within six years; 15 percent had died within eight years.

While Dr. Kitihata did not detail the exact causes of death, it is believed that mild immune suppression and untreated HIV infection is associated with an increased risk of potentially fatal cardiovascular disease, non-AIDS-related cancers and problems stemming from coinfections like hepatitis. Future NA-ACCORD research will investigate the impact of earlier ARV treatment on various AIDS- and non-AIDS conditions and other causes of death in the study.

A problem with the most recent NA-ACCORD results is that they don’t differentiate between patients beginning treatment with CD4 counts within more narrow ranges above 350 cells. In other words, is the risk of dying significant greater among those starting ARVs between 350 and 400 compared with those starting with CD4s between 500 and 550?

Data from the North American and European When to Start Consortium, reported by Jonathan Sterne, PhD, of the University of Bristol may help answer this question. Evaluating data involving more than 21,000 HIV-positive individuals participating in one of 15 cohorts, Dr. Sterne’s group compared rates of AIDS and death among those starting within two specific ranges of CD4 cell counts. All patients included in the analysis started ARV therapy after 1997 with CD4 counts below 550.

The first meaningful comparison involved patients starting therapy between 351 and 450 CD4 cells, compared with those starting between 251 and 351 CD4 cells. The estimated hazard ratio for AIDS or death was 1.28, or a 28 percent increased risk of death among those in the lower CD4 range. There was a less pronounced effect—a 19 percent increase of AIDS or death—in a comparison between patients starting therapy with CD4s between 376 and 475 with those with CD4s between 276 and 375, a difference that was not statistically significant. Comparisons between patients in higher CD4 ranges also fell short of statistical significance.

While both studies confirm that starting treatment earlier than is currently recommended may increase rates of disease-free survival among HIV-positive people, they differ in their designs and results and won’t likely lead to a singular conclusion as to when, in fact, ARV treatment should be started. Dr. Kitahata and others argue that a large randomized clinical trial is necessary to answer this question and to support changes to established treatment guidelines. Others, including experts seeking clarifications and expressing viewpoints at the end of Drs. Kitahata’s and Sterne’s presentations, question this logic when considering the enormous expense of such studies,

compounded by the fact that many individuals in the U.S. do not learn they are infected with HIV and can be offered treatment until they already have low CD4 cell counts.
