Cohort Study: No AIDS-Free Survival Benefit to Starting HIV Treatment at CD4s of 500 or More

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Starting antiretroviral (ARV) therapy with a CD4 count above 500 doesn't decrease the risk of AIDS or death from any cause—at least over an average follow-up period that approached five years—according to a new report from a large cohort study published in the September 26 issue of *Archives of Internal Medicine*.

For people living with HIV with CD4s below 350, the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) study confirmed the clinical benefits of starting and remaining on ARV treatment. As for those with CD4s between 350 and 500, CASCADE indicated slower rates of disease progression associated with starting treatment, though there were too few new AIDS cases or deaths in this particular group during the study to yield firm conclusions.

The question of when ARV therapy should be started has not yet been answered. Though there are data from at least one major study indicating that HIV treatment, initiated as early as possible, profoundly reduces the risk of ongoing transmission of the virus--an important public health benefit of ARV therapy--many advocates contend that it will be necessary to prove that early treatment also protects the health and lives of those actually taking the medications, without an increased risk of side effects or drug resistance.

Three large cohort studies indicate that people should not wait until their CD4s fall below 350 to start ARV therapy to protect their own health. As for waiting until the CD4 count falls below 500, one cohort—the NA-ACCORD study—suggested this is detrimental, whereas another did not; the third cohort only included patients with fewer than 500 CD4s, thus a detailed analysis was not possible. NA-ACCORD also pointed to disease-free survival advantages when therapy is started when the CD4 count is between 500 and 800.

Acting on the initial cohort findings, the U.S. Department of Health and Human Services changed its ARV treatment recommendations in 2009. Whereas the guidelines previously recommended treatment for all people living with HIV with CD4s below 350, the threshold was increased to below 500 in light of the important—but inconclusive—findings.

Some experts argue that the only way to know the absolute benefits and risks of starting therapy

early—indeed, even immediately after HIV is diagnosed—is to examine the results of a randomized prospective study. The international Strategic Timing of Antiretroviral Treatment (START) trial is exploring this question, but data are unlikely to be available until 2015. Taking place at roughly 90 sites in nearly 30 countries, START is randomizing more than 4,000 antiretroviral-naive HIV-positive individuals with CD4s above 500 cells to either begin treatment immediately or defer treatment until their CD4s are less than 350 cells.

In the meantime, additional data are available from the CASCADE study, a large cohort consisting of 23 small cohort studies being conducted throughout Europe, Australia and Canada. The report published in Archives of Internal Medicine by Michele Jonsoon-Funk, PhD, of the University of North Carolina at Chapel Hill and her colleages is similar to a preliminary review of the data orally presented in July 2010 at the XVIII International AIDS Conference in Vienna, which involved a little more than three years of follow up data.

Unlike other cohorts, which began following people from the time they started therapy, the new CASCADE analysis involved 9,455 people who were infected within the previous two years and followed them until they started ARV therapy. In other words, CASCADE researchers were in the unique position to document what happened to patients before they began treatment.

Between January 1996 and May 2009, the CASCADE researchers enrolled new patients every month, thereby created 161 small groups of patients for comparisons purposes. Patients were followed, on average, for 4.7 years in the study. When ARV treatment was started, the investigators noted the patients' CD4 counts. Where there were AIDS-defining conditions or deaths, the investigators noted how long they occurred after each patient joined the cohort.

The greatest benefits were seen among those who started therapy with immune systems that were clearly compromised. For example, those who started treatment as soon as their CD4 count fell below 50 were nearly 70 percent less likely to develop an AIDS-defining illness or die, compared with those who waited. Among those with CD4s between 50 and 200, starting therapy as quickly as possible reduced the risk of AIDS or death by 70 percent, compared with those who delayed treatment.

Of interest, the researchers reported a number-needed-to-treat (NNT) analysis for patients starting HIV treatment in each CD4 group. An NNT analysis is a relatively simple measure of effectiveness of a particular medical intervention, and it aims to determine the average number of people living with a disease who need to be treated to prevent one additional outcome. For example, the NNT analysis employed in CASCADE set out to determine the number of people living with HIV and a CD4 count within a particular range who need to be treated with ARV therapy to prevent one new AIDS case or death.

Not surprisingly, the NNT among patients starting with very low CD4s was also low—a total of three people living with HIV with CD4s below 50 needed to be treated with ARV therapy to prevent one AIDS case or death. Among those with CD4s between 50 and 100, the NNT was 7. The NNT for those with CD4s between 200 and 350 was 21.

There was also an appreciable benefit for those who started therapy as soon as their CD4s landed between 350 and 500, compared with those who delayed therapy—a 25 percent reduction in the risk of AIDS or death. However, Funk and her colleagues note, when treatment was started with CD4s in this range, “the benefits of treatment initiation become evident only beyond two years, suggesting that patients need to consider the long-term course of treatment, including the risk of adverse effects of [ARV therapy] during an extended period.”

Here the NNT was significantly higher—34 HIV-positive individuals with CD4s between 350 and 500 needed to be treated with ARV therapy to prevent a new AIDS case or death.

As for those with CD4s above 500, there was no advantage in terms of AIDS-free survival. Here, no NNT could be calculated in terms of preventing AIDS or death, though the researchers did suggest that 239 people living with HIV and high CD4 counts would need to be treated with ARV therapy to prevent a single death, from any cause.

A limitation of the CASCADE study is that it didn’t monitor participants for some of the non-AIDS-related health complications that are believed to be more common among people living with HIV. “Patient well-being is adversely affected by many serious non-AIDS-defining conditions,” Funk’s team writes. “For example, immunodeficiency and uncontrolled viremia have been implicated in the development of cardiovascular disease and non-AIDS-defining malignancies. Although CASCADE does not pool data on non-AIDS morbidity, this analysis reflects the most serious outcome (death) due to non-AIDS conditions.”

Another limitation is that the average length of follow-up for the individuals participating in CASCADE is under five years, at least thus far. In turn, it is not yet possible to determine if there are any long-term AIDS-free survival benefits—or, conversely, untoward effects—associated with starting therapy when the CD4 count is above 500.

While awaiting the results of SMART, treatment decisions for those with CD4s above 350 “will need to be made based on the available evidence from observation cohorts,” Funk’s team concludes. “We used a novel approach applied to a unique cohort of seroconverters to reduce the potential for lead time bias. We found that treatment initiation and CD4 cell counts of 350 to 499 was associated with slower disease progression. We did not observe any benefit to treatment initiated at 500 to 799.”

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