From TreatmentUpdate 170

New evidence changes guidelines about when to start treatment

In the past year, HIV treatment guidelines from high-income countries and regions such as the United States, United Kingdom and Western Europe have changed. Generally, these guidelines now recommend that HIV positive people begin HAART when their CD4+ count has fallen below 350. This is a major shift from the beginning of this century, when treatment was usually delayed until CD4+ counts fell below the 200-cell mark.

New information from clinical trials and large database studies has, in the past two years, resulted in these changing treatment guidelines. In favour of this trend are the following arguments:

- Over time, even during the mostly symptom-free years of early HIV infection, the virus eats away at the immune system and slowly wears down other key organ systems, such as the heart, bones, kidneys and brain. This increases the risk of heart disease and other complications.
- Currently available therapies are very good at suppressing HIV and maintaining protection from life-threatening AIDS-related infections.
- Over the past six years, there seems to be a trend toward better tolerance of HIV medications. This has probably happened because newer HIV medications have fewer side effects.
- Studies have found that commonly used anti-HIV drugs can be effective for many years. Indeed, some regimens have been used for up to eight years.
- Although the early years of HIV infection are generally free of serious symptoms, certain complications regardless of CD4+ counts can still occur, including certain cancers (lymphoma) and neuro-cognitive decline.

On the other hand, arguments such as the following have been made against the early initiation of therapy:

- Medication-taking may be inconvenient for some patients.
- Regimens can have side effects and the long-term toxicities of HAART are not yet known.
- The risk of HIV-related complications is decreased in people whose CD4+ counts are above the 500-cell mark.

Big databases

Driving the changes in treatment guidelines in North America and Western Europe are results from several studies that monitor large numbers of HIV positive people. These are called observational studies and they collect huge amounts of health-related information in databases where they are eventually analysed. In general, results from these observational studies suggest that people who begin therapy after their CD4+ counts have fallen below 350 cells are at increased risk of death, compared to people who begin therapy when their counts are above that number.

Next we take a brief look at some of the specific results from analyses of large databases.

ART Cohort Collaboration

One of the largest databases combines health-related information from 13 observational studies in North America and Western Europe. Researchers assessed the impact of starting HAART early or late in more than 20,000 HIV positive adults between 1995 and 2003. They found that among people who began therapy with a CD4+ count between 200 and 350 cells, the risk of death was 40% greater than that among people who started therapy at CD4+ counts greater than 350 cells.

Cascade

After 1996 (when HAART became widely available) another large observational study monitored nearly 10,000 HIV positive people for up to eight years. During this time, 67% of participants began taking HAART, and nearly 600, or
6% of the entire group died. The factors linked to death from AIDS, AIDS-related cancers and complications unrelated to AIDS were as follows:

- having a recent low CD4+ cell count
- having had a very low CD4+ count in the past or a prolonged period where the count was less than 350 cells

**High CD4+ count = low risk of cancer**

A French observational study called the Aquitaine cohort has enrolled more than 4,000 HIV positive adults. This study has drawn attention to an important and overlooked change over the past decade: complications unrelated to AIDS are an increasing source of illness and death in some HIV positive people. Such complications include hepatitis-related illness and cancers of the anus, kidney, liver, lungs and skin. In this study, 109 people developed AIDS-related cancers and 142 people developed cancers unrelated to AIDS.

The risk of developing a cancer unrelated to AIDS was linked to the length of time a person had their CD4+ count below the 500-cell mark. For instance, for each year that a person had a count of less than 500 CD4+ cells, his or her risk of developing cancer (unrelated to AIDS) rose by 11% in the Aquitaine cohort.

**A big study**

In a combined analysis of patients from many high-income countries, researchers focused on more than 47,000 HIV positive people whose CD4+ counts were greater than 350 cells. In this study, 487 people died and only 16% of deaths were due to complications from AIDS.

In this study of people whose CD4+ counts were greater than 350 cells, the higher the cell count, the lower the risk of dying. So, having CD4+ counts close to at least the lower end of normal (500 cells) will probably become a future goal of treatment guidelines.

**What about toxicity?**

One of the reasons for delaying the initiation of HAART is to avoid any possible toxicity from medications. HOPS, an observational study in the United States, reviewed health-related information collected from 2,165 HIV positive people. The HOPS researchers found that people who started therapy when their CD4+ counts were higher than 350 cells had a reduced risk of side effects, particularly anemia and nerve damage.

**Clinical Trials**

So far we have summarized data collected from observational studies. When interpreting their results, these studies cannot exclude the possibility of bias. For important clinical decision-making, many doctors prefer evidence from randomized, controlled clinical trials, which have less chance than observational studies of being affected by possible bias.

A clinical trial that has provided much insight into what happens to people's health when they start HAART at higher CD4+ counts is the SMART study. Details about this study appear later in this issue of TreatmentUpdate.

What is relevant from SMART when it comes to the issue of starting therapy is the analysis of what happened to 249 people who entered this study without having previously used HAART and 288 participants who discontinued HAART six months before entering SMART.

Researchers found that the risk of serious events (death, life-threatening infections and complications) was about four times greater (21 events) in people who delayed therapy until their CD4+ count fell below 250 compared to people who began therapy immediately (six events).

The SMART analysis supports the earlier initiation of HAART. However, because the number of people in the subgroup analysis is relatively small, the interpretation of the results is not definitive, and so a larger study is needed.

**REFERENCES:**

1. Wilkin TJ, Gulick RM. When to start antiretroviral therapy? *Clinical Infectious Diseases*. 2008 Dec
Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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