

# When to start treatment

The evidence behind new guidelines

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Ideas about the best time to begin treatment with antiretroviral medications (ARVs) change constantly as we find out more about HIV. Over the years, treatment guidelines have swung between starting treatment early and starting treatment later based on concerns about the development of resistance, limited treatment options for drug-resistant virus, and the impact of side effects on quality of life and adherence to therapy.

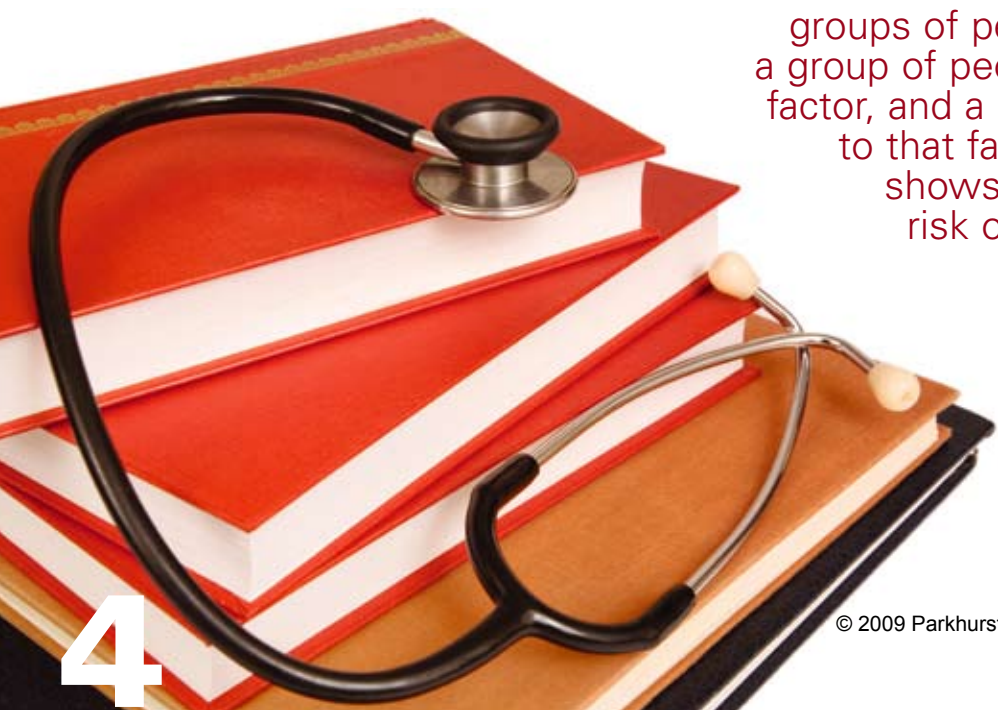
New guidelines (see sidebar, page 5) have recently raised the recommended CD4 count threshold for starting treatment to 350 cells/mm<sup>3</sup>. Two excellent reviews on the subject (see sidebar, page 5) were recently published. I've drawn on them here to help explain the arguments used to justify recommendations for starting treatment earlier.

## When should people with clinical symptoms start treatment?

Highly active antiretroviral therapy (HAART) increases life expectancy in people who have significant immunodeficiency (low CD4 count). Treatment should be started in people with AIDS-defining conditions or severe clinical symptoms, which now include nephropathy associated with HIV.

A randomized controlled trial called **ACTG 5164** aimed to determine the best time to start ARVs in people with an acute opportunistic infection other than tuberculosis. Results suggest that people do better when they start HAART treatment within two weeks of the opportunistic infection being diagnosed, rather than starting later. Based on this study, recent treatment guidelines recommend that ARVs be started alongside treatment for the particular opportunistic infection.

A cohort study is one that follows two groups of people over a period of time: a group of people exposed to a particular factor, and a group of people unexposed to that factor. Comparing the groups shows how that factor affects the risk of developing disease or the course of the disease.



## The evidence for earlier treatment of asymptomatic HIV

Early initiation of HAART is supported by new research findings and new theoretical arguments:

1. Data from a number of cohort studies show a survival benefit for participants who started HAART when their CD4 count was greater than or equal to 350, compared to people who started HAART at lower counts.
2. Data from cohort studies also shows that immunosuppression (low CD4 counts) at the start of therapy worsens your prognosis, or chance of staying well.
3. A sub-analysis of the SMART study looking at people without prior exposure to HAART at the start of the study showed that participants who started treatment earlier did better.
4. Medications are now easier to take and seem to have fewer side effects in the medium term.
5. Researchers are now looking into how uncontrolled viral replication contributes to metabolic disorders.
6. Some researchers have observed a reduced risk of HIV transmission when viral replication is suppressed (See Treatment as prevention, in *Relay*, Vol 4, no 3, Fall 2008).

## Evidence from cohort (observational) studies

The **HOPS** cohort study looked at people with CD4 counts between 201 and 350, and found that the mortality (death) rate was lower among those who started HAART early than in those who delayed starting treatment. The benefit of starting treatment early wasn't statistically significant in study participants with higher CD4 counts, but this analysis was limited by the small number of deaths and the short follow-up period. The **PISCIS** study showed comparable findings.

The **Alive** cohort study involved mostly injection drug users, both HIV-positive and HIV-negative. For those with HIV and CD4 counts over 350, the mortality rate was lower among those who started on HAART than in those who didn't. Participants with HIV whose CD4 count was greater than 350 when they started treatment had a mortality rate no worse than study participants without HIV. However, those with CD4 counts lower than 350 who did not start treatment had a greater risk of death than participants without HIV.

These findings are hard to interpret because social conditions that could have contributed to the results weren't described in the study.

## Find out more

Read the complete guidelines. Panel on Antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services, 29 January 2008. Available at: [http://www.aidsinfo.nih.gov/ContentFiles/Adult\\_and\\_AdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/Adult_and_AdolescentGL.pdf).

The two review articles are: Hirsch, Martin S. Initiating Therapy : When to Start, What to Use. *JID* 2008;197(Suppl 3):S252-260. Wilkin, T and Gulick R. When to Start Antiretroviral Therapy? *CID* 2008;47:1580-6.

Findings from the **ART** study showed a decrease in death rates and disease progression when treatment was started at CD4 counts over 350. In the **CASCADE** study, more deaths from AIDS-related and non-AIDS-related causes were associated with a recent or current CD4 count under 350, and a low nadir (lowest-ever) CD4 count.

In the **Johns Hopkins HIV Clinical Cohort**, starting HAART when CD4 counts were equal to or greater than 350 allowed for the normalization of CD4 levels, something that wasn't seen when treatment was started at lower CD4 counts. Participants with CD4 counts less than 350 who were taking HAART had a lower incidence of conditions not traditionally associated with HIV than those who were untreated.

In the **Aproco and Aquitaine** studies, the mortality rate for participants who maintained a CD4 count of 500 resembled that of the general population. Taking into account the data from the Johns Hopkins cohort, this supports the idea that normal CD4 counts can be achieved when treatment is started early enough. Analyses of the **Athena** cohort point in the same direction, showing that CD4 counts can reach more than 800 cells/mm<sup>3</sup> after seven years of HAART in most participants who start treatment when their CD4 levels are greater than or equal to 350.

The **DAD** cohort study looked at causes (both AIDS-related and not) of mortality and illness in people with HIV. The most common cause of death was liver disease, which isn't traditionally associated with HIV infection. Researchers found a very strong risk of death from liver disease in people with worse immunosuppression (lower CD4 counts). They also found a strong link between the risk of dying from cancers — both AIDS-related and non-AIDS-related — and low CD4 levels (the nadir, or lowest-ever count and the last count before death or disease) as well as the length of time that CD4 counts were low.

## Evidence from controlled trials: the SMART study

There's little information from controlled trials about the best time to start HAART in order to produce a survival benefit in people without symptoms of HIV whose CD4 counts are higher than 200 cells/mm<sup>3</sup>. The SMART study compared two treatment strategies: one group received intermittent treatment guided by CD4 counts, while the other group received continuous HAART therapy to achieve constant virologic control. The study included 5472 patients, most of whom had previously been exposed to ARVs. The continuous control strategy was shown to result in less illness and death. Intermittent treatment appears to lead to higher risk of death, opportunistic infection and kidney, heart and liver disease.

The longer the time that people were off treatment, the higher was the risk of opportunistic infections, AIDS-defining cancers and deaths. What's more, a sub-analysis of people who had never received ARVs, or hadn't received them in the six months before the study, found that delaying treatment brought a four-fold increase in AIDS-related conditions, deaths, and non-AIDS-related conditions, compared with people who started treatment earlier.

## Other considerations for starting treatment

Apart from CD4 counts, the risk of progressing to AIDS was increased by any one or more of the following factors:


- a viral load greater than or equal to 100 000 copies/ml
- age over 50
- past or current injection drug use
- a previous diagnosis of AIDS

Based on this evidence, the new guidelines recommend that people at higher risk be advised to start treatment even if their CD4 count is higher than 350 cells/mm<sup>3</sup>. As well, given the evidence emerging about the role of inflammation in cardiovascular disease, the International AIDS Society has included high risk for cardiovascular disease as a consideration in recommending that some-one start treatment.

Because medications used to treat hepatitis B are also used in the treatment of HIV, it's recommended that HIV treatment begin at the same time as treatment for hepatitis B. It's also recommended that people start HIV treatment if they are co-infected with hepatitis C, because immunosuppression leads to worse outcomes with liver disease.

## The study never stops

Findings from the SMART study and the large cohort studies have made us re-think the criteria for starting treatment. There are, however, limitations to using data from cohort studies to determine when HAART should be started. These studies don't really take into account medication side effects or toxicities or the development of resistance. On the other hand, the other major type of study — clinical trials — can underestimate the value of early treatment because follow-up is generally short and treatment regimens can improve.

Current recommendations to start treatment earlier have been formulated while we wait for the hypothesis to be extensively tested in a double-blind randomized controlled clinical trial.\*\*\* However, the number of participants required to conduct such a trial, its duration, cost, potential biases, and changes in treatment regimens make it unlikely that we will see definitive data soon. At present, the guidelines are based primarily on data from cohort studies and mathematical modelling. 



## Find out more

The START (Strategic Timing of AntiRetroviral Treatment) study, conducted by the International Network for Strategic Initiatives in Global HIV Trials, will start recruiting at about 70 centres in the spring of 2009.