

# Immune system reconstitution

The importance of keeping CD4 cell counts high

by Dr. Jean-Pierre Routy

Immune system reconstitution is defined as the increase in CD4 cell counts that occurs after starting antiretroviral (ARV) therapy. Without treatment, the ongoing replication of HIV results in the destruction of CD4 cells. When ARVs control the multiplication of HIV, CD4 cells can then start multiplying without being attacked by the virus, often rebounding to normal levels.

It took many years of research to understand that CD4 cells are killed more often by immune activation (inflammation of the immune cells in response to the virus) than by the virus itself. The level of this immune activation also affects how much CD4 levels rebound with treatment.

## Is the increase in CD4s really that important to health?

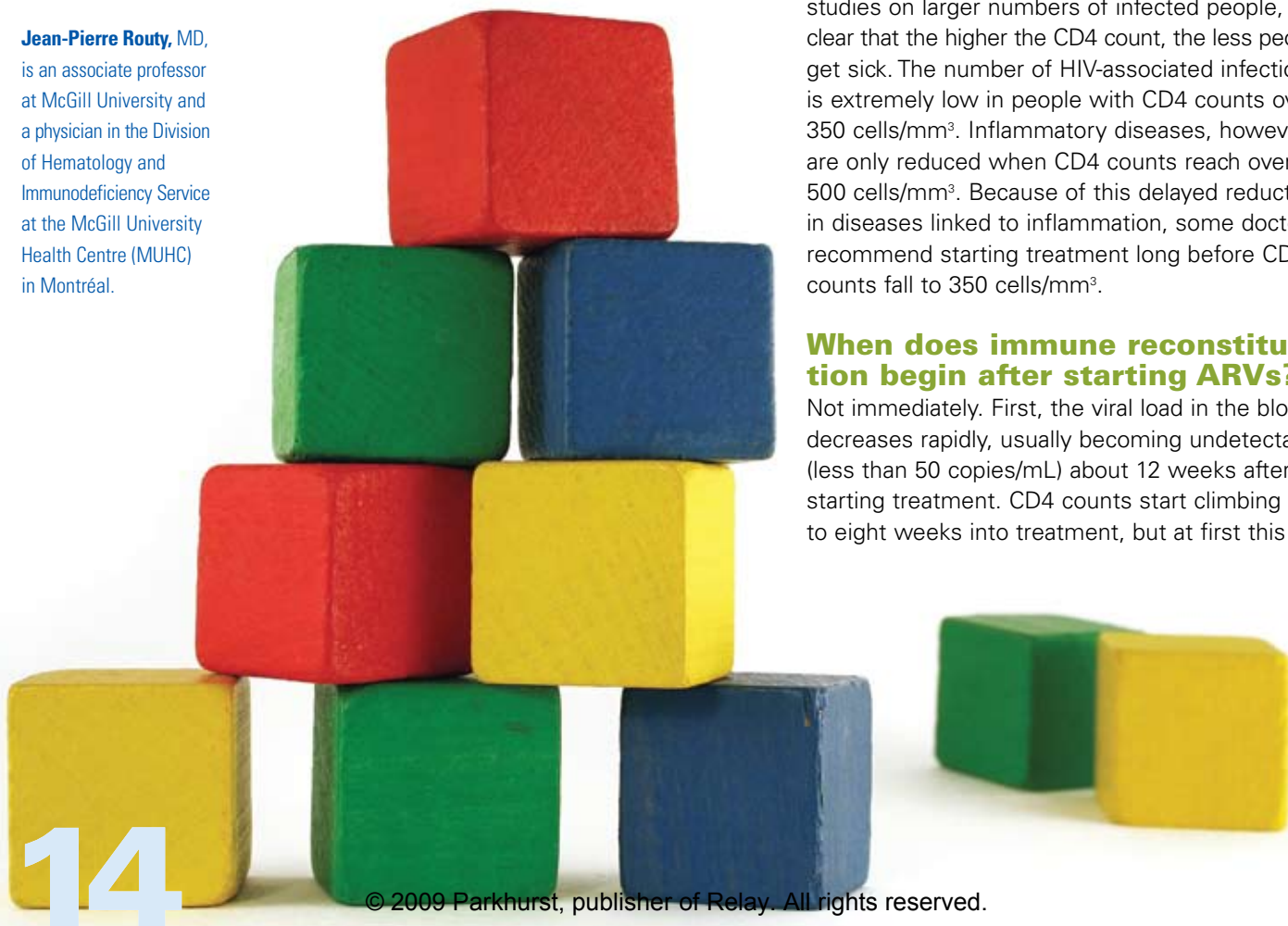
The answer is a definite yes. The more your CD4 counts increase toward levels similar to people without HIV, the less chance you have of developing HIV-associated infections (AIDS). As well, prolonged immune activation when CD4 counts are low increases the risk of inflammatory diseases such as heart, liver and kidney disease. These risks are more significant when CD4 counts are less than 350 cells/mm<sup>3</sup>, which is one reason it's now recommended that ARV treatment start before CD4 counts drop to that level.

While the difference in the rate of HIV-related illnesses at CD4s above 350 is small and we need studies on larger numbers of infected people, it's clear that the higher the CD4 count, the less people get sick. The number of HIV-associated infections is extremely low in people with CD4 counts over 350 cells/mm<sup>3</sup>. Inflammatory diseases, however, are only reduced when CD4 counts reach over 500 cells/mm<sup>3</sup>. Because of this delayed reduction in diseases linked to inflammation, some doctors recommend starting treatment long before CD4 counts fall to 350 cells/mm<sup>3</sup>.

## When does immune reconstitution begin after starting ARVs?

Not immediately. First, the viral load in the blood decreases rapidly, usually becoming undetectable (less than 50 copies/mL) about 12 weeks after starting treatment. CD4 counts start climbing four to eight weeks into treatment, but at first this

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increase is the result of existing CD4s moving from the lymph nodes into the bloodstream.

After three to six months of treatment, the development of new CD4 cells starts. These are produced by the thymus (a small organ located in front of the heart) or through the multiplication of young (naïve) CD4 cells “fertilized” by chemical messengers called interleukins (IL). These interleukins (IL-2, IL-7, IL-15) are now being used in clinical trials to try to make CD4s grow more rapidly in people whose counts are increasing very slowly despite ARV treatment.

Starting about six months into treatment, CD4 counts begin to increase slowly over a period of up to five years. After several years of ARV therapy, about two thirds of people attain a normal number of CD4s, around 500 to 600 cells/mm<sup>3</sup>.

### What factors affect the rebound in CD4 counts?

A number of factors have been identified to explain the speed at which CD4 counts rebound after starting ARVs. People with a very high viral load before treatment (more than 100,000 copies/mL) tend to have a rapid rebound in CD4s. Researchers think that the body has to fight so hard to produce enough CD4 cells to compensate for viral destruction that when the viral load falls, the production of CD4s continues at this accelerated rate in the first six months after starting treatment.

The lowest ever (nadir) CD4 count is a determining factor in the body’s ability to generate new CD4 cells. If you don’t start treatment until your CD4 count is under 100 cells/mm<sup>3</sup>, the increase will be slow and will plateau around 350 cells/mm<sup>3</sup> in some people even after several years of treatment. Age is also a factor. A 20-year-old who starts treatment with a CD4 of 200 to 250 cells/mm<sup>3</sup> will often reach a CD4 count of 600 cells/mm<sup>3</sup>, while a 50-year-old will seldom reach a CD4 count over 350 cells/mm<sup>3</sup>.

When immune activation continues in the presence of ARVs, this acts as a brake on the rebound of CD4 counts by blocking the response of growth cytokines such as interleukin-7. Clinical trials are now in progress to try and block immune activation (with treatments such as chloroquine) and use interleukins to try to speed up CD4 cell growth in people whose counts are slow to increase despite ARV treatment.

### Does the type of ARV influence CD4 count increase?

In general terms, no. As long as the treatment makes the viral load undetectable, there’s little dif-

ference between classes or types of ARV medication. However, we have seen that tenofovir (Viread®) is associated with slightly less CD4 cell increase than other medications in the nucleoside reverse transcriptase inhibitor (NRTI) class, though this difference doesn’t seem to compromise health. Lopinavir/ritonavir (Kaletra®) is often associated with a slightly more rapid increase in CD4 counts than other protease inhibitors (PIs) or the non nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (Sustiva®), but again this hasn’t been shown to be associated with a significant health advantage. CCR5 inhibitors are also associated with a slightly larger increase in CD4 counts, once again without proven health advantage.

### Is there anything I can do myself to increase my CD4 count?

There isn’t much research evidence available on the impact a healthy lifestyle with good diet and lots of exercise can have on the recovery of CD4 cell counts. Some studies have shown an advantage in taking supplements containing selenium or multivitamins. A large study led by Dr. Bill Cameron at the Ottawa General Hospital is now underway to look at the benefits of multivitamins in the control of immunity.

These days, many people living with HIV succeed in maintaining control of their viral load over the long term. Increasing CD4 counts to more than 350 or 500 cells/mm<sup>3</sup> is therefore now an additional goal of treatment. The easiest way to obtain good results is to start treatment early, before CD4 counts fall to 350 cells/mm<sup>3</sup>. However, one-third of people experience little increase in CD4 counts during ARV treatment; for this group research is underway to find medications that can increase the number and effectiveness of CD4 cells. **R**

