



# Long-term non-progressors

What helps them keep HIV at bay? **by Drs. Cécile Tremblay and Nicole Bernard**

**Without antiretroviral drugs, it takes, on average, about 10 years for HIV infection to progress from its initial stages to full-blown AIDS. Thankfully, the medications we now have at our disposal can prevent this from happening for quite some time. But even without medication, some people can live with HIV for over 20 years without any signs of progression. Though they make up only a tiny minority of those living with HIV, these long-term non-progressors (LTNPs) can teach us a great deal about how to successfully fight the virus.**

AIDS is the advanced stage of HIV infection where people become vulnerable to many diseases and opportunistic infections: as CD4 counts fall below 200 cells/mm<sup>3</sup>, the body's immune system basically stops working. The amount of time it takes to reach this stage (without medication) varies greatly: some people will develop AIDS as early as two years after they're infected, while LTNPs can live without symptoms of AIDS for two decades. There's no way to predict how fast or slow the infection will progress in a given person.

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## Who are LTNPs?

Since the first group of slow progressors was identified in the early 90s, researchers have learned a great deal about them. We now know that LTNPs are extremely rare: fewer than 1% of those living with HIV. We also know that no

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single reason can explain their unique ability to fight off HIV — LTNPs are just too different, from one person to the next, for there to be a single explanation.

By definition, a LTNP is a person whose CD4 count remains normal (i.e. above 500 cells/mm<sup>3</sup>), after a minimum seven years of infection and without ever having taken antiretrovirals (ARVs). But that's about the only thing they have in common. Their viral load, for example, varies widely: "elite controllers" are LTNPs who have an undetectable viral load (i.e. less than 50 copies per millilitre [ml] of blood). Others have low but detectable viral loads (2,000 to 3,000 copies/ml) and others still have higher amounts of virus in their blood. LTNPs differ also in ethnicity, gender, lifestyle and the environment in which they live.

### What's their secret?

What is it about LTNPs that allows them to fight HIV so effectively? Is there something different about them that prevents the virus from taking hold? Or is the virus they're infected with somehow less effective? Researchers hope that the more we understand about LTNPs, the closer we'll be to finding new treatments.

### Weakened viruses

The first group of LTNPs described in the scientific literature was from Sydney, Australia. They were all hemophiliacs who had received a blood transfusion from the same HIV-positive donor. Fifteen years later, they were all still alive, which was extremely unusual in 1991.

After isolating the HIV virus from their blood, researchers discovered that it was a very mildly infectious strain. It had a mutation (in a viral gene called "nef") that made it unable to replicate and hide effectively from the body's immune system. Over the course of several years, though, the infection did eventually start to progress. It was as if the virus had suddenly changed and began to gain ground against the body's defences.

Other types of viral mutations have also been associated with slow progression and may

explain why the evolution to AIDS is delayed in LTNPs. Unfortunately, we now understand that HIV can evolve very quickly, and there's no guarantee that these "mild" strains won't eventually find another way to overtake the immune system.

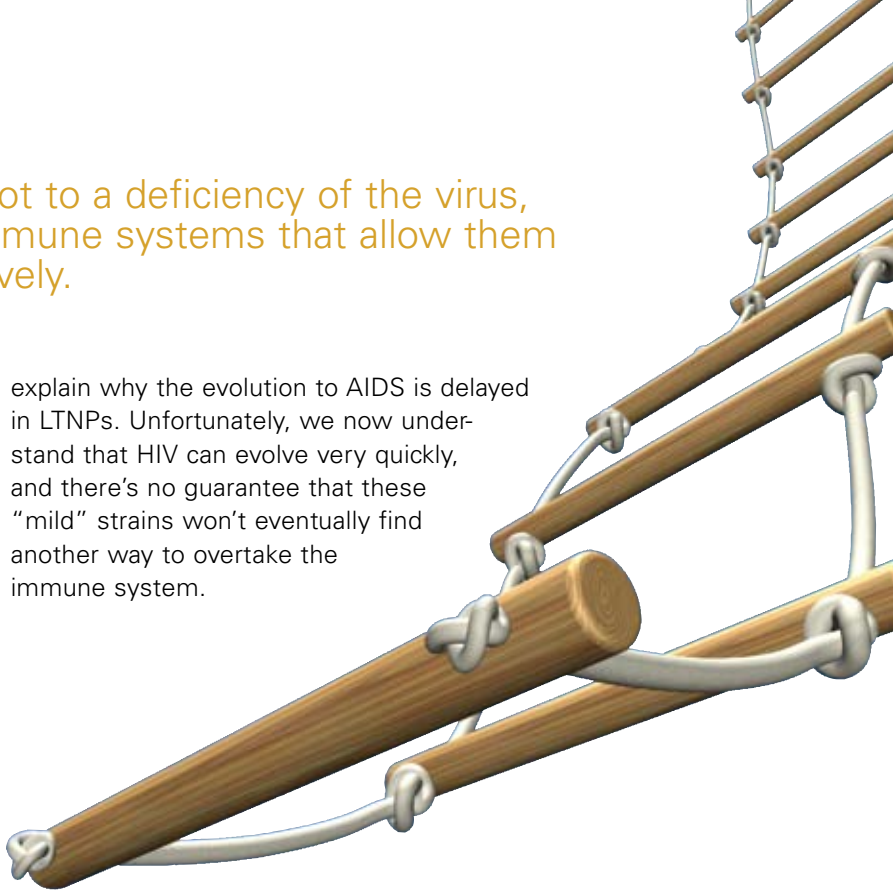
### Superior immunity

Some LTNPs owe their survival not to a deficiency of the virus, but to differences in their own immune systems that allow them to fight the infection more effectively.

When we're infected with a virus, our body normally retaliates by producing neutralizing antibodies against it. Several different types of immune cells are needed for this to happen: CD4 cells have to activate B cells, which then produce the antibodies. One of the reasons HIV infection is so hard to fight is that CD4 cells are precisely the ones that the virus attacks. As more CD4 cells become infected with HIV, fewer B cells become activated and fewer neutralizing antibodies are produced. Most people living with HIV are incapable of producing enough high-quality antibodies to neutralize the virus.

Some LTNPs, though, *are* able to produce enough good antibodies to keep the virus under control, allowing them to control the infection over the long-term.

The other important component of the immune system's defence against HIV is a group of cells called cytotoxic T cells, which target and destroy HIV-infected cells. Like B cells, cytotoxic T cells need to be activated by CD4 cells. But they also need the help of another group of immune cells that recognize and "present" foreign invaders, like





viruses and bacteria, to the immune system. These are called antigen-presenting cells (APCs).

Normally, HIV disrupts all these elements — CD4 cells, cytotoxic T cells and APCs — but some LTNPs are still able to mount an effective cytotoxic response to HIV. They may have better APCs, or the communication between the different immune cells may be especially efficient. One theory is that their immune system takes a more “slow and steady” approach to fighting off the virus: rather than exhausting itself by producing large amounts of poor-quality immune cells, it may produce fewer but more effective cells. These are all questions that researchers are still trying to answer.

## Genetic differences

Finally, some LTNPs just seem to be naturally better equipped to tackle HIV. One group, for example, was found to have a mutation in the **CCR5 co-receptor**, which HIV often uses to get inside human cells. Once they understood the concept, researchers actually used this information to develop an entirely new class of ARVs (see “From research to reality,” below).

Recently, researchers have also found a link between non-progression and particular versions of a molecule called HLA. The immune system needs these molecules to identify foreign invaders like HIV and effectively eliminate them. People that have certain versions of the HLA molecule (namely HLA B\*57 or B\*27) have, on average, a slower progression of HIV disease than those with other HLA types.

As you can see, there’s no single explanation for LTNP’s unique ability to fight HIV. Even though they are few and far between, we can learn a great deal from them. Already, the information they have provided has led to new treatments and there’s no telling how much more there remains to discover.

*With the support of the Fonds de la recherche en santé du Québec AIDS and infectious disease network and the International Consortium of Slow Progressors, the authors have launched a new study of LTNPs. If you’d like to participate, please contact Mr. Mario Legault at 514-934-1934, ext. 32600. **R***

## From research to reality

Most strains of HIV need the CCR5 co-receptor to get inside human cells. In some LTNPs, though, this receptor is different: it has a naturally occurring mutation that prevents HIV from using it to get inside the cell.

Researchers began searching for a way to reproduce this situation with a drug. Several years later, they found the answer: CCR5 inhibitors. These drugs block the CCR5 receptor, preventing HIV from using it.

Only one CCR5 inhibitor is currently available in Canada. Maraviroc (Celsentri™) was approved by Health Canada in October 2007, for use in combination with other ARVs in people who have experienced treatment failure with multiple drug classes.

CCR5 inhibitors only work in people whose HIV virus uses the CCR5 co-receptor to get inside CD4 cells. A blood test called a “tropism assay” can determine which people have this type of virus.

For more information on how these drugs work, see “Why CCR5 inhibitors won’t work for everyone” in Relay’s summer 2007 issue. Find it online at [www.relaymagazine.com](http://www.relaymagazine.com)

