Exploring HIV and inflammation

Chronic HIV infection is associated with relatively high levels of inflammation and a growing body of evidence suggests that inflammation may increase the risk for a range of health problems. Before delving into potential approaches to reduce inflammation, it is important to understand why inflammation occurs and persists.

What usually happens with a viral infection

In the case of ordinary viral infections, such as a cold or flu, cells of the immune system capture the invading virus and take it to nearby lymph nodes. Inside the lymph nodes, which house many other cells of the immune system, the captured germ is presented or shown to cells as something that they need to recognize and attack. B-cells and T-cells in the lymph nodes that have been educated about the virus become activated and release chemical signals (cytokines) that cause inflammation and help mobilize the immune system. B-cells produce antibodies, and T-cells can attack the virus directly as well as virus-infected cells. Both activated B- and T-cells are stimulated to clone themselves and are sent from lymph nodes to the rest of the body to fight the infection. Eventually the tide turns against the infection and virus-infected cells decrease. Once the infection has been vanquished, cells of the immune system release further chemical signals that dampen inflammation and activation.

HIV and inflammation

In the case of HIV, the virus becomes a chronic infection in people. In the early stages of infection, the activation of the immune system and its attendant inflammation do not seem to control this virus. Initiating HIV therapy (ART) greatly helps to lower levels of the virus and immune activation and inflammation. However, the overall levels of immune activation and inflammation are higher in ART users than in HIV-negative people.

Why is persistent immune activation and inflammation important?

The activation of the immune system and inflammation are important responses used by the immune system to help control infections and tumours. However, researchers are concerned that prolonged immune activation and inflammation could slowly degrade vital organ-systems in the body. Research suggests that persistent inflammation (and likely immune activation) probably plays some role in the following conditions:

- cardiovascular disease
- degenerative conditions of the brain (such as Alzheimer’s and Parkinson’s diseases)
- type 2 diabetes
- inflammatory diseases of the digestive tract (such as Crohn’s disease)
- arthritis
- psoriasis

It is also possible that persistent chronic immune activation and inflammation could gradually weaken and age the immune system. Therefore, research teams in North America and Western Europe are studying the issue of HIV-related inflammation and immune activation and conducting clinical trials to try to dampen it.

Why do persistent immune activation and inflammation occur in chronic HIV infection?

There are at least several possible explanations for this, including the following:

HIV in the lymph nodes

When taken as prescribed and directed, ART can drive down the production of HIV in the blood to very low levels
(these low levels are commonly called “undetectable”). However, despite good adherence to ART, some researchers have found that HIV can still be infecting cells of the immune system in the lymph nodes and lymphatic tissues. This occurs because ART does not penetrate the lymph nodes and lymphatic tissues in high concentrations as it does in the blood.

**Unfriendly bacteria in the intestines**

There are many lymph nodes and small collections of lymphatic tissue around the intestines. HIV accumulates in those tissues because many cells of the immune system are there. As HIV attacks cells in those tissues, this causes inflammation, which also affects the intestines, weakening the barrier in the gut. This inflammation also likely plays a role in the malabsorption that is a feature of untreated HIV infection. Due to HIV infection, certain bacteria that are naturally present in the intestine in small proportions can grow as the balance of bacteria is altered. These bacteria produce proteins that can incite and prolong inflammation. These proteins can cross a weakened gut barrier and become absorbed into the blood and spread throughout the body. The scientific term for the passage of high levels of bacterial proteins across the gut to the blood is called bacterial translocation. Researchers have found that over time ART can greatly reduce the passage of these bacteria across the gut to the blood. However, ART does not decrease the level of these bacterial proteins to very low levels seen in healthy, HIV-negative people.

**CMV co-infection**

There is a growing body of research suggesting that co-infection with the common sexually transmitted cytomegalovirus (CMV, a member of the herpes family of viruses) plays a role in the aging of the immune system and persistent immune activation and inflammation. Researchers have conducted a clinical trial with the anti-CMV drug valganciclovir (Valgan) in HIV-positive people who were taking ART. Valganciclovir did reduce inflammation but it was toxic to the bone marrow. A newer, safer anti-CMV drug, letermovir (Prevymis), has been approved in the U.S. and will hopefully be approved in Canada in the future. Lab experiments with CMV-infected cells suggest that letermovir has potential to reduce immune activation and inflammation. Researchers in the U.S. hope to test letermovir’s impact on immune activation and inflammation in HIV-positive people who are co-infected with CMV.

**Timing is everything**

It is difficult to study the immunological events that occur very early (in the first 24 hours after infection) in the course of HIV infection, as most people are not yet aware of their infection at that point because symptoms do not immediately appear and, when they do, they can resemble those of a cold or flu. To overcome this, researchers conducted experiments with monkeys susceptible to a virus called SIV (simian immunodeficiency virus), which is closely related to HIV. Monkeys that are susceptible to SIV eventually develop an AIDS-like condition over a period of months or years, depending on the virulence of the strain of SIV used.

These experiments have revealed that within 24 hours of infection with SIV, the virus has spread relatively far, hitching a ride on infected cells of the immune system and reaching the bone marrow and spleen, major organs of the immune system.

Researchers have found that within 72 hours after genital infection, SIV has spread even further in the body—to the thymus gland (another organ of the immune system), tonsils, and cells of the immune system that reside in the liver, lungs and brain.

Not only did SIV spread very quickly after initial exposure, in the same monkeys used in the experiments above, it also quickly triggered activation and inflammation of the immune system.

That SIV, a virus closely related to HIV, caused inflammation and activation of the immune system so early in the course of infection suggests that these are consequences that may be difficult to fully suppress, as they appear to be key features of viral infection with SIV and HIV.

**What hasn’t worked**

These findings with SIV and HIV have stimulated researchers to explore avenues that could be used to reduce immune activation and inflammation that persists despite the use of ART. Initial steps to try to reduce HIV-related inflammation and immune activation have involved the use of simple anti-inflammatory drugs. However, well-
designed studies have found that these drugs do not significantly address the issue of inflammation. These drugs have included the following:

- Aspirin (this drug is still useful for reducing the risk of excessive blood clots)
- sevelamer (Renagel)
- mesalamine (Mesasal)

The antibiotic rifaximin (Zaxine) is a very poorly absorbed drug. This property makes it useful for treating infections of the intestine, as the antibiotic concentrates in that organ. In an attempt to reduce the inflammation associated with bacteria in the gut in HIV-positive people, researchers conducted a clinical trial of this drug. Unfortunately, rifaximin did not significantly reduce levels of immune activation and inflammation. However, clinical trials of friendly bacteria (probiotics) are planned or underway to see if this can help.

**New approaches—The Reprieve study**

Statins are a group of medicines used to help normalize cholesterol levels in the blood. Examples of commonly used statins include the following:

- rosvastatin (Crestor)
- atorvastatin (Lipitor)

Clinical trials of Crestor in people with HIV have found that it can help to normalize cholesterol levels in the blood and, by some measures, perhaps reduce inflammation. However, clinical trials of rosuvastatin in people with HIV were not designed to assess its impact on heart attacks and stroke.

A newer statin, pitavastatin, is undergoing a massive clinical trial (called Reprieve) in HIV-positive people in Canada, the U.S. and other countries. (For further information about Reprieve see the next article.)

**Other approaches**

Clinical trials are underway in the U.S. with antibodies designed to capture or blunt the effects of chemical signals that incite inflammation. Some of the targets of these clinical trials include the following chemical signals or cytokines:

- IL-1b (interleukin-1beta)
- IL-6 (interleukin-6)

In this issue of *TreatmentUpdate* we will review some emerging strategies that researchers are exploring in their efforts to reduce HIV-related inflammation and immune activation.

**In the meantime**

Until the results of clinical trials with newer anti-inflammatory agents (some of which we describe in this issue of *TreatmentUpdate*) are completed and analysed, there are many steps that HIV-positive ART users can take to remain healthy, such as the following:

- getting advice and support from a doctor, nurse or pharmacist to help quit smoking
- engaging in doctor-approved exercise on a regular basis (this can be something as simple as walking briskly)
- getting advice from a registered dietitian about making helpful changes to the diet, such as eating more colourful fruits and vegetables; using whole grains (rich in fibre) instead of refined grains; eating a handful of tree nuts two to three times weekly, getting sufficient protein
- getting help for anxiety or depression
- getting help for addiction
- regular screening for—and, if necessary, treatment of—sexually transmitted infections

—Sean R. Hosein

**REFERENCES**


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