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I INFLAMMATION AND HIV

A. 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:

- rosuvastatin (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

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B. Inflammation in arteries vs. lymph nodes

As mentioned earlier in this issue of *TreatmentUpdate*, chronic HIV infection is associated with excessive levels of inflammation and activation of the immune system. Some of this is reduced when people initiate HIV therapy (ART) and achieve and maintain very low levels of virus in their blood (these low levels are commonly called "undetectable"). However, researchers are concerned that the residual inflammation that persists in ART users could cause health problems over the long term.

Researchers in San Francisco have conducted an intensive study of inflammation in the arteries and nearby lymph nodes of 74 men, some of whom were HIV positive and using ART. The researchers found that inflammation in the arteries of HIV-positive people was "modestly increased" and linked to having higher levels of proteins associated with inflammation, such as IL-6 (interleukin-6) and CRP (C-reactive protein). Furthermore, among HIV-positive people, the level of inflammation in the lymph nodes was generally higher than in the arteries. This finding prompted the researchers to conclude that inflammation in the arteries and lymph nodes "is not closely linked." Another finding from this study is that the factors that drive inflammation in the arteries are somewhat different from those that drive inflammation in the lymph nodes. The researchers suggest that therapies that reduce HIV "disease activity" may not reduce inflammation in the arteries or the consequences of such inflammation, namely heart attacks and strokes.

A note about scans

In the present study, the research team used a technique called FDG PET/CT scans. In these scans, a small amount of radioactive sugar (FDG) is given to the person via intravenous infusion. Researchers then wait some time for this sugar to be taken up by active tissues; in this case, in the lymph nodes and arteries, where inflammation was taking place. The PET (positron emission tomography) scan detects the radioactive material and its location, while the CT (computer tomography) scan helps to form detailed images of the tissues where the FDG has concentrated. FDG usually concentrates in cells/tissues where there is a very high level of inflammation.

Study details

Participants had a similar profile upon entering the study (regardless of HIV infection): They were in their early 50s and the proportion of HIV-positive and HIV-negative people with risk factors for cardiovascular disease was similar. Some HIV-positive participants were taking ART and had undetectable viral loads.

Results

Inflammation in the lymph nodes was greater among HIV-positive participants. Among HIV-positive people, inflammation in the lymph nodes was greatest among those who were taking ART and who did not have an undetectable viral load. In a subset of participants, researchers were able to assess the spleen (a major organ of the immune system) and found that levels of inflammation

there were similar to levels of inflammation in the lymph nodes.

Links to inflammation in the lymph nodes

Among HIV-positive people, high levels of inflammation in the lymph nodes were associated with the following blood test results:

- a high viral load
- higher numbers of CD8+ cells
- a lower CD4/CD8 ratio

The researchers did not find any links between these three factors and inflammation in the arteries.

Links to inflammation in the arteries

Levels of IL-6 and CRP in the blood were linked to inflammation in the arteries. (Elevated levels of IL-6 were also linked to inflammation in the lymph nodes.) Inflammation in the arteries was also linked to a group of the immune system's cells called monocytes (in their mature form these are called macrophages).

What the findings mean

The researchers think that it is likely that the drivers of immune activation and inflammation in the arteries are different from those in the lymph nodes. These findings are supported by another U.S. study.

Taking the findings from both studies into account, it is very likely that ART alone will be insufficient to significantly reduce inflammation in the arteries.

Some of the researchers from this study are now exploring the impact of the antibody canakinumab on arterial inflammation in people with HIV. Their findings are reported later in this issue of *TreatmentUpdate*.

REFERENCE:

Tawakol A, Ishai A, Li D, et al. Association of arterial and lymph node inflammation with distinct inflammatory pathways in human immunodeficiency virus infection. *JAMA Cardiology*. 2017 Feb 1;2(2):163-171.

C. Pitavastatin found to reduce levels of bad cholesterol and inflammation

Pitavastatin is approved in the U.S. but not yet in Canada for the normalization of cholesterol levels. A clinical trial of pitavastatin, called Reprieve, is underway in Canada and other countries.

Pitavastatin is a potent statin. A one-year clinical trial has found that it can help to normalize cholesterol levels in HIV-positive people. This study was called Intrepid and compared the effects of 4 mg/day of pitavastatin against an older statin called pravastatin (40 mg/day) in 252 HIV-positive participants. Researchers found that levels of "bad" cholesterol (LDL-C) were reduced by about 31% in pitavastatin users vs. 21% in pravastatin users. Pitavastatin was able to significantly reduce the following measures of inflammation:

- levels of oxidized LDL-C (which can increase inflammation in the arteries)
- a protein called soluble CD14 (some studies have found elevated levels of sCD14 to be associated with HIV-related inflammation and immune activation)
- an enzyme called Lp-PLA2 (which is associated with inflammation in HIV-negative people; HIV-positive people can have elevated levels of this enzyme, which is associated with an increased risk for cardiovascular disease in both HIV-negative and HIV-positive people)

Taken together, these reductions in proteins associated with inflammation and the decrease of bad cholesterol strongly suggest that long-term use of pitavastatin has potential to reduce the risk of heart attack and stroke.

Importantly, neither drug increased the risk for developing type 2 diabetes.

In general, both drugs were well tolerated. Common side effects in the study were as follows:

- diarrhea (in 10% of pitavastatin users)
- upper respiratory tract infection (in 10% of pravastatin users)

The results from Intrepid strongly support the ongoing Reprieve clinical trial to assess pitavastatin's impact on reducing the risk of heart attack, stroke and death from cardiovascular complications. More information about the Reprieve study appears later in this issue of *TreatmentUpdate*.

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D. Inflammation-related illness among HIV-positive people

Chronic HIV infection is associated with increased levels of inflammation. Researchers suspect that over the long-term this inflammation may be associated with an increased risk of health problems. To explore this idea, rather than launch a new and expensive clinical trial, researchers in Europe and the U.S. re-analysed data from two large, well-designed studies of the cytokine IL-2 (interleukin-2) in people with HIV. Specifically, researchers sought to assess the impact of chronic inflammation on major clinical events—heart attack, stroke, cancer, other serious complications and the risk of death. Both studies were randomized; participants received either IL-2 and HIV therapy (ART) or continued use of ART. The researchers who re-analysed the data focused on participants who continued to use ART alone (no IL-2). They found that some of the participants who continued to take ART and who had higher levels of inflammation had an increased risk of serious complications. An increased level of the chemical signal IL-6 (interleukin-6) in the blood of participants over time was linked to an increased risk for serious inflammation-related problems. The researchers say that potent anti-inflammatory treatment that is able to suppress chronic HIV-related inflammation "could greatly impact the health of people with HIV."

Study details

Researchers reviewed data from the following two studies:

- SMART – a study assessing the impact of continuous ART vs. interrupting ART. All participants had at least 300 CD4+ cells/mm^3 when they entered the study.
- ESPRIT – a study comparing IL-2 + ART vs. ART alone. All participants had at least 300 CD4+ cells/mm^3 when they entered the study.

Researchers focused on the following outcomes:

- heart attack, stroke, hospitalization to undergo cardiovascular procedures/surgery
- severe liver injury (cirrhosis)
- severe kidney dysfunction (end-stage renal disease)
- cancers unrelated to HIV
- serious or other potentially life-threatening events

Researchers reported that their re-analysis focused on data collected from 3,568 patients whose average profile at the time they entered the parent studies was as follows:

- 77% men, 23% women
- age – 42 years
- CD4+ count – 547 cells/mm^3
- lowest-ever CD4+ count – 210 cells/mm^3
- duration of ART before entering the parent studies – five years

Results

In total, 252 participants had at least one of the following diagnoses:

- AIDS-related complications
- severe cardiovascular disease (heart attack, stroke or hospitalization for cardiac procedure/surgery)
- cancer unrelated to AIDS

In general, complications due to cardiovascular disease were more common than AIDS-related complications.

A total of 339 participants experienced signs/symptoms of a potentially life-threatening health

complication; such complications are sometimes called "grade 4" events by researchers. These grade 4 events were unrelated to the problems mentioned above. In half of the 339 people, grade 4 events were related to chronic inflammation. Examples of chronic inflammation that were found were as follows:

- gastrointestinal inflammation
- severe liver injury
- acute kidney failure
- acute inflammation of the pancreas gland

The researchers gave the following examples of health issues that occurred that were not related to chronic inflammation:

- depression
- back pain
- groin hernia
- attempted suicide

Grade 4 events and diminished survival

Overall, people who experienced grade 4 events were at heightened risk of death. The greater the number of such events, the greater the risk of death. People with a diagnosis of cancer unrelated to HIV were at very high risk of death in this study.

Researchers found that people who entered the studies with high levels of proteins associated with inflammation (IL-6, D-dimer) in their blood were more likely to die when they developed complications.

Taking many factors into account, researchers found that people who developed grade 4 events were more likely to have the following characteristics/features:

- of African descent
- use medications to help normalize blood pressure
- co-infected with hepatitis-causing viruses

Note that this does not mean that taking blood pressure medicines caused grade 4 events. Rather, it suggests that people who were using such medicines in this analysis were likely in very poor health and therefore likely to develop serious complications.

Why did grade 4 problems occur?

Researchers strongly suspect that grade 4 events in this study were likely caused by an intersection of several factors, including the following:

- underlying HIV infection
- co-infection with hepatitis-causing viruses
- age (some older people had poorer health)
- hypertension

The researchers did not have data on participants' history of exposure to tobacco, alcohol and other substances.

The researchers noted that elevated levels of IL-6 and D-dimer occurred several years before life-threatening complications happened. This strongly suggests that chronic inflammation plays a role in the life-threatening complications that the study examined.

Note that researchers did not have detailed information about the general health of participants from the distant past. This could have affected their interpretation of the data. For instance, some people who experienced grade 4 events could have been experiencing recurrent problems, not new ones. It is possible that some grade 4 events were scheduled hospitalizations for procedures or conditions that were not life threatening.

However, there is a clear trend in the re-analysis: Over time, elevated inflammation is linked to an increased risk for some complications in HIV-positive people even if they are using ART.

REFERENCE:

Hart BB, Nordell AD, Okulicz JF, et al. Inflammation-related morbidity and mortality among HIV-positive adults: How extensive is it? *Journal of Acquired Immune Deficiency Syndromes*. 2018; *in press*.

E. Why is there renewed interest in the antibody canakinumab?

Canakinumab is an antibody that has been designed to block a receptor on cells for the chemical signal (cytokine) IL-1b (interleukin-1beta). This receptor and IL-1b have been linked to diseases of inflammation. When canakinumab binds to and blocks access to the receptor, IL-1b cannot use the receptor. In lab experiments with cells and in

clinical trials in people, canakinumab can stop or greatly reduce certain inflammatory reactions and their consequences.

Although canakinumab was originally developed for rare conditions, emerging research strongly suggests that this antibody may play an important role in at least two more common conditions: heart attacks and lung cancer. As canakinumab has shown promise in these two conditions, some researchers are becoming excited about its potential for treating inflammation-related complications. Since chronic HIV infection is associated with inflammation, researchers are conducting a clinical trial of canakinumab in HIV-positive people to assess its long-term safety and effectiveness.

In this issue of *TreatmentUpdate*, we delve into studies of canakinumab in HIV-negative people to better understand its potential in HIV-positive people.

F. Canakinumab—effect on reducing inflammation and heart attacks in the Cantos study

In a double-blind, placebo-controlled, randomized study called Cantos, researchers gave placebo and different doses of canakinumab (sold as Ilaris) every three months to 10,061 HIV-negative participants. Prior to entering the study, all participants had experienced a heart attack and had elevated levels of C-reactive protein in their blood (suggestive of inflammation). Many participants were past and current smokers.

The trial lasted for about four years. Participants who received canakinumab had significantly reduced levels of C-reactive protein. Canakinumab did not decrease levels of bad cholesterol (LDL-C) or triglycerides in the blood. Yet people who received this drug at a dose of 150 mg every three months were less likely to have a heart attack than people who received placebo at the same schedule. Canakinumab significantly reduced levels of inflammation. However, it was associated with a greater risk for fatal infections than placebo. Canakinumab also reduced the risk of developing lung cancer.

The Cantos study is very important because it was the first to prove that reductions in inflammation are associated with a modestly reduced risk for heart attack and lung cancer. The results from this study will likely increase research on inflammation, its effect on cardiovascular disease and lung cancer, and ways of reducing inflammation by targeting the IL-1b receptor.

Study details

Researchers assigned participants to receive one of the following, given by subcutaneous injection (under the skin) every three months:

- canakinumab – 50 mg
- canakinumab – 150 mg
- canakinumab – 300 mg
- placebo

The average profile of participants upon entering the study was as follows:

- age – 61 years
- 74% men, 26% women
- current or past smokers – 71%
- 67% of participants had previously undergone procedures/surgery to improve the flow of blood to the heart
- most participants (at least 80%) were taking prescribed medicines to help normalize blood pressure, lower bad cholesterol and reduce the formation of blood clots
- all participants had at least a modest elevation of inflammation with levels of C-reactive protein (CRP) of around 4.20 mg/L (the test used was high-sensitivity CRP – hsCRP)

Most people were in the study for about 3.7 years.

Results—Changes in inflammation

Compared to people who received placebo, those who received canakinumab had their level of hsCRP reduced by the following proportions:

- canakinumab 50 mg – 26%
- canakinumab 150 mg – 37%
- canakinumab 300 mg – 41%

All of these differences between canakinumab and placebo were statistically significant; that is, not likely due to chance alone.

Among canakinumab users, hsCRP levels fell within three months of receiving the drug and stayed low for the duration of the study.

Similar trends were seen with another chemical signal of inflammation, IL-6 (interleukin-6), in people who received canakinumab vs. placebo.

There was no significant decrease in levels of cholesterol among canakinumab users.

Cardiovascular events

Researchers found that rates of heart attack were generally higher among people who received placebo compared to people who received canakinumab. Analysis of the data found that the canakinumab 150-mg dose was associated with a significant reduction in the following:

- non-fatal heart attack
- non-fatal stroke
- death from other complications of cardiovascular disease

Overall, the researchers found that death from serious cardiovascular disease was reduced by between 15% and 17% in people who received the 150-mg and 300-mg doses of canakinumab (compared to placebo).

According to an editorial in *The New England Journal of Medicine* by cardiologist Robert Harrington, MD, from Stanford University, when these results were further analysed, canakinumab's "modest overall effect was completely driven by a lower incidence of [heart attacks]."

The 50-mg and 300-mg doses did not result in statistically significant differences in these outcomes compared to placebo.

Adverse events

The term *adverse events* is used to describe a range of unfortunate incidents that can occur in a clinical trial. Only some of these events are caused by the study medicine. As this was a placebo-controlled study, researchers have a good idea of which side effects canakinumab had. The two main adverse events were as follows:

Neutropenia

- lower-than-normal levels of neutrophils in the blood (neutrophils are important cells that help control infections)

Infections

When the researchers reviewed data from all three groups of participants who received different doses of canakinumab, they found that there were significantly more deaths from complications of infections in those on canakinumab than those on placebo. Why this happened is not clear; the study authors did not link these deaths to lower-than-normal levels of neutrophils. According to the researchers, "the patients who died from infections tended to be older and more likely to have diabetes than those who did not die from infection."

Inflammatory-related conditions

The receptor for IL-1b is involved in inciting many inflammatory conditions in the body. By interfering with this receptor, canakinumab is able to significantly reduce levels of inflammation.

A benefit

Researchers found that participants in the Cantos trial who received canakinumab experienced a reduced intensity of certain preexisting inflammatory conditions such as arthritis, gout and osteoarthritis.

The following report in this issue of *TreatmentUpdate* reviews canakinumab's impact on cancer.

REFERENCE:

Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *New England Journal of Medicine*. 2017 Sep 21;377(12):1119-1131.

G. Canakinumab's anti-cancer potential

Canakinumab is an antibody that is used to treat rare inflammatory conditions. It works by interfering with a receptor for the chemical signal interleukin-1b (IL-1b). IL-1b binds to this receptor found on the surface of many cells. By binding to this receptor, a reaction is triggered; if sustained, it leads to inflammation. Research increasingly

suggests that inflammation likely plays some role in the development, growth and possibly the spread of cancer within the body.

In a study called Cantos, researchers investigated the ability of canakinumab to reduce inflammation linked to serious cardiovascular disease and cancer. Their rationale for this was that "patients with atherosclerosis commonly smoke, which is a risk factor for cancer." For this study, researchers recruited more than 10,000 HIV-negative participants at high risk for major cardiovascular events (heart attack, stroke). About 67% of participants had previously undergone cardiovascular procedures/surgery, about 71% were either past or current smokers, and at least 80% were taking medicines to reduce blood pressure, lower abnormal lipids, reduce blood clotting and so on. All participants had elevated levels of inflammation. Participants were randomly assigned to receive one of several doses of canakinumab (50, 150 or 300 mg) or placebo once every three months, via injection under the skin.

After an average of 3.7 years in the study, participants on canakinumab experienced significantly reduced inflammation and heart attacks compared to those taking placebo. Also, overall, there were fewer cases of cancer (principally lung cancer) among canakinumab users compared to placebo users. A significant decrease in new cases of cancer occurred only in participants who received the 300-mg dose of canakinumab. Researchers found that deaths due to complications from infections was more common among canakinumab users, but these deaths were more or less balanced by a reduction in deaths from complications of lung cancer.

The Cantos study was primarily designed to assess the cardiovascular benefit of canakinumab. Its anti-cancer effect, while promising, should be considered preliminary. Clinical trials specifically designed to explore canakinumab's anti-cancer potential are now needed, particularly in the field of lung cancer.

Study details

Please see the previous report for the full details of the Cantos study.

Results—Who was diagnosed with cancer?

During the study, people with the following characteristics were more likely to be diagnosed with cancer:

- older people
- current smokers

Inflammation and cancer

Previous studies have found a link between inflammation and cancer. Specifically, elevated levels of the chemical signal IL-6 (interleukin-6) and high-sensitivity C-reactive protein (hsCRP) in the blood have been linked to heightened inflammation. Participants who entered the Cantos study with higher-than-average levels of inflammation markers (IL-6, hsCRP) were more likely to subsequently develop cancer. For instance, people who had high levels of hsCRP (6.0 mg/litre vs. 4.2 mg/litre) were more likely to develop cancer. A similar pattern was seen with IL-6: People who entered the study with relatively high levels of IL-6 (3.2 ng/litre vs. 2.6 ng/litre) were more likely to develop cancer.

These differences in the risk of cancer diagnosis between high and low levels of hsCRP and IL-6 were statistically significant.

Inflammation and canakinumab

Participants who received canakinumab had significant reductions in hsCRP (between 26% and 41%) and in IL-6 (between 25% and 43%) compared to people on placebo. These differences between canakinumab and placebo were statistically significant.

Survival and cancer

Overall, participants who received canakinumab were less likely to die from cancer-related complications. The greatest difference in death rates was seen in people who received canakinumab 300 mg vs. placebo. This difference was mainly due to a reduction in deaths from complications of lung cancer among canakinumab users.

The distribution of cancers and cancer-related deaths was as follows:

Placebo
- 26% of all cancers were lung cancers
- 47% of all deaths due to cancer arose from lung cancer

Canakinumab
- 16% of all cancers were lung cancers
- 34% of all deaths due to cancer arose from lung cancer

Researchers found that the effect of canakinumab on lung cancer was "slightly stronger in current than past smokers." This was most noticeable in people who received the 300-mg dose of canakinumab.

Inflammation and cancer

Researchers noted that rates of lung cancer did not differ significantly between participants who received canakinumab or placebo who had levels of hsCRP greater than 1.8 mg/litre at the third month of the study. A similar effect was seen with participants whose IL-6 levels were greater than 1.64 ng/litre at the third month of the study. These findings suggest that some participants whose inflammation was not sufficiently reduced by canakinumab did not experience its anti-cancer effect. It may be that there is a subgroup of people who do not fully respond to canakinumab. This idea will require further study.

Adverse events

The term *adverse events* is used to describe a range of unfortunate incidents that can occur in a clinical trial. Only some of these events are caused by the study medicine. As Cantos was a placebo-controlled study, researchers have a good idea of which side effects canakinumab had. The main ones were as follows:

Neutropenia
- lower-than-normal levels of neutrophils in the blood (neutrophils are important cells that help control infections)

Infections
When the researchers reviewed data from all three groups of participants who received different doses of canakinumab, they found that there were significantly more deaths from complications of infections in people on canakinumab than those on placebo. Why this happened is not clear; the study authors did not link these deaths to lower-than-normal levels of neutrophils. According to the researchers, "the patients who died from infections tended to be older and more likely to have diabetes than those who did not die from infection."

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Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017 Oct 21;390(10105):1833-1842.

H. Issues to consider with canakinumab

As mentioned earlier in this issue of *TreatmentUpdate*, the antibody canakinumab, in a study called Cantos, showed modest benefits in reducing the risk of heart attack and lung cancer in people at very high risk for both conditions. Canakinumab significantly reduced inflammation but did not affect levels of lipids (cholesterol and triglycerides).

It is noteworthy that in Cantos more deaths from infections occurred in people who received canakinumab than in those who received placebo. These deaths were largely balanced by fewer deaths from cancer (mainly lung cancer) among canakinumab users.

Emerging research has suggested a link between inflammation and certain conditions, including heart disease and some cancers. The Cantos study proves that there is a link between inflammation and the risk of a heart attack. The study also strongly suggests that there is a link between inflammation and the risk for lung cancer. Although these results are very important, there are issues related to the potential use of canakinumab that need to be resolved, such as the ones below:

Heart attacks
More research is needed to better understand the impact of canakinumab on heart attacks, specifically, which types of heart attacks are prevented.

Cancer
Canakinumab decreased the risk of developing lung cancer. In Cantos, the 300-mg dose (compared to the 50-mg and 150-mg doses) was associated with the greatest reduction in the risk of cancer. Researchers who were not part of the Cantos study noted that the main purpose of Cantos was to assess its impact on serious cardiovascular disease; it was not primarily designed as a cancer study. Therefore, its findings on cancer should be considered promising but preliminary. It is not clear if canakinumab will work on all patients with lung cancer or only those with a history of smoking who also have cardiovascular disease. Recall that a large percentage of participants in Cantos (more than 70%) were past or current smokers.

Infections
Canakinumab was associated with an increased risk for serious infections and, in some cases, fatal infections. Researchers need to find out why this occurred. This is important, as it will inform future calculations of the drug's risk/benefit ratio.

Cost issues

Canakinumab was approved in Canada, the U.S. and other high-income countries for the treatment of rare inflammatory conditions. When used monthly, its annual cost is estimated to be about US $200,000 per person. Even if it is to be administered once every three months, the cost will be about US $67,000 per person per year. At best, this cost is unreasonable if canakinumab is to be used for a relatively common condition—cardiovascular disease. Note that canakinumab reduced the risk of non-fatal heart attacks by a very modest 16%. If canakinumab is to be more widely used to prevent heart attacks, massive reductions in price will be necessary.

Canakinumab is not the only game in town

In the U.S., researchers have conducted a six-month study of the anti-cancer drug methotrexate given in low doses. Results from this study should become available in 2018. If low-dose methotrexate can safely reduce excess inflammation in people with HIV, we can expect larger and longer clinical trials with this drug.

A number of other clinical trials are underway in the U.S. and Canada to study therapies that can help reduce inflammation and that have other beneficial effects in people who are using HIV therapy.

The Cantos study has underscored the clinical importance of interfering with the IL-1beta receptor, as it is linked to inflammation and now cardiovascular disease and likely lung cancer. It is likely that, in addition to canakinumab, other drugs are being considered for development to reduce inflammation, as cardiovascular disease is relatively common in people with and without HIV infection.

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1. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *New England Journal of Medicine*. 2017 Sep 21;377(12):1119-1131.

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I. Canakinumab in HIV reduces inflammation

As mentioned earlier in this issue of *TreatmentUpdate*, chronic HIV infection is associated with inflammation. Initiating HIV treatment (ART) and achieving and maintaining an undetectable viral load helps to partially reduce but not eliminate excess inflammation. Researchers think that HIV-related inflammation may gradually increase the risk for health complications over the long-term.

In a pilot study, researchers in San Francisco tested a single injection of canakinumab 150 mg under the skin of HIV-positive people taking ART. They found that the drug significantly reduced inflammation and did not cause harm, at least in the short term. A larger and longer study of canakinumab in this population is now underway.

Study details

Researchers enrolled 10 participants (nine men, one woman) who were between 55 and 65 years old. The average profile of participants upon entering the study was as follows:

- current smoker – 20%
- higher-than-normal blood pressure – 90%
- abnormal cholesterol levels – 80%
- history of heart attack and/or stroke – 30%
- history of heart attack among parents or siblings – 40%
- taking medicines to lower cholesterol levels – 80%
- CD4+ count – 638 cells/mm^3
- lowest-ever CD4+ count – 238 cells/mm^3
- viral load – less than 50 copies/mL in all participants
- history of hepatitis C co-infection – 20%

All participants received a single subcutaneous injection of canakinumab 150 mg and subsequently underwent close clinical and laboratory monitoring.

Results—Safety

The drug was well tolerated by participants.

Canakinumab caused a significant decrease in the levels of neutrophils (cells needed to fight infections) in the blood at two and three weeks after the injection. At those time points the decrease in neutrophil levels was 30%. However, four weeks after receiving the canakinumab injection, neutrophil levels began to enter the normal range.

One person developed shingles (herpes zoster) during the study. It is unclear if this was related to canakinumab, as there were no changes in CD4+ counts or HIV viral load prior to the episode of shingles. It subsequently resolved without complications.

Across all participants there were no significant changes in CD4+ counts and no change in CD4/CD8 ratio. During the first week of the study, CD8+ cell counts decreased by an average of 17% in participants but this resolved the following week.

Viral load did not rise above the 200-copy/mL mark in any participants during the study.

Changes in inflammation

Elevated levels of the chemical signals IL-6 (interleukin-6) and high-sensitivity C-reactive protein (hsCRP) are seen in inflammatory conditions such as HIV infection.

In the present study, a single dose of canakinumab gradually and significantly reduced IL-6 levels in the blood—by 24% at the fourth week of the study, and by a total of 30% by the eighth week of the study.

The drug also reduced hsCRP levels by 61% at the eighth week of the study.

No significant changes in the proportion of activated T cells in the blood were detected. However, there was a significant reduction in a subgroup of cells called monocytes. The specific subgroup of monocytes that were diminished were ones that displayed the HIV co-receptor CCR5 on their surface.

Participants underwent FDG PET/CT scans. In these scans, a small amount of radioactive sugar (FDG-glucose) is given to the person via intravenous infusion and researchers wait for some time (up to two hours) for this sugar to be taken up by active tissues. In this case, inflammation was taking place in the lymph nodes and arteries. The PET (positron emission tomography) scan detects the radioactive material and its location, while the CT (computer tomography) scan helps to form detailed images of the tissues being scanned. The researchers found that canakinumab caused a significant decrease in inflammation—10% in the arteries and 11% in the bone marrow—compared to pre-study levels.

What's next?

A larger (100-person) and longer randomized, placebo-controlled study is underway with canakinumab in which two doses of the drug will be given to ART users. Participants are randomized in a 2:1 ratio, so about 67% will receive canakinumab. This study will provide more information about the short- and medium-term safety of canakinumab in HIV-positive people.

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J. The potential of Ixolaris

SIV (simian immunodeficiency virus) is closely related to HIV. In some monkeys, SIV infection causes a syndrome similar to AIDS. Researchers sometimes use SIV-infected monkeys to conduct preliminary experiments with antiviral drugs and potential vaccines.

In experiments with SIV-infected monkeys, researchers at the U.S. National Institutes of Health (NIH) and the University of Pittsburg, Pennsylvania, have found that SIV-infected cells of the immune system produce a protein called tissue factor (TF). This protein plays an important role in helping blood to form clots. In conditions where there is elevated inflammation, such as some cancers and HIV (and SIV) infection, there is an increased risk for blood clots forming. These can block vital blood vessels and cause heart attacks and stroke.

Monkeys

HIV treatment, also known as ART, works on monkeys with SIV because the viruses are so closely related. In experiments with SIV-infected monkeys, ART greatly reduced the amount of virus in their blood. However, a group of immune system cells called monocytes continued to produce excessive amounts of TF. In turn, elevated levels of TF seemed to drive inflammation by increasing the amount of the following chemical signals:

- TNF-alpha (tumour necrosis factor-alpha)
- IL-1b (interleukin-1beta)
- IL-6 (interleukin-6)

Enter Ixolaris

The saliva of ticks that spread Lyme disease contains proteins that interact with the human immune system. One such protein is Ixolaris.

In lab experiments with cells of the immune system harvested from monkeys with SIV and humans with HIV, Ixolaris reduced the inflammatory effects of TF.

In another experiment, researchers infected eight monkeys with SIV and gave Ixolaris to five of them on the same day of infection. The Ixolaris-treated animals showed less inflammation and immune activation in their CD4+ and CD8+ cells. Furthermore, monocytes in the Ixolaris-treated animals had less TF compared to untreated monkeys. Also, Ixolaris-treated monkeys had reduced levels of another protein called D-dimer, elevated levels of which are associated with inflammation and excessive blood clot formation. These results with monkeys are interesting, but Ixolaris may have other benefits.

In the above experiments, monkeys were infected with an aggressive strain of SIV that causes the rapid development of an AIDS-like syndrome in as few as 100 days after infection. One of three SIV-infected monkeys not given Ixolaris developed AIDS in less than 100 days after SIV infection. In contrast, none of the Ixolaris-treated monkeys developed significant injury to their immune systems in that time.

Next steps

These experiments with monkeys have resulted in preliminary evidence about the potential of Ixolaris. The studies were small and not randomized or placebo-controlled, so their results are not definitive. A next step would be to test Ixolaris in a larger number of monkeys with SIV and conduct more complex and sophisticated immunological analyses. If such studies confirm the preliminary results of Ixolaris, researchers should then move forward and create purified Ixolaris under sterile conditions. This would be a minimum requirement prior to experiments with people.

Ixolaris is a protein with exciting potential but it will be several years before experiments in people begin. Still, the experiments with monkeys have helped scientists better understand how important

immunological activation and inflammation are to the complex changes caused by SIV and HIV.

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Schechter ME, Andrade BB, He T, et al. Inflammatory monocytes expressing tissue factor drive SIV and HIV coagulopathy. *Science Translational Medicine*. 2017 Aug 30; 9(405). pii: eaam5441.

K. Clinical trials in Canada to explore reducing inflammation in HIV

A number of clinical trials are underway to study therapies that can help reduce inflammation and have other beneficial effects in people on HIV treatment (ART). Here are some in Canada:

Reprieve
Pitavastatin is approved in the U.S. but not in Canada for the management of cholesterol levels. Small clinical trials suggest that pitavastatin not only helps to normalize cholesterol levels but can also reduce some measures of inflammation. Also, pitavastatin does not increase the risk of developing type 2 diabetes, a problem with some statins.

The main purpose of the Reprieve study is to find out if the use of pitavastatin can reduce deaths from heart attack, stroke or other complications of cardiovascular disease.

Researchers are seeking volunteers with the following basic profile:

- living with HIV between the ages of 40 and 75
- on antiretroviral therapy (ART) for at least 6 months prior to study entry
- no history of cardiovascular disease (including heart attack or stroke)
- not currently using a statin drug
- low-to-moderate risk for developing heart disease
- not pregnant or planning on becoming pregnant

To find out more about Reprieve and consider participation, readers can contact study centres in Canada listed in this link: http//www.hivnet.ubc.ca/clinical-trials/ctn-293-reprieve-trial/

CTNPT 028
This study, taking place at McGill University in Montreal, is assessing the impact of extracts of marijuana on inflammation in people with HIV: http://www.hivnet.ubc.ca/clinical-trials/ctnpt-028-cannabinoids-hiv-infected-individuals-effective-art-safety-tolerability-effect-immune-function.

CTNPT 022B (Proov It 2)
This study, taking place in Toronto, involves the use of friendly bacteria (probiotics) that researchers hope to show will reduce inflammation in the gut and possibly general inflammation in HIV-positive people: http://www.hivnet.ubc.ca/clinical-trials/ctnpt022b/

There are also clinical trials in the U.S. that are trying to reduce inflammation in people with HIV: one with low doses of the anti-cancer medicine methotrexate and another study of the antibody canakinumab (reported earlier in this issue of *TreatmentUpdate*). There are likely other studies being planned, as researchers have different ideas about how to suppress excess inflammation and immune activation in HIV.

L. suPAR—an early warning signal

One important aspect of research on inflammation in HIV is the ability to monitor inflammation. Researchers in Copenhagen, Denmark, have been studying levels of a protein that is released into the blood of people. This protein, called suPAR (soluble urokinase plasminogen activator receptor), is released during chronic inflammation. In a study of more than 900 HIV-positive people, the researchers have found that having an elevated level of suPAR at the start of the study was linked to an increased risk for subsequent serious health problems as well as diminished survival. Further research on suPAR in people with HIV is underway in Denmark and the U.S.

About suPAR

Before discussing suPAR we first explain its precursor, uPAR (urokinase plasminogen activator receptor). uPAR is a protein found mainly on

activated cells of the immune system, including the following:

- T-cells
- neutrophils
- macrophages

When inflammation occurs, these cells release uPAR into circulation, where it is called soluble uPAR, or suPAR. Many studies have found a connection between high levels of suPAR and a range of health conditions in which inflammation is involved and injury to major organ-systems is involved in HIV-negative people. In HIV-positive people, studies have found that the highest levels of suPAR occur in AIDS and high levels are linked to diminished survival.

Study details

Researchers collaborated with Denmark's ongoing HIV observational database. They analysed blood samples collected in 2007 (the start of the study) and monitored participants until May 2015, assessing what complications subsequently developed.

A total of 947 participants were in this study. Their average profile upon entering the study was as follows:

- age – 45 years
- 73% men, 27% women
- 46% were gay or bisexual men
- suPAR level – 2.65 ng/mL

On average, participants were in the study for seven years.

Results—New health conditions

A total of 270 diagnoses of complications all unrelated to HIV were made after the start of the study, grouped as follows:

- cardiovascular disease – 68 cases
- cancer – 66 cases
- chronic lung disease – 56 cases
- diabetes – 34 cases
- chronic kidney disease – 23 cases
- chronic liver disease – 23 cases

Statistical analysis found that participants with high levels of suPAR at the start of the study were significantly more likely to get these conditions (except for diabetes).

suPAR and survival

During the study, 121 (13%) participants died. These people had significantly higher levels of suPAR at the start of the study (4.09 ng/mL) than people who survived (2.56 ng/mL).

Researchers found that for every 1 ng/mL increase in suPAR levels, there was a 23% increased risk for dying. Researchers divided people into four groups or "quartiles" based on their suPAR levels (the first 25%, or quartile, had the lowest suPAR levels and the final 25%, or fourth quartile, had the highest levels). They found that people in the upper quartile had a six-fold increased risk of death compared to people in the lowest quartile.

Bear in mind

1. Additional risk factors
This prospective study has shown a relationship between elevated suPAR levels and an increased risk for a range of complications and death all unrelated to HIV disease. The relationship between elevated suPAR levels and these unfortunate outcomes was still valid, particularly in the case of cardiovascular disease, after researchers took into account factors that incite inflammation, including smoking and injecting street drugs.

2. Populations
When researchers segregated participants by suPAR level and how they acquired HIV, they found that the ability of suPAR to predict future unfortunate events was "strongest in individuals with no other potential drivers of inflammation such as injecting street drugs and smoking."

The role of suPAR

As the researchers did not conduct additional monitoring of other proteins associated with inflammation (such as interleulin-6, CD14, CD163) and lab studies of cells and suPAR, it is not clear if suPAR is merely a marker for future unfortunate events or plays some role in directly causing inflammation.

What's next for suPAR

Researchers with the U.S.-based ACTG (AIDS Clinical Trials Group) have been conducting a study of suPAR and will release their results in 2018. Additional studies with suPAR are underway in that country.

In Denmark, researchers are continuing to study suPAR in people with HIV who initiate ART and achieve an undetectable viral load and are comparing their suPAR levels to those of HIV-negative people.

suPAR has much potential as a tool to monitor the health of people and high levels of this protein indicate that there are likely problems to come.

Acknowledgement: We thank Jesper Eugen-Olsen, PhD, University of Copenhagen, Denmark, for helpful discussion, research assistance and expert review.

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Disclaimer

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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