



INFLAMMATION INFORMATION

Derek Thaczuk explains why the concept of HIV as a disease of inflammation is the talk of the HIV research community.

ILLUSTRATION BY KEVIN GHIGLIONE

Inflammation

is not a new concept in medicine, but it has recently become the big new buzzword in HIV. Inflammation is part of the body's response to infection, and fighting a long-term chronic infection like HIV throws the immune system into an ongoing state of activation, or chronic inflammation. This idea of chronic inflammation is hot right now because researchers are discovering that it may play a major role in many widespread problems among people with HIV/AIDS (PHAs)—such as heart attacks and cardiovascular disease as well as brain, liver and kidney damage. The metabolic problems experienced by many PHAs were long thought to be mostly due to the side effects of certain antiretroviral drugs, which has led many people to delay or interrupt treatment.

Antiretroviral therapy (ART) may be both friend and foe when it comes to heart disease. While certain (but by no means all) anti-HIV drugs are known to raise the risk of heart disease, we are also learning that successfully controlling HIV with ART may reduce the risk of the same problems, by reducing the chronic inflammation caused by untreated HIV. So, is your heart better off with or without ART? What does this apparent contradiction mean when it comes to starting or staying on ART? Experts are still trying

to answer these questions, but in the meantime, here's an exploration of what we know so far.

SMART TO STAY ON ART

Many antiretroviral drugs are notorious for causing metabolic disorders—disruptions in the body's normal biochemistry. Some of these metabolic problems, such as abnormal lipid (fat) and glucose (sugar) levels in the blood, greatly increase the risk of heart attack, stroke and other cardiovascular disease.

However, metabolic complications have also been seen in HIV-positive people who are not taking ART, so drug toxicities clearly cannot be the only cause. A trial called the SMART study gave the first conclusive evidence that prolonged and excessive immune activation—inflammation—is another major cause of ongoing damage in HIV disease. This large international trial looked at PHAs who either remained on continuous ART or took structured treatment interruptions—stopping ART when their CD4+ counts climbed above 350 and resuming when their counts fell below 250.

The SMART study did not even finish before the evidence was in: Compared to people who stayed on continuous

therapy, those who took treatment interruptions were more than twice as likely to become seriously ill or die. This was not limited to death from AIDS-related conditions; treatment interrupters also had higher rates of heart, liver and kidney diseases—problems that are often associated with inflammation.

Researchers highlighted two messages from the SMART study: First, it is a bad idea to stop treatment once started. SMART hammered the final nail into the coffin of structured treatment interruptions. Second, researchers interpreted SMART results as follows: When people stopped ART, their virus came out of hiding, made copies of itself and cranked up the immune system, that is, caused inflammation. These bouts of inflammation increased the risk of inflammation-related conditions such as heart disease.

GOOD INFLAMMATION TURNED BAD

But what does inflammation—an immune response to infection—have to do with heart disease? “Inflammation is a much broader process than simply an immune response to infection,” explains Marek Smieja, associate professor of pathology and molecular medicine at St. Joseph’s Health-care hospital in Hamilton, Ontario. “Inflammation also includes mechanisms that repair and defend against damage to bodily tissue.”

Smieja adds, “There has been an idea prevalent in cardiology for quite a long time, which is that the process that leads to heart disease, atherosclerosis, is an inflammatory response to injury.” The process goes something like this: Blood vessels are damaged—by high blood pressure, high blood sugar, cholesterol or whatever factor—and the body produces inflammation in attempt to repair the vessel wall.

BUZZWORDS

INFLAMMATION: The immune system’s response to infection or tissue damage, also called immune activation. Inflammation helps to fight infection and also repairs damaged tissues. Inflammation can be short-lived (acute), such as the redness and swelling around an infected cut or the body-wide aches and fever when you’re fighting off the flu. However, lower levels of inflammation can persist for years without any obvious symptoms. This is called chronic inflammation.

METABOLIC DISORDERS: Disruptions in the body’s normal biochemistry, such as abnormal levels of cholesterol and fats (lipids) in the bloodstream and abnormal levels of blood sugar (glucose). Over the long term, these problems can increase the risk of cardiovascular disease.

CARDIOVASCULAR DISEASE: Disease that affects the heart or the blood vessels. The most common is **atherosclerosis**—the stiffening and thickening of blood vessel walls due to a build-up of fatty clots—which can lead to **heart attack** or **stroke**.

However, since the damage continues—unless we listen to our doctor’s advice and are able to reduce our blood pressure, blood sugar levels, cholesterol or whatever—the inflammation persists and becomes chronic.

The problem is that chronic inflammation, which begins as a healing mechanism, eventually has the opposite effect—it causes more damage to the vessel. The accumulating damage causes atherosclerosis: The blood vessels stiffen and thicken due to the build-up in the walls of fatty clots called plaques. These plaques contain cholesterol as

THE SINGLE BIGGEST DRIVER OF HEART DISEASE AMONG PEOPLE WITH HIV REMAINS SMOKING, WITH HIGH LIPIDS A CLOSE SECOND.

well as large numbers of immune cells, including T cells, macrophages and other, more exotic, creatures such as foam cells.

Problems really start when the plaque gets so large that it blocks the flow of blood or it ruptures. A ruptured plaque forms a fatty plug that can travel through the bloodstream and become lodged in a blood vessel. If the blocked vessel is in the heart or brain, the result is a heart attack or stroke.

UNIFYING HIV AND HEART DISEASE

So, where does HIV fit in? It’s well known that HIV activates the immune system when it replicates (makes copies of itself) and that untreated HIV disease leads to constant low-level activation—a sort of permanent state of inflammation. Researchers hypothesize that this inflammation caused by HIV (or another infection) might trigger atherosclerosis in blood vessels or it might promote atherosclerosis that has already started. (In support of this, Smieja points out that an episode of pneumonia increases the risk of heart attack for several months thereafter, presumably due to the sudden burst of immune response to the infection.)

While it might not be intuitive that an infection could cause heart disease, it makes sense if we consider that what we call “inflammation” is actually a physical process involving immune cells and chemical messages, and these cells and messages travel through blood vessels while fighting an infection. It’s possible that in doing its job of battling infection, “inflammation” also has the unintended effect of promoting atherosclerosis in the blood vessels.

Cardiovascular disease is generally thought to be caused by multiple factors working together. Infection, including

THE CANADIAN HIV VASCULAR STUDY

The Canadian HIV Vascular Study is investigating the relationships between HIV medications, metabolic abnormalities and cardiovascular disease among PHAs. Originally sponsored by the Ontario HIV Treatment Network (OHTN) for two years, additional funding from the Canadian Institutes of Health Research (CIHR) has resulted in a five-year, multi-site cohort study following roughly 300 PHAs from seven major Canadian cities.

“We’re using a measure called carotid intima media thickness—essentially a measure of how much the arteries are thickening, which is a very good predictor of heart attack risk,” says Marek Smieja, the study’s lead investigator. “We are looking at how this is affected by cholesterol levels, by aging, by smoking and by different antiretroviral drug regimens; and we are also looking at a number of markers of inflammation.”

Studies like this will continue to tease out the complex interactions between traditional cardiac risk factors, HIV infection, inflammation and antiretroviral treatments. So far, Smieja says, “we’ve shown that protease inhibitors and stavudine (d4T, Zerit) cause more atherosclerosis than other drugs, and that high cholesterol, smoking and high blood pressure are all major risk factors.” The risk of heart disease due to inflammation has appeared to be “borderline,” he says. “You do get more cases of heart disease in people who have more inflammation, but the jury is still out on whether inflammation adds a risk over and above the traditional risk factors like smoking, age, high cholesterol levels and blood pressure.”

it’s more controversial whether we should start ART earlier specifically because of heart disease.” He is certain that the “single biggest driver of heart disease among people with HIV” remains smoking, with high lipids a close second. Those lipid levels “may be partly due to HIV disease, but they are mainly driven by the antiretrovirals.”

So, while experts may not yet agree as to the precise role that inflammation plays in the damage that HIV disease inflicts on our bodies, it is clear that there are many things we PHAs can do to better our heart health, such as: quitting smoking, controlling blood pressure, keeping diabetes and cholesterol in check and getting exercise. +

For practical advice on heart health, check out CATIE’s Fact Sheet “HIV and cardiovascular disease: keeping your heart and blood vessels healthy.” Find it at www.catie.ca/facts.nsf or call 1.800.263.1638 to order a copy.

Derek Thaczuk has been writing and speaking on HIV and health topics for 12 years. He has been blessed with good health since his own diagnosis in 1992 and thinks that everyone with HIV should be able to expect the same.

HIV, might be one more of these causes to add to the list. In fact, researchers are now thinking that many of these factors may cause inflammation and this explains how together they lead to cardiovascular disease. Inflammation, Smieja says, may be “kind of a unifying hypothesis, meaning that it’s still the smoking or the diabetes or the hypertension that’s ultimately causing cardiovascular disease, but inflammation is a final common pathway that allows us to better integrate all these different risk factors.” Seeing inflammation in this central role allows researchers to better understand how cardiovascular disease risk factors, including HIV infection, influence each other. This may one day help physicians decide how to best treat PHAs who are at risk for heart disease.

The consequences of ongoing immune activation do not begin and end with cardiovascular disease. In fact, chronic inflammation seems to drive what can be seen as an accelerated aging process, much like what is being seen in people with long-term HIV infection. Marianne Harris, a family doctor and clinical research advisor for the AIDS Research Program at St. Paul’s Hospital in Vancouver, says that with normal aging “you have a low-grade, chronic inflammatory state, which eventually ceases to be beneficial and instead causes tissue damage to slowly accumulate.” The chronic immune activation of long-term HIV infection accelerates the process: “The changes you see with chronic HIV—heart, bone, brain and kidney disease—are very similar to what happens in the normal aging process.”

DO HEARTS ♥ ART?

Research into the role of inflammation is gathering momentum, and many details remain to be investigated. One central issue, as mentioned earlier, is that ART may have two opposing effects. On one hand, certain antiretroviral drugs are known to increase the risk of heart attack and maybe stroke. On the other hand, the inflammation theory argues that effective treatment reduces inflammation caused by the ongoing viral replication of untreated HIV disease and, overall, lowers cardiovascular disease risk. What exactly does this mean for a PHA who is thinking about the pros and cons of starting treatment?

So far, the medical community has acted on the evidence that leaving HIV infection untreated poses greater future health risks than ART does, as SMART and other studies suggest, by recommending earlier treatment (that is, by recommending treatment initiation at a higher CD4+ cell count). The most recent guidelines published by the U.S. Department of Health and Human Services (DHHS)—the granddaddy of guidelines for HIV treatment—now recommend starting treatment when CD4+ counts fall below 500, with some members of the expert group even calling for treatment at counts above 500 cells. (Check out *Treatment-Update 176* at www.catie.ca/tu.nsf for an in-depth report on the changes to the DHHS guidelines.)

Whether starting ART is going to reduce the risk of heart attack and stroke for PHAs is an open question. Not all experts are convinced, and Smieja is among them: “I think