GMHC treatment ISSUES

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# Treatment ISSUES

## HIV and Inflammation

*By Liz Highleyman*

Inflammation has become a major concern of HIV medicine in recent years. Experts now recognize that persistent HIV infection leads to long-term immune activation and chronic inflammation, even among people on antiretroviral therapy (ART) with undetectable viral load. Ultra-sensitive tests show that a small amount of residual HIV remains in the body despite effective treatment, and a growing body of evidence shows that even this low-level virus can cause a range of problems long before a person's CD4 T-cell count falls into the danger zone for opportunistic illness.

### What Is Inflammation?

Inflammation is a broad term for what happens when the immune system recognizes and responds to a threat. Many different types of immune cells go into action, including macrophages that ingest invaders, CD4 helper T-cells that coordinate the overall immune response, and CD8 killer T-cells that disable virus-infected and malignant cells.

In response to an acute threat, injured tissues alert white blood cells such as macrophages that are present throughout the body. A protein called nuclear factor kappa-B (NF-kB) is released, switching on genes involved in immune response.

Immune cells communicate using chemical messengers known as cytokines. These signals exert a variety of effects, from calling white blood cells to a site of injury, to stimulating cell proliferation, to making blood vessels more permeable so immune cells can more easily maneuver.

Activated macrophages and other early responders produce pro-inflammatory cytokines including interleukin 1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-alpha), and interferon gamma. Neutrophils and other immune cells migrate to the affected area, where they ingest or poison pathogens and release their own chemicals. In addition, the liver produces acute-phase proteins such as C-reactive protein (CRP), fibrinogen, and plasminogen. Some of these chemicals can be detected in the blood and are used as biomarkers to assess inflammation.

At the local level, these chemicals cause physiological changes responsible for the classic inflammatory signs of redness, swelling, heat, and pain. They also play a role in blood clotting and tissue repair. System-wide, pro-inflammatory chemicals act on the brain and elsewhere, causing fever, loss of appetite, fatigue, and other "flu-like" symptoms.

This innate response is active against a range of invaders. Early responders also trigger adaptive or specific immune responses carried out by lymphocytes, known as B-cells, T-cells, and natural killer cells. These cells learn to recognize and directly target particular antigens (for example, pieces of bacteria or virus displayed by macrophages).

T-cells differentiate into CD4 helper cells and CD8 killer cells. CD4 T-cells, which direct the immune response, are the primary target of HIV. Young B-cells (which produce antibodies) and T-cells are naive, meaning they can respond to new antigens. After an immune response, a subset of these cells become long-lived memory cells that remember a specific threat in order to respond quickly if it appears again.

***HIV infection leads to long-term immune activation and chronic inflammation.***

Normally immune responses are self-limiting and "turn themselves off" when no longer needed. Just as pro-inflammatory cytokines trigger immune activation, anti-inflammatory cytokines such as IL-4, IL-10, and transforming growth factor-beta (TGF-beta) inhibit or shut down immune responses.

While a robust immune system is key to good health, it is not designed to sustain a continuous inflammatory response over the long term. But when faced with an ongoing threat such as chronic HIV infection, the immune

response remains engaged, leading to problems throughout the body.

Over time, persistent cytokine elevation and other immune processes can damage organs including the heart and brain. Furthermore, continuous activation accelerates progression of immune cells though the cycle of growth and division, causing them to "burn out" prematurely, a state known as immunosenescence. In an article published in *Topics in HIV Medicine*, Steven Deeks reports that middle-aged HIV-positive people show signs of immunosenescence resembling those of HIV-negative people over age 70.[1]

## How does HIV Cause Inflammation?

Inflammation is implicated in almost every type of health problem and its consequences tend to be worse for people with HIV since the ongoing presence of the virus maintains CD4 and CD8 T-cells in a constant state of activation. Combination ART has dramatically reduced the risk of AIDS-defining opportunistic illness and death. But as HIV-positive people survive longer thanks to effective treatment, they are at increased risk for a variety of non-AIDS conditions even while CD4 cell counts are relatively high.

**Chronic immune activation and inflammation contribute to higher rates of cardiovascular disease in people with HIV.**

At a recent forum, Deeks suggested AIDS should perhaps be thought of as "acquired inflammatory disease syndrome." "HIV is causing high-level inflammation and inflammation-associated disease," he explained. "Antiretroviral therapy can help people live longer, but it does not restore health and they do not have a normal lifespan." Starting treatment earlier, he said, might mitigate these effects.

Experts think chronic immune activation and inflammation contribute to higher rates of cardiovascular disease and other non-AIDS conditions seen in people with HIV. But given that HIV disease is characterized by immune suppression, how can it also cause excessive immune activation and inflammation? The answer lies in the complexity of the immune response. As Peter Hunt and colleagues from the University of California, San Francisco (UCSF) explained at the 2010 Conference on Retroviruses and Opportunistic Infections (CROI), "HIV has its foot on the accelerator and the brakes at the same time."[2]

While late-stage HIV/AIDS involves severe immune deficiency, immune activation and dysregulation are more common at earlier stages. Throughout the course of disease, however, the percentage of infected CD4 T-cells does not seem large enough to explain the extent of immune dysfunction. Most CD4 cells in the blood and lymph nodes of people with chronic infection do not carry the virus, but it appears that only a small amount is needed to sustain an inflammatory state. Even "elite controllers," the small proportion of HIV-positive people who naturally control the virus without treatment, show greater immune activation than HIV-negative people, and they are at higher risk for cardiovascular disease and other non-AIDS conditions.

HIV proteins including Tat and gp120 appear to directly stimulate immune responses by altering cytokine signaling. HIV also contributes to inflammation in less direct ways. At the earliest stages of infection, the virus establishes itself in lymphoid tissue in the gastrointestinal tract, the body's largest reservoir of susceptible CD4 T-cells. Brenchley et al. explained in a 2006 report in *Nature Medicine* that HIV infection damages the intestinal lining and makes it more permeable, allowing bacteria that normally reside in the gut to escape, a process known as microbial translocation.[3] As they enter the bloodstream, these bacteria and a toxin they produce called lipopolysaccharide (LPS) trigger a strong systemic immune response.

Viral and bacterial coinfections also play a role in HIV-related inflammation. Decreased immune function, even while CD4 cell counts are still relatively high, can lead to loss of control of other disease-causing organisms in the body. HIV-positive people with active chronic viral coinfections, such as herpes simplex virus, cytomegalovirus (CMV), and hepatitis B and C viruses, typically have higher HIV viral load, lower CD4 T-cell counts, and faster progression to AIDS.

UCSF researchers showed that HIV-positive people with stronger CMV-specific CD8 T-cell responses had higher levels of inflammation biomarkers and more early atherosclerosis. At CROI 2010, they reported that treating CMV with valganciclovir reduced CD8 cell activation.[4] Similarly, Kovacs et al. found that among HIV-positive women coinfected with hepatitis C, those with the most activated CD8 cells had three times the risk of progression to AIDS.[5]

Finally, metabolic abnormalities such as elevated low-density lipoprotein (LDL) cholesterol and body composition changes associated with HIV and its treatment can trigger inflammation, and these inflammatory changes in turn can affect metabolism.

While some antiretroviral drugs can contribute to metabolic abnormalities, the overall effect of ART is to reduce inflammation. Experts advise that lowering viral load as much as possible is the most effective way to reduce persistent immune activation and inflammation in people with HIV.

## Inflammation Biomarkers

It is increasingly clear that complications seen in HIV-positive people are not only due to the effects of the virus on the immune system, but also the immune system's response to the virus. The idea that persistent immune activation and inflammation influence HIV disease progression is not new. Since the early years of the epidemic, research-

ers have reported that HIV-positive people have elevated levels of various markers of inflammation. Hunt et al. have shown that greater T-cell activation predicts faster CD4 cell decline among untreated people, and poorer CD4 cell recovery on ART despite viral suppression.[6]

The large Strategies for Management of Antiretroviral Therapy (SMART) treatment interruption trial prompted the latest wave of interest in HIV-related inflammation and its consequences. SMART enrolled more than 5,000 HIV-positive adults with a CD4 count above 350 cells/mm$^3$. They were randomly assigned either to stay on continuous ART or to stop treatment when their CD4 count rose above this level, resuming when it fell below 250 cells/mm$^3$.

The treatment interruption arm was halted ahead of schedule in January 2006 after an interim analysis showed that these participants not only had a higher rate of opportunistic illness and death, but also were at higher risk for serious non-AIDS conditions including heart, liver, and kidney disease. These results, and those of subsequent studies, led to an intensive search for an explanation. Researchers began looking at biomarkers of increased inflammation, coagulation, and endothelial (blood vessel lining) dysfunction.

**Age-related conditions are associated with elevated levels of inflammation biomarkers.**

At the 2008 CROI and in a follow-up report in *PLoS Medicine*, Lewis Kuller and colleagues from the SMART team reported that elevated levels of the pro-inflammatory cytokine IL-6, the coagulation marker D-dimer, and the acute-phase protein CRP were associated with increased cardiovascular mortality and all-cause mortality.[7] IL-6 and D-dimer rose along with viral load after treatment interruption, but remained stable in people on continuous therapy.

The Swiss-Thai-Australia Treatment Interruption Trial (STACCATO), in which participants restarted ART when their CD4 count fell below 350 cells/mm$^3$ (rather than 250 cells/mm$^3$ in SMART), also revealed a link between HIV viral load and inflammation biomarkers.[8] A variety of markers, including D-dimer, VCAM-1, P-selectin, MCP-1, and leptin, decreased as HIV was suppressed on ART and rose during treatment interruption. In contrast, levels of anti-inflammatory biomarkers, including IL-10 and adiponectin, increased as viral load declined and fell during treatment breaks.

In a comparison of inflammation biomarkers in people with and without HIV, Neuhaus et al. looked at SMART participants and HIV-negative individuals in two large population-based cardiovascular studies, Multi-Ethnic Study of Atherosclerosis (MESA) (age 45–76) and Coronary Artery Risk Development in Young Adults (CARDIA) (age 33–44).[9] People with HIV had significantly higher levels of markers including IL-6, CRP, and D-dimer. Levels were higher in HIV-positive participants both on and off ART compared with HIV-negative people, and this link remained after adjusting for traditional cardiovascular risk factors.

While SMART revealed more inflammation among participants who interrupted ART, even people on continuous ART with stable suppressed viral load have higher inflammation biomarker levels than HIV-negative individuals.[10] Furthermore, Baker et al. recently reported increased inflammation biomarkers in HIV-positive people who still have high enough CD4 cell counts that they do not yet need treatment.[11] Indeed, even elite controllers show more inflammation than HIV-negative people.

In summary, it is now widely acknowledged that HIV has harmful effects well before it causes serious immune deficiency, and these effects can persist despite undetectable viral load and high CD4 cell counts.

## Consequences of Inflammation

Changes in biomarker levels reflect physiological processes that can ultimately lead to serious clinical consequences. Not long after the advent of effective combination ART, researchers began to notice that as HIV-positive people lived longer, they were at higher risk for chronic progressive conditions such as cardiovascular disease, kidney disease, bone loss, neurocognitive impairment, and certain non-AIDS-related cancers.

Numerous studies have shown that these age-related conditions are associated with elevated levels of inflammation biomarkers. HIV infection has been shown to promote immunosenescence and many people with HIV and their doctors have noted that the virus seems to accelerate aging in general. HIV-positive individuals tend to develop these progressive conditions sooner than their HIV-negative counterparts. For example, people with long-term HIV infection have brain function similar to that of HIV-negative people 15–20 years older, on average, while blood vessel function resembles that of people 10 years older.[12]

Large general population studies have shown that blood levels of inflammatory chemicals involved in atherosclerosis, or "hardening of the arteries," can predict future cardiovascular events. Not coincidentally, these are the same biomarkers linked to cardiovascular events and death in SMART and other studies of people with HIV.

Observational studies since the advent of ART in the mid-1990s have seen higher rates of cardiovascular disease among people with HIV. This may be attributable to the virus itself, antiretroviral drugs, greater frequency of risk factors such as smoking, or some combination of factors, with inflammation playing a key role.

As described at CROI 2010, Priscilla Hsue and her team at UCSF found that HIV-positive people experienced faster atherosclerosis progression, as measured by intima-media thickness, or thickness of blood vessel walls, than HIV-negative individual over two years.[13] This was the case for people with undetectable viral load on ART and even for elite controllers. People with HIV also had

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impaired ability of arteries to respond to changes in blood flow.[14] Both measures were associated with inflammation, as indicated by elevated CRP levels.

At the same meeting, Robert Kaplan and colleagues reported that increased carotid artery intima-media thickness and reduced distensibility (ability of blood vessels to expand) were linked to greater CD4 and CD8 cell activation and T-cell senescence in HIV-positive women.[15]

Looking at actual clinical events among patients at Massachusetts General Hospital and Brigham and Women's Hospital in Boston, Triant et al. found that HIV-positive people with high CRP had four times greater risk of myocardial infarction than HIV-negative people with normal CRP.[16] More recently, Phyllis Tien and fellow investigators with the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study reported that HIV-positive people with elevated CRP and fibrinogen had a significantly higher risk of death over five years.[17]

While the detrimental effects of inflammation have been most clearly demonstrated for cardiovascular disease, similar associations are seen for cognitive impairment, non-AIDS-related cancer, and other progressive age-related conditions.

## Managing Inflammation

The initial goal of HIV medicine was simply to keep people alive by managing opportunistic illnesses, and over time shifted to viral load suppression and managing ART side effects and complications. Today, the focus is on improving overall health and enabling HIV-positive people to live as long as their HIV-negative counterparts.

A number of different strategies have been proposed for managing inflammation in people with HIV. As noted, optimizing ART to keep viral load as low as possible for as long as possible, as well as treatment of coinfections, are the most reliable current approaches. Numerous studies have shown that suppressing HIV decreases T-cell activation and reduces inflammation biomarkers, while stopping ART worsens inflammation. Managing inflammation is a major rationale for the current trend toward earlier treatment.

Researchers have looked at a wide variety of anti-inflammatory and immune-suppressing agents for managing inflammation in HIV-positive people. Many of these work by altering production or activity of cytokines. Some researchers are particularly interested in CCR5 antagonists, drugs that prevent HIV from using the CCR5 co-receptor to enter cells. CCR5's role in immune response is not fully understood, but drugs like maraviroc (Selzentry) appear to have anti-inflammatory as well as antiretroviral properties. Some clinical trials of maraviroc have shown that even though it does not suppress HIV better than other antiretroviral classes, it appears to produce larger CD4 cell gains, reduce T-cell activation, and decrease inflammatory biomarkers.[18, 19, 20]

At CROI 2010 and at the XVIII International AIDS Conference this past July, researchers presented data on a novel experimental drug, TBR-652, that blocks both CCR5 and CCR2 cell surface receptors. Early studies suggest it has anti-inflammatory as well as antiretroviral activity.[21]

But interfering with immune response can be dangerous in people who have HIV, which already suppresses immune function. Furthermore, there is potential for unintended consequences when altering cytokine activity and other cell-signaling pathways that are not fully understood.

A safer approach involves lifestyle changes to reduce inflammation, including smoking cessation, weight loss, diet modification, exercise, adequate sleep, and stress management.

## Conclusion

Over the past few years, researchers have learned a great deal about inflammation and its relationship to HIV. Today, studies routinely collect data about biomarkers and other indicators of inflammation and immune activation, and clinicians are starting to think about how such measures could be applied in real-world patient care.

Inflammation may ultimately prove to be the key that unlocks some of the mysteries of HIV disease. In turn, advances in HIV medicine may contribute to the development of anti-inflammatory approaches that will also benefit people with other diseases.

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For a full list of references, please visit: *gmhc.org/research/treatment-issues*