# HIV and Aging: The Potential Role of Inflammation

The good news is we're living longer with HIV. The bad news is we're aging faster than those not infected HIV. The body's hyperactive response to the virus, even among those being successfully treated with antiretrovirals, is being eyed as the culprit. Fortunately, researchers already have potential anti-aging and anti-inflammatory treatments in sight.

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"Aging" and "inflammation" have become familiar words in the HIV lexicon, up there with terms like "CD4 cells," "viral load" and "antiretrovirals." There's a good reason for this: People living with HIV appear to age faster—as seen in the premature onset of age-associated diseases and immune system deficits—than those not infected with the virus. This is likely because of chronic inflammation, a lingering effect of HIV's perseverance, even when antiretroviral (ARV) therapy is working to the best of its ability.

The connection between inflammation and aging isn't simply a quirky phenomenon. It is now a major variable in HIV research, notably in studies exploring the "natural history" of untreated HIV infection and treatment clinical trials. In fact, researchers are taking note of the anti-inflammatory properties of various compounds—agents that can work alone or in tandem with viral load–reducing ARVs to calm the body's overzealous inflammatory response to HIV and potentially slow the aging process in people living with HIV.

After years of research exploring ways to muscle up the immune system's response to the virus, we're now learning it might be best to calm it down. To better understand this paradox, AIDSmeds attended the first Immune-Based Therapies Strategy Workshop held in February in San Francisco, hosted by Project Inform and Treatment Action Group. Steven Deeks, MD, professor of medicine at the University of California at San Francisco, was on hand to summarize the latest inflammation and aging research and to provide a glimpse at the potential future of anti-inflammatory treatments to facilitate both long and healthy living with the virus.

## HIV and Aging

Thanks to the powerful and long-lasting effects of ARV therapy, people diagnosed with HIV in their 20s and 30s are living to see their 50s, 60s and beyond. According to data from the U.S. Centers for Disease Control and Prevention (CDC), approximately 24 percent of people living with HIV/AIDS

in 2005 were 50 years of age or older—an increase of seven percent since 2001.

Treatment adherence struggles and side effect problems aside, prolonged survival with HIV isn't without its risks. "HIV infection and its treatment may affect the presentation and management of common age-associated complications," Deeks said. "There are also poly-pharmacy issues, in which there is a greater risk of drug interactions when drugs used to manage HIV are combined with medications used to treat diseases typically associated with aging."

A growing number of individuals are acquiring HIV at an advanced age. According to the CDC, 15 percent of newly diagnosed people with HIV are older than 50. Deeks added that HIV infection later in life might come with its own set of disease-progression challenges. "The natural history of HIV infection in older individuals may be unique," he said.

Finally, there's the more curious issue researchers have been setting out to explore—the observation that HIV infection is associated with accelerated aging. "We're seeing premature onset of age-associated complications in people living with HIV," Deeks explained. "We're also seeing deleterious effects on the immune system."

## Inflammation: The Basics

Inflammation refers to a cascade of events, usually orchestrated by the immune system, to help defend against disease-causing stimuli such as pathogens (for example, viruses), damaged cells or irritants. Without inflammation, wounds and infections would never heal. When people feel ill after being infected with a microorganism such as the common cold virus or influenza, it is the immune system's inflammatory process that produces fever, swelling and aches and pains—unpleasant, yes, but crucial to the disease-fighting process.

Prolonged or chronic inflammation—the ceaseless production of oxidative chemicals to attack and kill microorganisms and infected cells—has a deleterious effect. In essence, it ends up causing serious, sometimes irreversible damage to healthy cells and tissues in the body. This, research has suggested, can contribute greatly to a host of other diseases such as thickened blood vessels (arteriosclerosis) and cancer.

Researchers, including Deeks, are now beginning to take the immune system's inflammatory response to HIV—a virus that can be suppressed but takes up permanent residence in immune system cells—very seriously. Though a number of plausible theories might explain why people with HIV are experiencing age-related diseases earlier in life than their HIV-negative counterparts, inflammation has become increasingly suspect.

## The Rise of Non-AIDS, Age-Related Diseases

There has been no shortage of studies indicating that untreated HIV increases the risk not only of "classic" AIDS-related opportunistic infections, but also of diseases typically associated with aging: cardiovascular disease, non-AIDS cancers, bone mineral loss, liver failure, kidney failure, cognitive

decline and frailty.

Though data have repeatedly confirmed that ARV therapy reduces the risk of several non-AIDS-related diseases, the risks remain elevated—again, compared with the age-matched HIV-negative population—among those who achieve undetectable viral loads using HIV treatment.

Using cardiovascular disease as an example, Deeks explained that so-called elite controllers—people living with HIV able to keep their viral loads undetectable and their CD4 counts well within the normal range without the use of ARV treatment—have a higher risk of heart disease compared with HIV-negative individuals.  "This finding," he said, "points to an effect of HIV-associated inflammation rather than to effects of the virus or its treatment."

Cognitive decline was another example Deeks explored. There are a number of possible reasons why neurologic deficits can be documented in some people otherwise responding well to ARV therapy, including low-level replication of HIV in the central nervous system, active substance abuse and the presence of other infections such as hepatitis C. "Persistent inflammation is another possibility to consider, especially in patients starting antiretroviral therapy with low CD4 cell counts."

Osteopenia and osteoporosis—moderate and severe bone mineral loss, respectively—may also be tied to ongoing inflammation in people on HIV treatment. "Alcohol use and the direct effects of certain drugs on bone metabolism may play a role," Deeks said. "Inflammation may also be an underlying cause."

## Inflammation and HIV-Associated Aging

"We know that antiretroviral therapy reduces HIV-associated inflammation," Deeks said. "We also know that this effect is often incomplete."

The ongoing inflammation in people living with HIV can likely be tied to the high levels of immune activation that kick in—and remain elevated—soon after infection is established. When HIV goes untreated, a significant proportion of CD8 and CD4 cells become "activated" in an effort to respond to the virus. "Although antiretroviral therapy reduces HIV-associated CD8 and CD4 activation, the suppression is not complete."

There are also inflammatory molecules, produced by other cells in the body, in people with both untreated and treated HIV. These include interleukin-6 (IL-6), a pro-inflammatory cytokine produced by macrophages and other cells; high-sensitivity C-reactive protein (hsCRP), an acute phase protein produced by the liver in response to infections; and d-dimers, small proteins in the blood associated with blood clotting—all of which are associated with an increased risk of cardiovascular disease.

Ongoing immune activity against other infections common among people living with HIV, such as CD4 cells active against cytomegalovirus (CMV) infection, may also contribute to arterial disease

and subsequently increase the risk of a cardiovascular event.

Markers of persistent inflammation that may affect other organ systems, such as the brain, have also been documented. According to Deeks, ARV therapy doesn't normalize CD8 cell activity in the spinal fluid. Neopterin, a marker of macrophage activity in the central nervous system, has also been found in patients receiving ARV therapy.

"The one thing we know is that signs of ongoing inflammation are most likely to be detected in people who started antiretroviral therapy after their CD4 cell counts fell below 200," Deeks said. "It's unclear if inflammation persists in those who start treatment earlier in the course of disease."

HIV-associated inflammation may also be linked with premature senescence—more rapid progression of immune system deterioration typically associated with natural age advancement. "The high level of CD4 cell proliferation and death seen in HIV disease may cause the immune system to become exhausted and exhibit a lot of the signs typically seen in older individuals," Deeks explained. Among the similarities seen in people with HIV and elderly HIV-negative individuals are reductions in the ability of stem cells and the thymus to produce new cells, low CD4/CD8 cell ratios, reductions in the repertoire of CD4 cells capable of responding effectively to various infections, and reductions in responsiveness to vaccines.

"It doesn't look as if antiretroviral therapy fully restores the health of the immune system," Deeks said. "Even after several years of therapy, especially in those starting antiretroviral therapy late, we're not seeing complete normalization of CD4 cell activity, which may account for the elevated risk of various non-AIDS-related diseases."

## Novel Therapeutic Strategies

The study of novel therapies to manage inflammation and aging in people living with HIV is in its infancy, but Deeks suggested a number of possibilities.

Among the approaches being considered to reduce inflammation include using immune-suppressants (such as prednisone, hydroxyurea, cyclosporine and mycophenolic acid); treating chronic and persistent infections such as hepatitis C virus or CMV; prescribing "intensified" ARV regimens to squash residual HIV replication; employing drugs (such as sevelamer) and supplements (colustrum) to prevent microorganisms from escaping the gut and worsening system inflammation; using Selzentry and other CCR5 receptor antagonists that appear to have anti-inflammatory as well as ARV properties; studying chloroquine, which is used to prevent malaria but has also been shown to reduce chronic immune activation; and using nonsteroidal anti-inflammatories (NSAIDs) such as aspirin, ibuprofen and naproxen.

Deeks also described efforts to enhance CD4 cell renewal in order to thwart premature senescence. This includes the using recombinant human growth hormone such as Serostim to jump-start the ability of the thymus to churn out new CD4 cells. Another possibility being explored is IL-7, being developed by France-based Cytheris, to expand disease-fighting CD4 cells. Truly

novel approaches include stem cell transplants to replace HIV-susceptible cells with those resistant to HIV; Esbriet (whose generic name is pirfenidone), a potential compound for fibrotic conditions that has shown promise as an immune-based therapy; and Lupron (leuprolide), a treatment for prostate cancer symptoms that might affect hormones responsible for immune system regulation.

Last but not least are anti-aging interventions. Caloric restriction, when not associated with malnutrition, is one possibility—it is one of the few dietary interventions that have been documented to increase lifespan in a variety of species, including rodents and dogs, and may hold similar promise for people living with HIV. There's also resveratrol, an experimental sirtuin activator that mimics several of the biochemical effects of caloric restriction. Telomerase activators may potentially slow the aging of cells every time they divide, a common occurrence in people living with HIV.  Vitamin D and omega-3 fatty acids may also show anti-aging promise, as does the immune-suppressant Serolimus (rapamycin), which was recently shown to prolong survival in mice.

"All have potential," Deeks said. "They need to be explored in clinical trials."

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