Anti-Retroviral Therapy alone won't solve the HIV epidemic, but BU Immunologist Dr. Jennifer Snyder-Cappione is on the case

By Alexandra Beem

Thanks to rapid advancements in anti-retroviral therapy (ART) people with HIV are living longer than ever before, supported by daily drugs that can suppress the amount of virus in the blood to undetectable levels. The importance of this treatment cannot be understated- by preventing the virus from replicating in the body, ART has transformed HIV infection from a death sentence into a manageable chronic illness for 20.9 million people across the globe.

However, emerging research indicates that anti-retroviral therapy not the silver bullet for the HIV epidemic. I sat down with Dr. Jennifer Snyder-Cappione, a professor of Microbiology and an HIV specialist at the Boston University Medical Center, to ask why.

She explained that because highly active anti-retroviral therapy has only been available for a few decades, we are slowly learning more about the effects of long-term therapy. As people on the leading edge of the HIV epidemic reach their 60s and 70s, Snyder-Cappione says "we're finding that these patients, who we would expect to do fine, are having more heart attacks, strokes, dementia and all of these diseases that we wouldn't normally associate with HIV." These diseases are characteristic of old age, and Snyder-Cappione explained that from a clinical perspective it looks like HIV infection is linked to premature aging. This means that, on average, people with completely suppressed viral loads still have shorter life expectancies than their HIV-peers. Studies conducted in high-income countries report a 10 to 30-year difference in lifespan, but these data depend on a number of factors. Drug regimen, timing of ART initiation (ie- early or late in the infection,) patient gender, and various lifestyle factors (injection drug use, smoking, etc.) all have a say in the life expectancy of someone on ART.

In light of this new evidence, Snyder-Cappione, and her network of HIV specialists are trying to figure out how we can give patients who are suppressed on ART a normal lifespan.

To elucidate the connection between suppressed HIV infection and the aging process the scientific community is focusing on their common denominator, a phenomenon known as chronic inflammation.

In our interview, Dr. Snyder-Cappione explained that when the immune system detects damage or infection it "activates," mounting a complex and tightly choreographed defense known as an inflammatory response. A myriad of activated immune cells rush to the site of the infection, regulating each other's behavior by secreting and detecting different chemical signals as they work together to neutralize the threat. Major players include CD4 "helper" T cells, CD8 "killer" T cells, B cells, macrophages, and other rarer immune cell types. The inflammatory response is highly effective but exhausting and intense. It is in the body's best interest to keep it as short as possible, so the army of cells "deactivates" when the threat has been neutralized and

everything is healed. This short and intense burst of immune activity is known as *acute* inflammation.

Unfortunately, the immune response doesn't always get turned off when it should, leading to *chronic* inflammation. As Dr. Joanna Eveland put it in a recent essay; "chronic inflammation is like a volume control knob on a stereo being stuck- with the volume turned all the way up." The intensity of the immune response is helpful when battling an infection, but leaving it on too long damages healthy cells and tissues. This damage contributes to a host of diseases- notably dementia, osteoporosis, certain cancers, and liver, kidney, and heart diseases.

Chronic low-level inflammation is a hallmark of the aging process, so these diseases are most often seen in elderly/older adults. However, chronic inflammation can also happen when the immune system encounters an infection it cannot eradicate, like HIV. These aging-associated diseases are affecting HIV+ people earlier than we would expect, making it look like they are aging faster than their HIV- peers.

Dr. Steven Deeks, a renowned HIV researcher, has issued repeated assurances that damage due to HIV-related chronic inflammation happens slowly. People with suppressed HIV won't start to feel the effects of prolonged immune activation until they have been infected for decades. Before this point, most patients will not have accumulated enough tissue damage to be at a significantly higher risk of age-associated diseases.

Given that few people have been virally suppressed for this long, Snyder-Cappione says that we still don't understand exactly why treated HIV infection makes the immune system stay active long past the point where it is helpful. We can't address the symptoms of chronic inflammation until we understand the cause, so to give HIV+ people a normal life expectancy we need to better understand the link between the infection and chronic inflammation.

Snyder-Cappione is tackling this problem as an immunologist, by looking into which immune cell types promote chronic inflammation in response to both HIV infection and aging. The inflammatory response is tightly regulated by a network of interacting cells, some of which send and/or receive signals that tell surrounding cells to activate in response to a threat. When these signals persist, an acute inflammatory response turns into chronic inflammation. Previous research has identified a host of cell-surface receptor proteins that immune cells use to detect each other's "on/off" chemical signals. Snyder-Cappione and her team reasoned that cells receiving and passing on signals for chronic inflammation would be identifiable by the pattern of inflammatory receptor proteins on their surface. Using flow cytometry, a technique that allows researchers to classify cells based on their external characteristics, she examined the cell-surface proteins on different people's immune cells. She and her research team at Boston University cast a wide net, looking carefully at every cell type involved in the detection and response to infection.

To cover all their bases, they analyzed the immune cells of four groups of people: HIV+ and HIV- younger people, and HIV+ and HIV- older people. In an exhaustive process, they compared

the inflammation-signaling receptors found on each individual cell type between the four groups. Dr. Snyder-Cappione was looking for a cell type which would have similar inflammatory receptors in all the groups experiencing chronic immune activation (HIV- older people and HIV+ people of all ages.) She hypothesized that this kind of cell would be integral to the chronic immune activation pathway.

After nearly five years of hard work, the team found their answer in gamma-delta T cells. Unlike the common CD4 "helper" and CD8 "killer" T cells, gamma-delta cells are relatively rare in the bloodstream. Although we don't yet fully understand their role in the immune system, Dr. Snyder-Cappione thinks that gamma-delta T cells can act like a number of different immune cell types, depending on what's in the environment. "They help drive the way your immune response will go, early on in the response to infection," she explained.

She noticed that gamma-delta T cells taken from HIV- young people had almost no copies of a receptor called TIGIT, known for detecting inflammatory signals in the environment.
As HIV- young people are not undergoing chronic inflammation it makes sense that their gamma-delta T cells aren't activated by TIGIT-specific activation signals. On the other hand, the gamma-delta T cells of older healthy people and all HIV+ people had lots of this inflammatory receptor. This makes them highly sensitive to TIGIT-specific activation signals and suggests that they are permanently activated in response to both aging and HIV infection.

These results have convinced Snyder-Cappione that this rare and relatively understudied cell population is important. "I think that gamma-delta T cells really need to be looked at in detail in HIV," she explained. "I think they're contributing to the inflammatory cycle." That's all Snyder-Cappione is comfortable concluding for now, but these results provide a jumping-off point as she starts to gather more data. She is already looking into functional differences in the gamma-delta T cells of her young and old, HIV+ and HIV- patients and wants to study these cells' interactions with other components of the immune response as soon as she can.

Indulging my request for speculation, she suggested that their role early in the immune response could mean gamma-delta T cells regulate of chronic inflammation in HIV infection. If this is true, Snyder-Cappione may have identified a potential target for anti-inflammatory therapy. This kind of medication could work alongside ART to limit tissue damage and reduce HIV+ people's risk of heart disease, osteoporosis, and dementia to age-appropriate levels.

Although her research is promising, Snyder-Cappione admits how much more we need to learn about chronic inflammation during HIV infection before we can start drug design. In the meantime, Dr. Steven Deeks suggests that long-term damage due to chronic inflammation is far easier to prevent than it is to reverse. Lifestyle changes that reduce inflammation and risk of associated health problems in geriatric medicine probably have a similar effect on HIV-related chronic inflammation. Not smoking, getting regular exercise, dropping excess body fat and eating a healthy diet can go a long way toward reducing immune activation, helping HIV+ people live longer, healthier lives while Snyder-Cappione works away the lab.

If you're interested in learning more about how you and/or your loved ones can prevent immune damage due to chronic inflammation, here are some scientifically-based resources.

- This is a readable, engaging article based on an interview with Dr. Steven Deeks, an MD on the forefront of HIV-inflammation research. He goes into some detail about other avenues of treatment for HIV-related chronic inflammation that are being explored.
- Here is a more scientifically-detailed overview of the causes and symptoms of "Inflammation, Immune Activation and HIV."
- In case you need persuading, this study proves that regular exercise reduces HIV-related inflammation.
- There is a lot of buzz around superfoods and "anti-inflammatory eating." If that's something you're interested in, here are some suggestions from Harvard Medical School.

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Target audience: People living with HIV and/or people who see HIV affecting those around them/their community.

Main Idea: ART is not working as well as we thought; HIV+ people are at greater risk for diseases usually associated with aging. There is still a lot we don't know about why these aging-like illnesses are seen in younger folks with HIV, but scientists like Dr. Jennifer Snyder-Cappione are on the case. Her research has identified an immune cell candidate for future therapy to reduce chronic inflammation in treated HIV infection, but research is slow-going. In the meantime, lifestyle choices people living with HIV can make to reduce inflammation and lower their risk of aging-associated diseases are really important.

About the Author: Alexandra Beem is a senior Biology major at Wellesley College. She spent the summers of 2015 and 2016 researching the effect of HIV on the immune system in the UCSF Division of Experimental Medicine. She has also spent some time looking at HIV treatment from the public health side, both in the US (through coursework at Wellesley) and Vietnam (through her work with HAIVN.) Growing up in San Francisco, California, a city still reckoning with the legacy and continued effects of the AIDS epidemic, has inspired her profound interest in HIV.