A Conversation with Dr. Malcolm John

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Thanks to years of HIV health advocacy, better understanding of HIV disease and its complications, and improved antiretroviral treatment regimens, people with HIV now are better able to maintain their health and live longer—perhaps even decades longer than they ever expected. For many, living longer with HIV brings new health challenges that positive people, clinicians, and researchers are only just beginning to understand.

As an infectious disease expert and the director of 360: The Positive Care Center at the University of California at San Francisco, Malcolm John, MD, MPH, sees daily the changes his HIV positive clients experience after age 50. I spoke with Dr. John about the evolving health issues these individuals encounter and the state of the science on getting older with HIV.

***BETA:* What do we know about how HIV and its treatment interact with the aging process, and what are some of the common health changes that people experience as they get older with HIV?**

Dr. Malcolm John: First of all, most of our data definitely center on what is being observed in terms of increasing non-HIV-associated complications. And the short answer is, we don't really know yet what's causing it. But we have some ideas.

There seems to be clearly a higher level of immune activation with HIV that is a part of the disease pathogenesis—the mechanism by which HIV causes not only destruction of T-cells [key players in the body's immune function], but probably some of these complications that we're seeing. Chronic HIV infection results in chronic inflammation, and that may in turn lead to immune activation, or complications from chronic inflammation. We've seen other disease states where that may play a role; for example, in connective tissue autoimmune diseases, such as lupus or rheumatoid arthritis. We know that, for example, with lupus, women have a higher rate of coronary artery disease, and one possible mechanism is chronic inflammation leading to abnormalities in cholesterol and lipids [fats in the blood], which also affects HIV disease.

Another complicating mechanism that is being investigated is premature aging of T-cells, which leads to a sort of premature senescence, or inactivity or low responsiveness of those T-cells. So those are three major mechanisms: inflammation, immune activation, and premature aging of T-cells.

The disease entities that seem to be clearly increased are cardiovascular disease, non-AIDS malignancies (particularly *fatal* non-AIDS malignancies), liver disease, and kidney disease. Those are the four big things that people are seeing. This past year at the Conference on Retroviruses and Opportunistic Infections, one study looked at cerebral blood flow and found that the blood flow patterns in HIV positive individuals were very similar to those of HIV-negative people who were 10 or 15 years older.

Another problem that we see is coronary artery disease,

or vascular disease. A study showed that HIV seems to be associated with vascular aging. That study looked at endothelial vasodilation—the ability of blood vessels to open up and allow more blood to flow through. And they found that there was less ability to dilate, which basically translates to stiffer vessel walls. And it again seemed similar to that of HIV-negative persons who were 25 years older. So now we have evidence that there's vascular function that is consistent with much older populations.

Another research group looked at T-cell senescence in people who had good immune reconstitution, where CD4 counts had gone up and viral load was low. They found that those individuals had T-cell populations that were consistent with those of people as much as 32 years older. The median age of the HIV-positive study population was 56, and yet they had T-cell patterns consistent with those of people that were about 88 years old. I could go into more subsets, but I think that's the take-home message. So now we have three studies showing that there seems to be a corollary to an older HIV-negative population, and the only difference that's being studied here is HIV.

Chronic Inflammation and Immune Activation

Inflammation is a normal physical response that occurs when the body attacks a pathogen—such as HIV—or repairs injured tissue. The inflammation response involves the transport of cells and fluids to the site of the injury, which causes the warmth, redness, swelling, and soreness you may notice around a cut as it heals.

However, inflammation doesn't only occur at the level of your skin or in response to a visible injury; it may appear in organs or body systems, such as the immune system, and it may last far longer than the time it takes for a cut to heal. *Chronic inflammation,* which is now known to be associated with HIV infection, persists over time and involves the continued healing and destruction of cells and tissues. This type of inflammation is thought to be linked to heart disease and other life-threatening conditions.

While *immune activation* may sound like a good thing, there is growing evidence that immune activation caused by HIV infection is in fact responsible for some non-AIDS-related health problems—like some forms of cardiovascular, liver, and kidney disease.

Soon after infection with HIV occurs, massive numbers of immune cells in the gut are destroyed. This allows bacteria that normally inhabit the intestines to leak into the bloodstream and circulate throughout the body—a process called "microbial translocation." HIV is also thought to interfere with certain cells, called "regulatory T-cells," which are essential to halting immune responses once an infection is eliminated from the body. Both microbial translocation and the dysfunction of regulatory T-cells appear to contribute to chronic immune activation, and to an overstimulated and overworked immune system.

In addition, a study published in 2007 looked at something called a "frailty index." (There are different frailty indices out there that measure functions of older individuals; a frailty index might be a measure of weight loss, grip strength, self-reported energy levels, slow walking speed, baseline level of activity day to day.) They found that if you lived with HIV for about 8 to 12 years, you had a higher odds ratio of being more frail; basically, you were 15 times more likely to be more frail than HIV negative individuals. They found that a 65-year-old person who is HIV negative has similar frailties to those of a 55-year-old who is HIV positive.

BETA: **I also understand that the thymus shrinks with age in HIV-positive and HIV-negative people alike. The thymus is a key region where CD4 cells originate; do we know anything about how this change affects health in the context of HIV disease?**

Dr. Malcolm John: Yes. So far, I've gone through four parameters: cerebral blood flow, which may be one of the risk factors for the cognitive impairments we see in the aging HIV-positive population; vascular aging, which may be a component for cardiovascular disease; immune senescence, or T-cell aging, which may explain some of the increased non-HIV cancers that we see (because immune cells are important for surveillance); and we talked about frailty indices. Number five: We find that older individuals—particularly those newly infected—do worse, with lower CD4 counts and more rapid CD4 declines, and that is believed to be related to thymic differences.

People who are older have smaller, or "involuted," thymuses, and therefore their T-cells are unable to generate

new CD4 cells like young individuals. If they go untreated, their HIV will progress more rapidly. Once we get them on therapy, there is some equalization, because older individuals tend to be more adherent to their antiretroviral regimens, but their T-cell rebound is not going to be as good, and that is definitely a factor in long-term health outcomes.

BETA: Are you seeing these issues in your own patient population, as well?

Dr. Malcolm John: Absolutely. We've seen non-AIDS-related malignancies. I've seen some very rapid cases of lung cancers. Generally, when a lung mass is found, I'll do a follow-up CT scan on the earlier side—maybe even a month earlier, because I've seen some rapid progression. We definitely see liver disease, no question. We know that hepatitis B and C are accelerated in HIV co-infection, leading to higher rates of cirrhosis and greater need for liver transplantation in the [HIV/hepatitis coinfected] population. We're also seeing more kidney dysfunction. Renal function declines as we all get older, but that renal dysfunction seems to be increased in some studies in HIV-positive patients.

Now, some of that's related to the HIV medications, right? There are some meds that we use very commonly that may be associated with some of the negative cardiovascular effects. A study conducted by the Framingham Heart Study group looked at intimal wall thickening and saw that HIV is an independent predictor of thickening of that vascular wall, meaning increased risk of coronary artery occlusion—so basically a predictor for vascular disease. We definitely see a lot of heart attacks. I've had quite a few patients, relatively young, have heart attacks or present with angina [chest pain due to insufficient blood flow to the heart] requiring intervention. And some really unfortunately cases of malignancies, not only of the lung but also some of the lymphomas [cancers typically originating in the immune system] that haven't been traditionally associated with HIV.

BETA: What do you think are the most important things about aging with HIV that positive people and their health care providers should be aware of?

Dr. Malcolm John: I think that the most important thing is to understand that even as we control HIV with medications, people are at increased risk for non-HIV-associated complications, and that those complications are those seen in the general population, but it's an accelerated process. We need to be very cognizant of that and screen for those changes. So, if someone has some evidence of increased forgetfulness compared with their peers, we do a neuro-psych screening and find out if they have significant cognitive changes. If they have risk factors for coronary artery disease, we not only use the Framingham guidelines to stratify their risk, but we are also a little bit more aggressive in terms of getting their cholesterol under control or their hypertension [high blood pressure] under control.

And now we're learning that some of these meds may contribute [to these complications], so it's important to think carefully about what regimen would be best for a patient, either because of direct contribution from the medication, or indirectly from the risk of increasing their cholesterol.

Stay tuned to the changing literature and data. Health maintenance: make that a top priority as you get your HIV under control. Be aggressive about getting those reversible factors under control. And do your standard screening health exams.

BETA: It sounds like, as people age, it becomes more and more important to work closely with a primary care provider who understands these complicating factors of HIV and HIV meds.

Dr. Malcolm John: That's exactly right.

Selected Sources

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