AIDS virus may accelerate aging, scientists say

June 8 2011, By Jeffrey Norris

Heart attacks out of the blue, bottom-scraping testosterone levels, nerve damage and bone-withering osteoporosis are not regarded as the normal fate of a man in his 40s or early 50s. Stuart Smith did not expect to have to deal with any of these maladies, let alone all of them.

It's not as if he looked forward to a healthy old age. It's just that he never expected to live even to middle age.

Smith was diagnosed with AIDS in the 1980s, but believes he was infected with HIV, the AIDS virus, several years before the diagnosis. Many of his friends had already died from the disease.

Through days of incessant blood draws, his CD4+ cells – the immune cells that are the main target of the virus – continued to decline in number. Smith was wasting away and frequently plagued by opportunistic infections. He credits his survival to aggressive treatment by UCSF physician Steven Deeks, MD, not long after protease inhibitor drugs became available to treat HIV infection.

With effective HIV-targeting drug cocktails Smith has persevered long past middle age. He's now 70. Despite his age and the maladies he has suffered, he neither sounds nor looks especially old. "I don't feel 70," he says.

Median Age of HIV Patients Approaches 50

Merely by surviving, Smith now finds himself, along with the medical

practitioners who help him look after his health, at a new frontier in medical research and clinical care.

A growing number of those living with HIV infection in the United States are over 50 years old, and in a few years this age group is expected to include the majority of those infected. While the incidence of new HIV infection has risen somewhat among older adults, most older HIV patients were first infected in their 20s and 30s.

Many researchers and physicians believe – supported by growing evidence – that aging is accelerated in HIV patients. However, where to lay the blame is still under investigation. Aging in HIV patients has been attributed to the ongoing presence of the latent virus – which is not completed eradicated by drug treatment – to side effects of the treatment itself, and to the high prevalence of conventional risk factors for unhealthy aging among the HIV-infected population.

Whether or not aging is indeed accelerated as a consequence of HIV infection, aging poses additional challenges for those who aim to provide the best possible preventive care and treatment for patients with HIV, according to UCSF's Paul Volberding, MD.

In the early days of the epidemic, Volberding helped establish the first dedicated outpatient HIV clinic in the country at San Francisco General Hospital (SFGH). Today he is co-director of the UCSF and Gladstone Institutes Center for AIDS Research and chief of medical service at the San Francisco Veterans Affairs Medical Center.

"Aging patients in general present management challenges that we need to better understand," he says. "There are more problems of drug interactions as people age. People are less able to stand the shock of simultaneously occurring illnesses than they were when they were young. There are issues related to the safety of their surroundings and their

independence in daily functioning."

Geriatrics Experts Sign On

When it comes to HIV and aging, there's plenty of research to be done, ranging from molecular biology, to epidemiology, to finding the best ways to care for aging HIV patients.

As has been the case since the AIDS epidemic first emerged 30 years ago, UCSF researchers and clinicians are at the forefront in advancing knowledge and clinical care.

"At UCSF we have so much depth in so many different areas," Volberding says.

"When you take on something like HIV and aging, it ends up being a big umbrella and it brings all these people together. We have created networks of investigators who in many cases didn't know one another before, but who are now working together."

The San Francisco Department of Public Health and UCSF have been awarded a grant from the California HIV/AIDS Research Program to develop innovative treatment models and a new standard of care for treating people over the age of 50 infected with HIV. The leaders in developing these models will be Brad Hare, MD, medical director of the UCSF Positive Health Program – Ward 86, the HIV/AIDS clinic at SFGH – and Malcolm John, MD, MPH, medical director of 360: The Positive Care Center – the HIV/AIDS clinic on the UCSF Parnassus campus.

"We have long known that providing the best care for someone with HIV requires a multidisciplinary team of health care professionals," Hare says. Depending on the needs of the individual patient, these teams may include doctors, nurses, nurse practitioners, pharmacists, nutritionists,

therapists, case managers, benefits counselors, substance abuse counselors and psychiatrists.

The average age of the 3,000 patients who visit Hare's clinic is 47. "As people live longer with HIV infection, we see chronic health conditions such as heart disease, bone loss, cancers and kidney disease show up 10 or more years earlier than what is typical for someone without HIV," Hare says. "Our goal with this grant is to assemble the right health care team to meet the unique health care needs of the growing number of people who are aging with HIV."

A priority is to recruit geriatricians. "We plan to find out which aspects of geriatric care apply to the population with HIV— or whether there is a totally different way to approach these issues."

According to Hare, medical conditions that disproportionately affect patients with HIV infection deserve special consideration. For example, many individuals aging with HIV infection suffer from depression and may lack good social support systems. In addition, hepatitis C infection is common and standards for treatment of hepatitis in all older people are evolving.

The goal is to maintain health and prevent disease, with an emphasis on screening for early signs of chronic disease. Initially, Hare says, the clinic will serve patients with HIV age 50 and older.

Inflammation and Aging

Even when they receive effective therapy, those infected with HIV generally are more likely to die younger than those not infected. It's less evident to some researchers that anything other than traditional risk factors and toxic side effects of antiretroviral drugs contribute to this increased risk for aging.

“It’s controversial whether chronic inflammation – which exists in these patients – is a true independent driver of this process,” says UCSF’s Deeks. He believes that it is.

Levels of several different molecular markers of inflammation are associated with heart disease, kidney disease, liver disease and death, he says. Some of the markers of inflammation commonly seen in aging also occur in HIV infection. Deeks suggests that HIV itself or chronic infection by another pathogen, such as cytomegalovirus (CMV), may be aggravating inflammation in HIV-infected patients.

“There’s no question that a lot of the HIV-caused immune damage is reversed by treatment,” Deeks says. Levels of CD4+ cells often return to normal in successfully treated patients, and the virus frequently becomes undetectable in the blood, even as it hides out in a latent state in some cells. But in many patients, immune system function does not completely return to normal, he says.

Like the elderly, these patients are more likely to have higher levels of activated T cells in their immune systems, as well as higher levels of specific molecules or cells that are biomarkers of inflammation. For instance, high levels of interleukin-6 (IL-6), an inflammatory protein secreted by certain cells of the immune system, often are present in older individuals and in those with HIV. “The higher the elevation of IL-6, the more likely you are to die or to get sick,” Deeks says.

This association does not prove cause and effect. “In order to prove that inflammation is causing disease we have to reverse the inflammation in a very specific way and show that people get better,” he says.

Deeks joins other immunologists who believe a protein called CCR5 plays a role. CCR5 is best known as the portal found on immune cells that enables HIV to infect the cells. Drugs that target CCR5 prevent the

virus from replicating. However, CCR5 also may directly affect immune function during HIV infection independently of its role as a facilitator of viral infection, according to Deeks.

To see if HIV-associated inflammation can be reduced by targeting CCR5, Deeks' UCSF colleague Peter Hunt, MD, is conducting clinical research with a Pfizer drug that targets the receptor. The clinical researchers also are involved in emerging studies to examine the anti-inflammatory effects of statins and aspirin in HIV patients.

What has been learned already about HIV and inflammation can be put to good use, Deeks says. For years physicians have been reluctant to begin therapy before CD4+ cell counts fall, out of concern for drug side effects and the development of drug resistance by the virus. But the evidence that treatment helps prevent transmission of HIV has led many to re-think this approach. Now Deeks advocates early treatment for another reason: to preserve as much normal immune function as possible.

"The residual immunologic decline associated with HIV is worse in people who delay treatment until they're pretty sick," he says. "I believe people should go on antiretroviral therapy as soon as they can."

In addition, he says, "We know from work in the general population that certain behaviors are successful in slowing clinical aging – among them exercise, adaptation of a Mediterranean diet and the avoidance of traditional risk factors, including abdominal obesity."

"All these things are important for everybody, but they are probably particularly important for people with HIV, given that they are at elevated risk for age-associated diseases."

HIV and Heart Disease

“I became interested in cardiovascular disease in the setting of HIV during my training at San Francisco General Hospital,” says UCSF cardiologist Priscilla Hsue, MD. “We noticed that a lot of HIV-positive men were presenting with heart attacks. I wanted to know if their coronary artery disease was due to their HIV medication, from HIV infection itself or from traditional risk factors.”

Treatment side effects, smoking, hypertension and harmful fats in the blood all contribute to cardiovascular disease risk among HIV patients, but it now appears that chronic inflammation resulting from HIV infection also increasese risk, Hsue says.

In her most recent studies, Hsue has been using non-invasive ultrasound imaging techniques to measure the thickness of two of the layers of the blood-vessel wall in the carotid artery. The carotid artery runs along the side of the neck and feeds oxygenated blood to the brain. “This is a noninvasive test, and even after adjustment for traditional risk factors it is a potent predictor of future heart attack and stroke,” she says.

Hsue first discovered that patients infected with HIV have more thickening of the carotid artery walls in comparison to age-matched, uninfected individuals. She then determined that even among successfully treated HIV patients, higher levels of inflammation were present, and that this inflammation was independently associated with increased thickness of the carotid artery wall.

Another group of HIV-positive patients studied by Hsue, called elite controllers, maintain undetectable levels of HIV without antiretroviral drug treatment. Even in this unique group she found that thickening of the carotid artery wall was greater than in a control group of uninfected individuals.

“This suggests that there is something very specific to HIV infection that

increases cardiovascular risk – independently of any effects of antiretroviral medication exposure or HIV viral load," Hsue says. In future research she aims to identify mechanisms that link HIV-associated inflammation and cardiovascular disease, and to develop treatments that reduce risk.

Cancer, Dementia Risks Unclear

It is unclear whether being infected with HIV increases risks for other diseases associated with aging, such as major cancers, or Alzheimer's disease and other dementias. This might surprise casual observers of the epidemic, because HIV infection has long been known to be associated with higher risk for certain cancers, and also with learning and memory problems.

Rates of virus-induced cancers, such as anal or cervical cancers caused by human papilloma virus, and Kaposi's sarcoma, caused by a herpes virus, are much higher among the HIV-positive population. Dementia due to AIDS was a frequent occurrence in the days before anti-retroviral treatment for HIV infection and milder cognitive problems are still frequent in treated patients.

It's not easy to identify health problems that are due to HIV infection in the context of other health problems that are common among people with HIV. Researchers are trying to sort it out, which would help them discover ways in which HIV might accelerate aging.

Data gathered to date may be too limited to determine whether HIV infection is independently associated with increased incidence or earlier onset of major cancers. Lung cancer strikes more often among the HIV-positive, but they also are more likely to smoke. Similarly, liver cancer is more common among those infected with HIV, but that is due at least in part to the high incidence of hepatitis.

“HIV-infected persons have a higher prevalence of several behavioral risk factors for cancer which must be accounted for when comparing them to individuals who are not infected with HIV,” says UCSF epidemiologist Jeffrey Martin, MD, MPH.

Confounding problems, such as arterial disease, diabetes, hepatitis and alcohol and substance abuse, also makes it even more difficult to sort out whether HIV infection increases risk for dementias normally associated with aging, says Victor Valcour, MD, a researcher with the UCSF Memory and Aging Clinic.

Valcour leads studies to examine the effects of HIV in the central nervous system, including studies of HIV-infected patients age 60 and older. He uses neuropsychological measures and brain imaging to evaluate attention and concentration, working memory and higher cognitive ability.

Unlike Alzheimer’s disease, the type of dementia frequently seen early in the AIDS epidemic often improves with antiretroviral treatment and declining levels of virus. With treatment, Valcour says, “We seldom see dementia, which is wonderful. However, we do see persistent cognitive problems that are milder, but that still impact day-to-day functioning.”

Among HIV patients of all ages, about 25 percent report concerns about mental performance. In fact, when formally tested, mild cognitive problems can be detected in about half, Valcour says.

Published research points to an increased risk for dementia among HIV patients with diabetes. There also is research to suggest that risks for stroke are associated with cognitive problems in HIV-infected patients. These findings highlight the importance of investigating whether HIV infection interacts with Alzheimer’s disease, diabetes and vascular disease to worsen cognitive performance in an aging population of

patients, Valcour says.

HIV Drives "Hyperactivation" of Immune System

Like Deeks, Eric Verdin, MD, of the Gladstone Institute of Virology and Immunology, has come to believe that HIV causes the immune system to misfire and to drive chronic inflammation, even in treated patients, and that chronic inflammation in turn drives aging.

In recent years Verdin has begun exploring chronic inflammation in HIV, a research field he never expected to enter. In fact, for 12 years, Verdin has been investigating the basic biology of enzymes called "sirtuins," which play a role in aging through their effects on cellular metabolism.

SIRT1, for instance, is the human counterpart to sir 2, a gene in yeast that controls aging. Scientists also have proposed, but not proved, that these sirtuins are responsible for increased life spans reported from studies in which organisms have been maintained on low-calorie diets. SIRT1 is activated by resveratrol, a compound found in red wine. Some pharmaceutical start-ups are developing drugs to boost SIRT 1 activity.

But it turns out that there also is a direct link between HIV and SIRT1, and an important role for SIRT1 in controlling the activity of the immune system.

Verdin and Melanie Ott, MD, PhD, another Gladstone and UCSF scientist, are collaborating to explore how chronic infection may wear out the T lymphocytes that target specific disease-causing pathogens. They are investigating how HIV specifically disrupts the smooth operation of the immune system, by acting through SIRT1.

"Like a car, if you drive the immune system too hard for too long, you're

likely to wear the engine out," Verdin says. "T lymphocytes that are constantly activated eventually become senescent."

Ott has discovered that an HIV protein called Tat directly blocks SIRT1. SIRT1 normally dampens T lymphocyte activity by inhibiting a protein called NF-kappa B. Acting through SIRT1 and NF-kappa B, HIV Tat causes T lymphocytes to become "hyperactivated." A high level of NF-kappa B also drives a pattern of gene activation within cells that often is seen in aging tissues, according to Verdin.

When cells of the immune system become exhausted, they don't necessarily die, but they do lose their ability to replicate. What's worse, they may begin secreting cytokines – normally a strategic weapon – in an uncontrolled manner, causing collateral damage and a state of chronic inflammation.

Verdin also is working with UCSF Nobel Prize laureate Elizabeth Blackburn, PhD, to further investigate senescence in immune cells and the role of an enzyme called telomerase. Telomerase is needed to keep cells healthy and capable of dividing to make new cells.

Early studies suggest that telomeres – protective DNA caps on the ends of chromosomes that are replenished by telomerase – are shorter in the lymphocytes of individuals infected by HIV. This also is a reflection of the chronic state of T lymphocyte activation, Verdin says. Shorter telomere length in immune cells has been associated with heart disease and other chronic diseases common among the aged.

Researchers also suspect that AIDS-fighting drugs known as nucleoside analogs might be interfering with telomerase activity, Verdin says. If this is true, treatment may in some cases be contributing to cell aging. Blackburn will be investigating this question as part of the ongoing research.

HIV May Be Key to Understanding Normal Aging

"We don't really know why some people live healthily for a long time, while others are burdened with many chronic diseases," Verdin says. Immune system dysfunction is becoming a prime suspect.

"I think in treated, HIV-infected patients the primary driver of disease is immunological. The study of individuals who are HIV-positive is likely to teach us things that are really new and important, not only about HIV infection, but also about normal aging."

Deeks emphasizes that success depends on collaboration. "I think there is a high potential for tremendous progress in understanding HIV if we can assemble a team of experts from the world of HIV immunology and the world of gerontology," he says. "Each field can dramatically inform the other. I believe HIV is a well described, well studied, distinct disease that can be used as a model by the larger community to look at issues of aging."

Stuart Smith is one of hundreds of patients who now have participated in studies related to HIV and aging at UCSF. "My hope is that the research I've had the opportunity to volunteer for will bring benefit to as many human beings as possible," he says, "not just to those living with HIV."

Provided by University of California, San Francisco

Citation: AIDS virus may accelerate aging, scientists say (2011, June 8) retrieved 20 April 2024 from https://medicalxpress.com/news/2011-06-aids-virus-aging-scientists.html