Immune Systems of HIV Patients Age More Rapidly

VITALS

Major Finding: Postponing antiretroviral therapy until CD4 counts are less than 200 copies/mm^3 may risk immune system damage.

Source of Data: Expert opinion.

Disclosures: Dr. Deeks has been an adviser to GlaxoSmithKline and has received research funds from Pfizer, Merck, Gilead, and Bristol-Myers Squibb. Dr. Maurer and Dr. Brooks reported having no conflicts of interest.

BY SHERRY BOSCHERT

SAN FRANCISCO — Antiretroviral therapy has allowed many HIV-infected people to live long enough to grow old, yet their immune systems seem to age rapidly for their chronologic age, a factor that appears to be contributing to increased risks for non-HIV diseases of aging in middle-aged patients, according to several speakers at a meeting on the medical management of HIV and AIDS sponsored by the University of California, San Francisco.

"There are striking similarities between the immune systems of some of our patients in their 50s and [those of] their parents," said Dr. Steven G. Deeks, professor of medicine at the university.

In 2007, 28% of people living with HIV were aged 50 years or older; that proportion will grow to 50% by 2015, Dr. Richard Brooks, also of the university, said in a separate presentation.

Also at the meeting, Dr. Toby Maurer reported that her clinic is seeing more HIV-infected patients with skin diseases associated with aging, including disseminated herpes zoster and indolent Kaposi's sarcoma, despite relatively healthy CD4 counts ranging between 300 and 700 cells/mm^3 and viral suppression on at least 18 months of antiretroviral therapy.

Disseminated zoster is "very unusual with a CD4 count of 350 cells/mm^3" or more, said Dr. Maurer, director of dermatology, San Francisco General Hospital. "Is [this finding] another indication of abnormal immune aging? I don't know, but it's something to think about."

The Kaposi's sarcoma cases are not the aggressive variety seen 20 years ago in HIV-infected patients, she said, but are the type typically found in older Mediterranean men.

To preserve immune function, Dr. Deeks advocates starting highly active antiretroviral therapy (HAART) in any HIV-infected patient who is motivated to begin treatment—a more aggressive approach than called for in treatment guidelines.

HAART reduces but does not eliminate T-cell activation and inflammation. Persistent, residual inflammation while on HAART is more extensive when patients start therapy at CD4 counts less than 200 copies/mm^3. "The longer you wait to start therapy, the more immunologic harm that's done," he said. The consequences of the inflammatory process are even worse for people with comorbid conditions such as heart disease or cancer.

Frailty was 11 times more common in HIV-positive men, 'confirming our impression that HIV-positive men are aging faster than their HIV-negative counterparts.'

Previous attempts to reduce HIV-associated inflammation and immunosenescence through the use of prednisone, hydroxyurea, cyclosporin, or mycophenolic acid were "like treating a subtle problem with sledgehammers," and patients did not fare well, Dr. Deeks said.

"We need to reduce inflammation in a safe way" through the use of statins, aspirin, exercise, omega-3 fatty acids, vitamins, and immunomodulators, he said.

Newer strategies could include investigational drugs that enhance recovery of CD4 cells or that fully eradicate the subtle levels of persistent or replicating virus.

An "overwhelming amount of data" show that even those patients with undetectable virus and increased CD4 counts on HAART are more likely than people without HIV to develop heart disease, non-AIDS cancer, bone disease and fractures, left ventricular dysfunction, liver or kidney failure, frailty, and possibly cognitive dysfunction, Dr. Deeks said.

After controlling for the effects of other factors, including lipids or hypertension, HIV-infected patients have a 75% higher risk for cardiovascular events than do uninfected people, several studies suggest.

Dr. Brooks noted that frailty was 11 times more common in HIV-positive men, compared with HIV-negative men, in one study (J. Gerontol. A Biol. Sci. Med. Sci. 2007;62:1279-86). HIV infection of 4 years' duration or less conferred a risk for frailty in a 55-year-old man that compared with risks for a 65-year-old HIV-negative man, "confirming our impression that HIV-positive men are aging faster than their HIV-negative counterparts," Dr. Brooks said.

To help HIV-infected patients stay healthy longer, he advised focusing on modification of traditional risk factors for non-HIV comorbidities of aging—smoking, hypertension, dyslipidemia, weight gain, diet, and exercise.

When possible, avoid HIV medications that can exacerbate illnesses associated with aging and check for drug-drug interactions, Dr. Brooks added. Older protease inhibitors and zidovudine increase the risk for insulin resistance. Tenofovir increases risk for renal dysfunction. Abacavir, didanosine, and protease inhibitors increase risk for cardiovascular disease. Zidovudine, protease inhibitors, and nonnucleoside reverse transcriptase inhibitors increase risk for dyslipidemia.

Dr. Brooks recommended the Beers Criteria, which lists medications to avoid in anyone older than 65 years or in older people with different disease states (Arch. Intern. Med. 2003;163:2716-24).

For iPhone users who subscribe to Epocrates, the criteria also are accessible in the Tables section of the program, he added.

Most physicians can check the top 30-40 medication interactions in their heads, "but I think you'd be surprised if we did it in a much more methodical way," Dr. Brooks said. ■

Start Anti-HIV Drugs Earlier, New Federal Guidelines Say

BY SHERRY BOSCHERT

SAN FRANCISCO — New federal guidelines recommend earlier initiation of antiretroviral therapy for adolescents and adults with HIV and come close to recommending therapy for nearly everyone with HIV.

"We're moving towards treating most people who are infected with HIV," Dr. Diane V. Havlir said at a meeting on the medical management of HIV and AIDS sponsored by the University of California, San Francisco.

She suggested, only somewhat tongue-in-cheek, that future guidelines may focus on which patients should *not* start antiretrovirals. Those future guidelines might look something like this: Do not start HIV therapy if there are no antiretroviral options due to drug intolerance, drug interactions, or transmitted multidrug resistance, and be cautious about starting antiretroviral therapy in a patient with a CNS lesion, said Dr. Havlir, professor of medicine at the university and chief of the HIV/AIDS division at San Francisco General Hospital.

Guidelines released Dec. 1, 2009, by the Department of Health and Human Services (HHS) recommend starting antiretrovirals for HIV in patients with CD4 counts of 350-500 cells/mm^3, patients with CD4 counts less than 350 cells/mm^3, pregnant patients, and those with a history of an AIDS-defining illness, hepatitis B, or HIV-associated nephropathy.

'We're moving towards treating most people who are infected with HIV.'

DR. HAVLIR

Of the guidelines committee members, half favored starting antiretrovirals in patients with CD4 counts higher than 500 cells/mm^3, while half viewed treatment as optional in these patients. "This really is a significant change," Dr. Havlir said.

The new guidelines eclipse 2008 recommendations from the International AIDS Society–USA to start antiretroviral therapy in asymptomatic patients with CD4 cell counts less than 350 cells/mm^3 or symptomatic patients, and to individualize therapy for patients with CD4 counts of 350 cells/mm^3 or greater.

Shortly before the HHS announcement, the World Health Organization (WHO) changed its guidelines to advise starting antiretrovirals in adolescents and adults with AIDS or tuberculosis or when CD4 counts drop below 350 cells/mm^3.

"Countries will have to weigh the pros and cons of the guidelines and their financial constraints to see if they will be able to adopt them," Dr. Havlir said.

The move toward earlier antiretroviral therapy is due to "tectonic shifts in thinking about HIV as a disease," she noted.

There is increasing recognition that HIV infection not only increases susceptibility to opportunistic infections, complications, and malignancies, but also damages the renal and cardiac systems and contributes to liver disease, CNS changes, and probably aging.

Antiretroviral therapy can prevent some of the newly recognized harms to organ systems as well as the classic AIDS complications, she said. Earlier treatment initiation also may result in less drug resistance and better cognitive function.

Two studies in particular prompted the guideline changes.

The North American AIDS Cohort Collaboration on Research and Design studied 17,517 people with asymptomatic HIV infection who had not taken antiretrovirals. Patients who deferred treatment until CD4 counts fell below 350 cells/mm^3 had a 69% higher risk of death compared with those who started antiretrovirals at CD4 counts of 350-500 cells/mm^3, and a 94% higher risk of death compared with those with CD4 counts higher than 500 cells/mm^3 when starting therapy (N. Engl. J. Med. 2009; 360:1815-26).

Another analysis of data on 21,247 antiretroviral-naive patients found a higher risk of death if treatment was deferred until CD4 counts fell to 350 cells/mm^3 or lower, compared with starting antiretrovirals at higher CD4 counts (Lancet 2009; 373:1352-63).

Dr. Havlir reported no conflicts of interest related to these topics. ■