Elevated Heart and Kidney Disease Risk Despite HIV Treatment?

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People with HIV have higher levels of blood markers associated with cardiovascular and kidney disease even when their virus is suppressed by antiretroviral (ARV) treatment, according to a new study published in the June 15 issue of *The Journal of Infectious Diseases*.

Mounting evidence strongly suggests that HIV causes inflammation, whereby cells in the body are in a state of chronic high alert. These inflamed cells produce proteins—including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL6), D-dimer and cystatin-C—that are associated with higher risk for developing cardiovascular and kidney disease. Researchers have documented that these inflammatory proteins are associated with disease risk in both HIV-positive and HIV-negative individuals.

What has remained unknown, however, is how much these inflammatory proteins are elevated in people with HIV, compared with HIV-negative people, and the degree to which suppression of HIV by ARVs might lower inflammation.

To distinguish levels of inflammatory proteins in HIV-positive and HIV-negative people, Jacqueline Neuhaus, MS, from the University of Minnesota, and her colleagues compared data on the proteins from three different studies: the Strategies for Management of Anti-Retroviral Therapy (SMART) study, the Multi-Ethnic Study of Atherosclerosis (MESA) study and the Coronary Artery Development in Young Adults (CARDIA) study. All of the participants in the SMART study were HIV positive, while the vast majority of those in MESA and CARDIA were believed to be HIV negative.

There were a number of important differences between participants in SMART and those in MESA and CARDIA aside from HIV status. SMART study volunteers were more likely to be male and black. They were also more likely to smoke, to take lipid and blood pressure medication, and to have higher total cholesterol to HDL (“good”) cholesterol ratios.

Neuhaus and her colleagues found that levels of all the inflammatory proteins were higher in HIV-positive people than in HIV-negative individuals. In general, levels of the proteins ranged from 18 to 118 percent higher in people with HIV, depending on the protein measured and whether the researchers compared SMART with MESA or CARDIA. The elevation in inflammatory proteins held true even when Neuhaus’s team factored in viral load, CD4 count, sex, smoking and other factors that could have influenced the results. Reductions in viral load due to ARV therapy did significantly

reduce inflammatory protein levels in people with HIV. Nevertheless, inflammatory protein levels remained higher in people with HIV—even in those with undetectable virus—than in HIV-negative individuals.

Among people on ARV medication, those taking a regimen including a protease inhibitor were likely to have lower inflammatory protein levels than those taking a non-nucleoside reverse transcriptase regimen (NNRTI). As has been previously reported, people taking Ziagen (abacavir) had elevated inflammatory protein levels.

The authors state that a potential weakness of the study is the significant differences in the make-up of the participants in SMART, compared with MESA and CARDIA. Though they attempted to account for differences in sex, race, smoking status and other factors, the researchers acknowledge that these or other differences could explain some of the elevation in inflammatory markers among people with HIV.

However, Michael Dubé, MD, and Fred Sattler, MD, from the University of Southern California, point out in an accompanying editorial how carefully Neuhaus and her coauthors preceded with their study. In discussing the study's results, Dubé and Sattler state, "Elevated levels of these markers/mediators represent an important potential explanatory variable in understanding the increased incidence of complications related to chronic inflammation among HIV-infected persons."

Dubé and Sattler conclude: "It will be critical that future studies examine mechanisms underlying persistent immune activation/inflammation, as well as test strategies for modulating inflammation, to effectively intervene in these long-term complications that are holding our patients back from more complete recovery from HIV infection."
