Markers of inflammation and blood-clotting tied to hazards of intermittent HIV treatment

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Episodic treatment of HIV/AIDS with antiretroviral drugs increases the overall risk of death when compared with continuous antiretroviral treatment (ART), but the reasons why have been unknown. Now, researchers have found that higher levels of certain markers of inflammation and blood-clotting are strongly associated with intermittent ART and with a higher risk of death from non-AIDS diseases.

The new report, published in the open access journal *PLoS Medicine*, is a further analysis of the "Strategies for Management of Antiretroviral Therapy" (SMART) study supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (http://www3.niaid.nih.gov/news/newsreleases/2006/smart06). SMART, which ended in 2006, compared the standard practice of continuous ART to suppress HIV in infected individuals with episodic ART based on CD4+ T-cell counts. The goal was to determine whether reducing exposure to antiretroviral drugs, which may have toxic side effects and can engender drug resistance, would be equally or more beneficial than suppressing HIV continuously. Unexpectedly, those who received episodic ART were more than twice as likely to develop disease or die, and the study ended early as a result.

Reflecting on this outcome, James D. Neaton, Ph.D., of the University of Minnesota, and his colleagues hypothesized that pausing ART and allowing HIV levels to rise stimulated inflammation and blood clotting in some patients, which could lead to disease or death.

To test their hypothesis, the scientists examined blood samples from the SMART trial for proteins that are biological markers of inflammation and blood clotting. They found that people who began the study with relatively higher levels of the biomarkers interleukin-6 (IL-6) and D-dimer were at greater risk of death than other study participants. They also found that IL-6 and D-dimer levels rose significantly in the intermittent-treatment group compared to the continuous treatment group after just one month of study.

Based on these observations, the authors conclude that HIV-infected patients who have relatively high levels of IL-6 and D-dimer are at greater risk of death. Most of the deaths in SMART were attributed to non-AIDS-related diseases, the authors write, and giving intermittent ART to volunteers who began that study with elevated levels of these biomarkers may have further increased their risk of death.

Article: LH Kuller et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Medicine* DOI:10.1371/journal.pmed.0050203 (2008).

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