# Study links inflammation and coagulation to non-AIDS deaths in people with HIV

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In an analysis of deaths occurring during a large international trial of treatments for HIV-positive patients, researchers have found a strong association between markers of inflammation and coagulation and increased risk of death from non-AIDS diseases, including cardiovascular problems. The research, published in the open access journal *PLoS Medicine,* may explain why interrupting antiretroviral therapy (ART) was found to increase the risk of death from non-AIDS diseases for people living with HIV.

The Strategies for Management of Anti-Retroviral Therapy (SMART) trial was carried out by the International Network for Strategic Initiatives in Global HIV Trials. SMART compared two different methods of treating HIV: either continuous ART – the current practice, aimed at viral suppression – or intermittent treatment aimed at drug conservation.

For the drug conservation strategy, ART was stopped until a patient's CD4 cell count, an indicator of immune system function, dropped below 250 cells per microliter (about a quarter of the normal adult level). At that time ART was re-initiated until the CD4 cell count returned to more than 350 cells. Unexpectedly, more people assigned to intermittent treatment in the trial died, mostly from non-AIDS diseases, leading to early closure of the trial. In the current follow-up study, James Neaton of the University of Minnesota and colleagues investigated the hypothesis that the increased risk of death among the participants who received intermittent ART was due to an inflammatory response caused by increased levels of HIV in the periods when ART was stopped.

Taking blood samples from the 85 people who died during the SMART trial – including 30 who had been assigned to receive continuous ART and a control group of 170 patients who had survived, the researchers used biomarkers – levels of proteins that indicate the presence of inflammation or increased coagulation of blood – to test this hypothesis. Across both treatment groups, increased risk of death was associated with three biomarkers: high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and D-dimer. Measuring the same biomarkers in the blood of 499 randomly chosen patients from the trial, the researchers found that IL-6 and D-dimer levels in patients in the intermittent treatment arm increased in the first month of the trial but were unchanged in the patients who received continuous ART treatment.

"The magnitude of the association between these biomarkers and mortality is clinically relevant and reasons for it require further study," conclude the researchers of the link between the biomarkers of inflammation and the risk of death from non-AIDS diseases. Whilst the association is strong in a number of analyses, they warn that the relatively small number of deaths among participants in the study's continuous treatment group means that the biomarker results should be treated with caution and confirmed in other studies before they can be applied to people taking currently recommended ART regimens. However, the findings raise the possibility that the development of therapies that reduce overactive inflammation and coagulation associated with HIV infection may extend the life expectancy of people living with HIV.

Citation: Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, et al. (2008) Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 5(10): e203. doi:10.1371/journal.pmed.0050203
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