Reduced inflammation linked to survival

Doctors can easily assess potential cardiovascular risk factors—such as cholesterol levels, blood pressure, age, gender, weight and smoking—to develop an idea of a person’s long-term risk for cardiovascular disease (CVD). However, these risk factors are not very useful when trying to predict events, such as heart attack or stroke, over the short term.

As a result, researchers have been trying to find easy-to-assess proteins in the blood of people that might be more useful at predicting short-term cardiovascular events. A few proteins that might fulfill such a role are described below:

- CRP (C-reactive protein). This is produced in the liver in response to inflammation. Large studies suggest that increasing CRP levels occur before major CVD events. The test that assesses CRP is called hsCRP (high-sensitivity CRP). CRP rises in people with infections such as HIV.
- Serum amyloid A. Also produced by the liver in response to inflammation. Elevated blood levels of serum amyloid A may signal an increased risk for uncontrolled blood clotting.
- D-dimer. Higher-than-normal levels of these proteins suggest an increase in the formation of blood clots.
- IL-6 (interleukin-6). This is a chemical signal produced by the immune system. High levels of IL-6 have been linked to infection, inflammation and stress. IL-6 can trigger the release of CRP and proteins that help blood to clot.
- Prothrombin fragment 1+2. These help increase the ability of blood to form clots.

The treatment interruption group in the SMART study, discussed earlier in this issue of TreatmentUpdate, developed a higher-than-expected incidence of heart attacks, stroke and deaths. A Euro-American team of researchers was interested in the investigation of inflammation and its potential role in these cardiovascular events. The team analysed blood samples from the SMART study. Their findings suggest that participants who interrupted therapy had significantly elevated levels of inflammatory markers in their blood compared to people who did not interrupt therapy. This result is consistent with the theory that the immune system activation caused by HIV may play a role in the increased CVD risk seen in some people. The implications of this are discussed in our report below.

Study details

Technicians tested blood samples collected at different points during the SMART study. They particularly sought out the samples collected from 74 people who died before January 11, 2006, and compared them to samples from SMART participants who did not die. Blood samples from people who died as a result of accidents, violence or suicide were not assessed, as researchers felt that these samples would interfere with their analysis.

Technicians matched each blood sample from a person who died in the study with samples from at least two people who did not die. These other samples acted as a comparison, or control. The control samples were selected from people of similar age and gender to those who died.

Results—overall

In general, the following factors were linked to an increased risk of death:

- older age
- smoking tobacco
- prior diagnosis of CVD
- co-infection with hepatitis B or C virus

Results—focus on inflammation
The researchers found that levels of IL-6 and D-dimer and, to a lesser extent, hsCRP, were significantly increased in people who died compared to controls. On average, having high levels of these proteins increased the risk of death in SMART by a factor of six.

**Key findings**

1. In this sub-study of SMART, participants who entered the study with high levels of IL-6 or D-dimer were at high risk of subsequent death.
2. Elevated levels of these proteins were more common in people who underwent treatment interruption than in people who took HAART continuously.
3. Increased levels of IL-6 and D-dimer were linked to rising viral load.

These findings suggest that uncontrolled HIV replication activates inflammation and clotting systems in the body. In turn, these reactions reduce a person’s overall health, even in people with relatively well-preserved CD4+ cell counts. Interrupting HAART may increase levels of IL-6 and D-dimer, which could result in death for some people.

Further research on these markers of inflammation and clotting in people with HIV/AIDS is needed, as the number of people studied for this in SMART was relatively small.

**Should inflammatory markers be routinely assessed?**

Researchers are only just beginning to understand inflammation and its relationship to serious events (such as heart attacks) in viral infections and chronic diseases.

Studies of inflammatory markers have been suggestive of disease in large groups containing hundreds or thousands of HIV negative people. But the SMART team does not encourage the routine use of such markers in individual HIV positive people, because the relationship between these markers and individual health is not yet clear (Jens Lundgren MD, personal communication).

The SMART team prefers that studies be done to confirm its findings in people with HIV/AIDS and to better understand precisely why inflammation in viral infections is sometimes linked to heart attacks and death.

There will also be a need for studies to test the effect of anti-inflammatory compounds in HIV infection to find out if these can reduce the risk of heart attacks and death.

This study is not the final word on SMART, as more analyses are in the works. But what all the analyses of SMART and at least one other treatment interruption study have found is that HIV probably plays a role in speeding up CVD and that treatment interruptions carry new and previously unrecognized dangers.

**REFERENCES:**

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

CATIE endeavours to provide the most up-to-date and accurate information at the time of publication. However, information changes and users are encouraged to ensure they have the most current information. Users relying solely on this information do so entirely at their own risk. Neither CATIE nor any of its partners or funders, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. Any opinions expressed herein or in any article or publication accessed or published or provided by CATIE may not reflect the policies or opinions of CATIE or any partners or funders.

Information on safer drug use is presented as a public health service to help people make healthier choices to reduce the spread of HIV, viral hepatitis and other infections. It is not intended to encourage or promote the use or possession of illegal drugs.

Permission to Reproduce

This document is copyrighted. It may be reprinted and distributed in its entirety for non-commercial purposes without prior permission, but permission must be obtained to edit its content. The following credit must appear on any reprint: This information was provided by CATIE (the Canadian AIDS Treatment Information Exchange). For more information, contact CATIE at 1.800.263.1638.

© CATIE

Production of this content has been made possible through a financial contribution from the Public Health Agency of Canada.

Available online at: