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## CATIE-News

CATIE's bite-sized HIV and hepatitis C news bulletins.

### Study finds HIV raises heart attack risk by 50 percent

27 March 2013

The benefits of combination anti-HIV therapy (commonly called ART or HAART) are profound. These drugs reduce production of HIV in the body and help the immune system begin repairing the damage caused by HIV. The result is that deaths from AIDS-related infections are now relatively uncommon in high-income countries such as Canada compared to the first decade of the AIDS epidemic.

ART's long-term benefits are tremendous. A young adult who is HIV positive *and* who begins treatment today *and* who takes his/her medicines every day exactly as directed *and* who has minimal co-existing health problems is expected to live for several decades.

However, not everyone automatically has such a rosy future. Researchers have found that some people at high risk for and who have HIV also have an elevated risk of poor health and, in some cases, reduced survival because of problems called co-morbidities, such as the following:

- smoking tobacco
- substance use
- mental health issues
- type 2 diabetes
- elevated blood pressure
- kidney disease
- abnormal levels of cholesterol in the blood
- co-infection with viruses that damage the liver, such as hepatitis B and hepatitis C
- co-infection with viruses that can cause ano-genital cancer, such as human papilloma virus (HPV)

For at least the past decade, studies have suggested that there is a link between HIV infection and an increased risk of heart disease. Part of the problem with these studies is that it has been difficult to separate the effect of other factors, which may have inadvertently biased conclusions, from HIV. Factors that could have had an impact on the conclusions of such studies include the above-mentioned co-morbidities, many of which can impact cardiovascular disease (CVD).

Now researchers across the U.S. have undertaken a massive study in an attempt to identify HIV's impact on heart health. Their findings suggest that HIV infection raises the risk of a heart attack by 50% in adults. This elevated risk is present even in people who do **not** smoke tobacco, use substances or have other health conditions.

These results underscore the need for HIV-positive people and their care providers to intensify efforts to reduce traditional risk factors for CVD. Furthermore, researchers need to conduct studies to understand precisely why HIV has such a devastating effect.

#### Study details

The U.S. team used health-related information collected from 82,459 veterans distributed into the following two groups:

- HIV positive - 27,350 people
- HIV negative - 55,109 people

This large study allowed the research team to compare CVD-related outcomes (such as heart attacks) among people of similar ages and ethnicities, with and without CVD risk factors and HIV.

The average profile of HIV-positive participants at the start of the study was as follows:

- age – 48 years
- gender – 97% men, 3% women
- CD4+ count – 362 cells
- HIV viral load – 680 copies/ml
- untreated high blood pressure – 25%
- type 2 diabetes – 14%
- very high levels of bad cholesterol (LDL-C) – 8.2%
- low levels of good cholesterol (HDL-C) – 51%
- elevated levels of triglycerides – 47%
- current smokers – 60%
- hepatitis C co-infection – 35%
- overweight – 14%
- kidney disease – 7%
- use of statins (these lower cholesterol and have anti-inflammatory activity) – 7%

Participants were monitored for about six years, from April 2003 to December 2009.

People who had been diagnosed with CVD were not enrolled.

## **Results**

After taking many risk factors into account, researchers calculated that HIV-positive people had a 50% increased risk for a heart attack. Even when researchers restricted their analyses to people who did not have risk factors for CVD, just being HIV positive was still associated with a significantly increased risk for a heart attack.

### **At greatest risk**

HIV-positive participants at greatest risk of a heart attack had a CD4+ count less than 200 cells and an HIV viral load of 500 copies/ml or greater. However, even among participants whose viral load was less than 500 copies/ml or whose CD4+ counts were greater than 200 cells, an elevated risk for heart attack remained.

### **Many strengths and some weaknesses**

The strengths of this study include its sheer size, the amount of health-related data analysed and researchers' ability to compare people with and without different risk factors. It was also able to compare similar people with and without HIV. Furthermore, the study was accurately able to determine if a heart attack occurred. This point is not trivial. Other studies attempting to assess cardiovascular risks in HIV-positive people have included reports of unconfirmed or uncertain heart attacks. Another strength of the present study is that it included data on substance use. This is important, as people who inject drugs are at increased risk for heart disease stemming from exposure both to street drugs and the infections that can arise from frequent injecting.

The present study was observational in design. This kind of study is good at finding associations but cannot prove that HIV does indeed cause an increased risk of heart attack. However, the evidence to date from many other studies is accumulating and clearly points to HIV being a major culprit in CVD risk.

### **The role of ART**

There was a trend that approached but did not achieve statistical significance in the study, suggesting that recent use of HIV protease inhibitors may have been linked to an increased risk for heart attack. However, this finding is not definitive. Moreover, the trend found by the researchers could be caused by other, related events. For instance, people who received protease inhibitors in this study may have had special features that placed them at heightened

risk for heart attack (for example, they could have been very ill, with high pre-treatment viral loads and low CD4+ cell counts). Such people may not respond rapidly to ART and their HIV-related risk for a heart attack may not have declined immediately on initiation of treatment. Thus the association of an increased risk of heart attack with protease inhibitors found in this study must be treated very cautiously.

## Why the elevated risk

The reasons for the elevated risk of heart attack among people with HIV are not clear but here are a few:

- Researchers suspect that long-term viral infections, such as those caused by HIV, trigger lasting inflammation. Such inflammation is only partially reduced with ART. Chronic inflammation may weaken many organ systems, including the heart and blood vessels, and has been linked to an increased risk for heart attack in studies of HIV-negative people.
- SIV, simian immunodeficiency virus, causes an AIDS-like condition in susceptible monkeys. SIV is closely related to HIV. Researchers studying SIV have found that this virus can cause unfavourable changes to the lining of blood vessels of infected monkeys. Other researchers have found that SIV directly affects the pumping ability of the heart.
- HIV causes the body to make unfavourable changes to the way it processes cholesterol, causing dysfunction within cells of the immune system. Such cells also play a role in the development of CVD. HIV infection also causes abnormally low levels of good cholesterol (HDL-cholesterol) in the blood.
- Emerging research suggests the possibility that members of the herpes virus family may play a role in inciting inflammation and cardiovascular disease.

## Research needs

This large U.S. study should serve as a reminder to research funding agencies that co-morbidities are a major problem for HIV-positive people and their care providers. Furthermore, cardiovascular disease prevention needs additional focus. Other steps that need to be taken include the following:

- Research is needed to find ways to help understand why HIV infection is associated with a significantly increased risk for a heart attack. Unfortunately, this will likely take many years.
- The present study was overwhelmingly male. Large, perhaps international, studies are needed to explore HIV's effect on the cardiovascular health of women, both before and after menopause.

## Estimating risk

The Framingham risk study is a large American study that monitored HIV-negative people over many years to determine possible risk factors for CVD. Based on the results of this study, risk calculators have been developed to help doctors and nurses assess the risk of serious cardiovascular events occurring in their patients. What the present study with HIV-positive veterans has found is that this method of assessing CVD risk greatly underestimates the risk of heart attack in HIV-positive people. Indeed, at the start of the study, Framingham risk calculations suggested that both HIV-positive and HIV-negative people had a similar risk for a heart attack. However, over the course of the study, this turned out not to be the case. Commenting on the results of the veterans study, researcher Patrick Mallon, MD, PhD, noted that there are now [HIV-specific calculators for cardiovascular and kidney-related risk](#) available.

Such tools are imperfect and their results require interpretation by a doctor experienced in using them.

## Clinical trials needed

Long-term, robustly designed clinical trials are needed to understand what treatments or interventions may work to help reduce the risk for heart attacks in HIV-positive people. Until researchers are certain about the cause(s) of the excess risk for heart attacks seen in HIV-positive people, clinical trials could focus on exploring possible measures that are available today. Such measures should be able to assess traditional CVD risk factors. **Clinical trials** could investigate one or more of at least the following interventions:

- smoking cessation
- taking low-dose Aspirin on a regular basis
- more widespread use of potent statins

- implementing a Mediterranean diet
- regular exercise programs
- stress-reduction activities such as meditation and yoga
- supplements, including antioxidants and B-complex vitamins such as high-dose niacin
- the use of anti-herpes drugs

## Resources

- [HIV and cardiovascular disease](#) – CATIE Fact Sheet
- [Niaspan study](#) – role of extended-released niacin on immune activation
- [MAINTAIN study](#) – a trial of antioxidants and micronutrients
- [VALIDATE study](#) – a study of the anti-herpes drug valacyclovir

—Sean R. Hosein

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