In addition to weakening the immune system, HIV infection appears to affect the health of many other organ-systems, including the heart and circulatory system. The reasons for this are not certain but there are several possibilities. For instance, some studies have found unfavourable changes to levels of lipids (fatty substances) in the blood in untreated HIV infection—specifically, increased levels of bad cholesterol (LDL-C) and triglycerides, together with decreased levels of good cholesterol (HDL-C). Over the long term, such changes can increase the risk for cardiovascular disease (CVD). But there may be other factors that play a role in intensifying the risk for CVD, such as the following:

- HIV infection causes the immune system to produce chemical signals that increase inflammation. Prolonged inflammation appears to weaken blood vessels.
- Proteins produced by HIV-infected cells not only affect the immune system but can be absorbed by other organ-systems, such as the liver. A dysfunctional liver may contribute to excessive levels of triglycerides and cholesterol in the blood.
- Experiments with simian immunodeficiency virus (SIV), which causes an AIDS-like disease in susceptible monkeys, suggests that this virus accelerates the development of cardiovascular disease, particularly in monkeys fed an unhealthy diet.
- Some therapies for HIV infection can cause unfavourable changes to lipid levels.

The need for improvement

At least one study has found that improvement to the diet alone is not enough to fully reverse the unfavourable changes to lipids brought about by HIV. And despite the use of lipid-lowering therapy, some HIV-positive people may not have the same degree of improvement seen in HIV-negative people on the same therapy.

An intensive combination

Researchers at the Baylor College of Medicine and at several clinics in Houston, Texas, conducted a randomized placebo-controlled study to assess the impact of a comprehensive approach to lipid health in HIV-positive people. The Heart Positive study compared different interventions, including the following:

- increasing doses of the B-vitamin niacin
- the lipid-lowering drug fenofibrate
- a diet low in saturated fat (30% of calories came from fat and 7% or fewer calories came from saturated fat)
- regular supervised exercise
- a combination of all of the above

After six months, researchers found significant improvements in lipid levels. Also, the use of niacin appeared to increase levels of the hormone adiponectin. Less-than-normal levels of this hormone have been associated with an increased risk for pre-diabetes, diabetes and obesity.

Researchers screened 441 HIV-positive people and found 221 that they could recruit and randomly assign to receive one of five interventions in the following groups:
Group 1: standard of care and general advice about a heart-healthy diet
Group 2: changes to the diet along with a supervised exercise regimen and two placebos (fake niacin and fake fenofibrate)
Group 3: changes to the diet along with a supervised exercise regimen, fenofibrate and niacin placebo
Group 4: changes to the diet along with a supervised exercise regimen, niacin and fenofibrate placebo
Group 5: changes to the diet along with a supervised exercise regimen, niacin and fenofibrate

Food
Participants in Groups 2 through 5 were taught how to maintain their weight by keeping track of their food intake, assessing the number of calories in foods, learning how to reduce their intake of saturated fat and how to select and prepare different types of food. For the first two weeks of the study, participants received pre-packaged meals from the study centre’s kitchens to help reinforce their training about healthy eating habits. Throughout the six months of the study, participants kept diaries to log the foods that they ate, which a dietitian assessed from time to time.

Exercise
Participants in Groups 2 through 5 engaged in supervised exercise regimens—a mix of aerobics and weight lifting at the study’s gym for between 75 and 90 minutes, three times weekly. Participants who were unable to go to the study’s gym were given a membership at a more conveniently located gym and fitness instructors monitored their exercise regimens.

Niacin
Participants in Groups 4 and 5 received an extended-release formulation of niacin (Niaspan) at an initial dose of 500 mg at bedtime every night. They increased the dose at two-week intervals until they reached a total daily dose of 2,000 mg per night.

Fenofibrate
Participants in Groups 3 and 5 took fenofibrate (145 mg) at bedtime.

At the start of the study, the average profile of participants was as follows:
- 87% men, 13% women
- age – 44 years
- CD4+ count – 500 cells
- 75% had a viral load less than 400 copies/ml because of the use of anti-HIV therapy
- hepatitis B virus co-infection – 5%
- hepatitis C virus co-infection – 3%

At least 50% of participants had a history of smoking tobacco and 10% had a history of substance use. About 37% of participants had a family history of diabetes and many were impoverished.

Results
In total, 127 participants completed the study. The best results were seen among people in Group 5, where all interventions were implemented. Compared to people in Group 1, who received no major intervention, participants in Group 5 experienced the following changes:
- 52% decrease in triglycerides
- 12% increase in good cholesterol (HDL-C)
- 19% decrease in non-HDL-C (this term describes several types of cholesterol that are not heart friendly, such as LDL-C)

At the end of the study, these changes were so significant that the levels of triglycerides and HDL-C of participants in Group 5 were within the normal range.
In theory, when taken together, the changes seen in participants in Group 5 have the potential to greatly reduce the risk for cardiovascular disease events, such as a heart attack. However, to prove such benefits, a larger and longer study is needed.

The ratio of total cholesterol to HDL-C has been validated in previous studies as having a high predictive value for future cardiovascular risk. This ratio was reduced (a favourable change) in Groups 3, 4 and 5 and was lowest in Group 5.

**Managing blood sugar**

Insulin is a hormone produced by the pancreas gland. This hormone helps control the amount of sugar (or glucose) in the blood. Cells use sugar as a source of energy.

In cases of pre-diabetes, cells gradually become resistant to the effect of insulin. So the pancreas gland is forced to produce ever-higher amounts of this hormone. Although this can initially help, insulin resistance continues to develop and blood sugar levels gradually rise. If left untreated, insulin resistance can lead to diabetes.

**Niacin and blood sugar**

In previous clinical trials with HIV-negative and HIV-positive people, exposure to niacin has, in some cases, increased the risk for insulin resistance. So, in the Heart Positive study, researchers paid special attention to insulin resistance and the body’s ability to manage blood sugar.

In general, the researchers found that the use of niacin resulted in “mild” increases in the following:

- glucose levels in the blood
- insulin levels in the blood
- assessments of insulin resistance

Furthermore, when such changes occurred they were generally within the normal range, according to the researchers.

**Considerations arising from Aim-High**

A Canadian-U.S. study called Aim-High was recently halted prematurely in part because of a relatively small increase in strokes among participants who received the lipid-lowering agent simvastatin (Zocor) and niacin (Niaspan). However, in analysing the preliminary data from Aim-High, investigators have not found evidence that niacin was linked to the small increase in strokes seen in that study. Moreover, previous controlled clinical trials did not find any association between the use of niacin and an increased risk of stroke. Indeed, niacin has been used safely over the past 50 years to help normalize lipid levels. For further details about Aim-High, see “Is there a link between niacin and stroke?”

**Focus on adiponectin**

Adiponectin, a hormone produced mostly by fat cells, increases the body’s sensitivity to insulin. Normal levels of adiponectin in the blood range between 5 and 30 micrograms/mL depending on the test used. Women tend to have greater adiponectin concentrations than men. Less-than-normal levels of adiponectin have been found in HIV-negative people with certain conditions, such as: obesity, insulin resistance, type 2 diabetes, inflammation and perhaps certain cancers such as breast, colon and prostate cancer. Factors such as eating a diet high in fat, smoking tobacco and not getting enough exercise have also been linked to low adiponectin levels.

The following activities have been associated with increased adiponectin levels in the blood, which reduces the risk for developing insulin resistance, diabetes and cardiovascular disease:

- regular exercise
- eating a Mediterranean-type diet (including whole grains)
- losing excess body weight
- eating nuts
Adiponectin and HIV

Research suggests that HIV infection may affect the body’s regulation of adiponectin (though precisely how this happens is not yet clear). As in HIV-negative people, associations between reduced adiponectin levels and abnormal lipid levels in the blood and higher-than-normal blood pressure have been found in HIV-positive people. It is possible that reduced adiponectin levels place HIV-positive people at increased risk for cardiovascular disease.

In the present study, the use of niacin doubled adiponectin levels in the blood from about 5 micrograms/ml at the start of the study to 10 micrograms/ml by the end. Among participants who did not receive niacin, adiponectin levels remained stable. This difference in adiponectin levels between participants who received niacin and those who did not was statistically significant.

However, while adiponectin levels increased in niacin users, over the short-term this increase did not apparently result in improved control of blood sugar. So the overall improvement in cardiovascular health because of increased adiponectin levels is not known from this study.

A very useful study

The Heart Positive study provided some very valuable information. Not only did it demonstrate that a combination of interventions is effective in managing abnormal lipid levels, but it also showed that this combination, which included high doses of the B-vitamin niacin, is safe and effective. Moreover, the unexpected impact of niacin on adiponectin levels in this placebo-controlled clinical trial may pave the way for further studies of adiponectin and other hormones produced by fat cells and their impact on human health. Future studies also need to explore the possibility of interactions between the combination of niacin and fenofibrate together with multiple anti-HIV drugs. Such possible interactions were only partially explored in the present study.

Exercise—easy to prescribe, hard to implement and maintain

The combination of modified diet, supervised exercise and a fibrate and niacin as described in this study was undoubtedly an intensive regimen for many participants. By the end of the study, only about 60% of the original participants remained enrolled. Also, adherence to the diet and exercise portions of the regimen was achieved by just 55% of participants. Perhaps the study’s results would have been strengthened had adherence to diet and exercise been greater.

In the everyday world outside of a clinical trial, it may be difficult for some people living with HIV (like other people with complex chronic health conditions) to sustain improvements in diet, intensive exercise and medication management unless they are given support. Additionally, some HIV-positive people can experience bouts of unexpected fatigue from time to time or may have complications and disabilities that make rigorous exercise difficult.

Regular exercise has many health benefits. It not only helps strengthen the heart and circulatory system, but it can also improve mood and the ability to cope with stress. So, in the future, researchers need to test a variety of interventions, including, at least initially, less intensive exercise regimens to assess what can help HIV-positive people improve and maintain their heart and overall health.

To find out about keeping your heart healthy, please see the CATIE in-depth fact sheet on "HIV and cardiovascular disease"

—Sean R. Hosein

REFERENCES:

4. Balasubramanyam A, Coraza I, Smith EO, et al. Combination of niacin and fenofibrate with lifestyle changes


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.

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