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I HEART- AND AGE-RELATED ISSUES

A. Dealing with heart- and age-related issues

Chronic HIV infection activates and inflames the immune system. Taking combination anti-HIV therapy (ART) every day and achieving and maintaining an undetectable viral load greatly help to reduce immune activation and inflammation. As a result, ART users in Canada and other countries are living longer, some into their 60s, 70s and into their 80s.

However, ART cannot cure chronic HIV infection; even with these medications, the virus continues to cause low-level infection in lymph nodes and lymphatic tissues. In those parts of the body, ongoing production of HIV and its proteins causes cells of the immune system to become activated and low-level inflammation ensues. These activated cells of the immune system also travel to other organ-systems, perhaps spreading inflammatory signals and affecting the health of these other organ-systems.

The heart and its blood vessels are called the cardiovascular system. Reports presented in this issue of *TreatmentUpdate* suggest that the cardiovascular system is particularly affected by HIV. As HIV-positive people age, staying in general good health and maintaining the health of the cardiovascular system becomes particularly important. Whatever is good for the heart is good for the brain and body. A great place to begin to learn about maintaining or improving heart

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health is CATIE's newly revised fact sheet HIV and Cardiovascular Disease. It has useful tips and links for information about support for quitting smoking, changes to the diet, incorporating exercise into your life and, if necessary, options about medical interventions.

In this issue of *TreatmentUpdate* we review studies on issues related to aging, survival and cardiovascular disease.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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B. Exercise + statin yields enhanced benefits

Regular exercise has a broad and beneficial effect on people, from improving general health to more specific effects such as feeling more energetic, better mood, increased endurance, weight loss, better control of blood sugar and improved heart health.

The heart is a muscular pump, pushing blood to different parts of the body. Its pumping action can be strengthened by exercise. However, exercise can also have other effects. For instance, in experiments with HIV-negative people, aerobic exercise (brisk walking, hiking, gardening, cycling, dancing, jogging, swimming, playing sports, strenuous yoga), resistance training (lifting weights) or a combination of both forms of exercise can do the following:

- improve circulation
- improve control of blood sugar
- improve levels of lipids (cholesterol and triglycerides) in the blood
- increase muscle mass
- decrease fat mass

Small studies have suggested that exercise can also be beneficial for HIV-positive people.

The Saturn study

Researchers in the U.S. conducted a 96-week placebo-controlled study of the lipid-lowering drug rosuvastatin (Crestor). A sub-study of Saturn explored the impact of unsupervised exercise (as reported by participants). The Saturn researchers found that participants who reported to have engaged in "at least two and a half hours of moderate-intensity exercise per week were likely to experience lower levels of inflammation and [improved cardiovascular health]." Two and a half hours of exercise per week is equivalent to about 22 minutes each day.

Study details

All participants in Saturn were taking combination anti-HIV therapy (ART) and had undetectable or low viral loads in their blood. Further details about Saturn will appear later in this issue of *TreatmentUpdate*.

Researchers assessed participants' physical activity using surveys that had been previously developed and validated in other studies. The surveys asked about many different types of physical activity and how much time was spent on each activity.

Additionally, blood samples were collected for analysis on a regular basis.

Results

A total of 119 participants completed surveys for the exercise sub-study. Overall, participants taking rosuvastatin reported engaging in more exercise than participants on placebo.

Physical activity was associated with improved measures of overall health. However, statistically significant improvement of the following assessments occurred only in statin users who also exercised:

- decreased levels of fatty tissue around the heart
- decreased levels of inflammation
- decreased levels of the chemical messenger IL-6 (interleukin-6; other studies have found that elevated levels of IL-6 are associated with an increased risk for inflammation and unfavourable events, including cardiovascular disease and reduced survival)

Researchers found that participants who did two and a half hours of moderate exercise each week were "likely to experience lower levels of inflammation and [had arteries that became more flexible]."

Thus, exercise has an important role to play in reducing excess inflammation.

Although the heart is chiefly thought of as a muscular pump, it keeps some fatty tissue as a store of energy. In people with cardiovascular disease, this fatty layer becomes larger, perhaps too large relative to the size of the heart. In the present study, participants who used a statin and who exercised lost greater amounts of this fatty layer compared to people on placebo who also exercised.

Bear in mind

This exercise sub-analysis does have shortcomings, such as the following:

- The time that participants actually spent on exercise was not supervised. Sometimes people in studies may over-report socially desirable activities. However, in this placebo-controlled study there seemed to be clear benefits that only accrued to people who exercised *and* who used a statin. So it would appear that, on the whole, people who reported a significant amount (two and a half hours per week) of moderate exercise did have measurable changes in inflammation and in their hearts.

The research team encourages additional studies of exercise in HIV-positive people. The team suggests that such studies consider "objective measures of exercise, including activity monitors and heart rate monitors."

Such future studies need to have more women involved, as men comprised nearly 80% of the participants in Saturn.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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C. What reduces survival 10 years after starting ART in North America and Europe?

In 1996 highly active antiretroviral therapy (HAART, now simply called ART) became widely available in North America and Western Europe. For the first time since the beginning of the AIDS pandemic, the immune systems of HIV-positive people became stronger and death rates began to fall.

It is important to find out what happened to people who began ART when it first emerged, as they began therapy with drugs that would be considered less effective and less tolerable than what is recommended for initial HIV therapy in 2016.

Researchers in Canada (British Columbia and southern Alberta), the U.S. and Western Europe pooled health-related information collected from about 13,000 HIV-positive people who began ART in the years 1996 to 1999. Participants in this analysis were alive for the first 10 years after starting ART.

Ten years later

The researchers found that 5% of participants died 10 or more years after starting ART. The most common causes of death in decreasing order of importance were cancers unrelated to AIDS, AIDS, cardiovascular disease and liver-related disease. Older people seemed particularly susceptible to death from cardiovascular disease. People who injected street drugs were at heightened risk of death from infections unrelated to AIDS and also from complications of liver disease. People who died from AIDS-related causes tended to have low CD4+ cell counts and detectable viral loads.

Study details

Data from participants were analysed in a project called ART-CC. Participants enrolled in this study were at least 16 years old when they began ART and had not previously taken anti-HIV drugs.

Participants started taking ART between 1996 and 1999. Researchers collected data up to July 31, 2013. The breakdown of participants by gender was 79% men and 21% women.

Results

In analysing data from 13,011 participants, researchers found that 656 had died at least 10 years after starting ART. The major factors associated with these deaths were as follows:

- older age (60 and up)
- low CD4+ cell counts (less than 100 cells/mm^3)
- injecting street drugs
- a viral load greater than 1,000 copies/mL
- a diagnosis of AIDS

Estimating the risk of death

Researchers presented the following two scenarios whereby they calculated the subsequent five-year risk of death among participants aged 40 to 49 years after they had survived their first decade on ART:

- Participants who did not inject street drugs and whose CD4+ counts were greater than 500 cells/mm^3 and whose viral loads were suppressed and who did not develop AIDS in the past decade had only a 2% chance of dying over the next five years.
- Participants who injected street drugs and who did not have a suppressed viral load and who had less than 100 CD4+ cells and who had AIDS during their first decade on ART had a 48% chance of dying over the next five years.

As a reference, researchers used the life expectancy of the average HIV-negative person in France around the same time. They used data from France as a comparison because a large fraction of HIV-positive people in ART-CC came from France. The average HIV-negative person from France had only a 1% chance of death over the subsequent five-year period.

Causes of death

It was possible to find a specific cause of death in medical records for 83% of participants in the present analysis. The most common causes of death were as follows:

- cancer unrelated to AIDS (or the liver)
- AIDS
- cardiovascular disease
- liver related

The researchers noted that among participants aged 60 and older, rates of death due to cardiovascular disease were "substantially higher" than in younger people. Causes of death unrelated to AIDS were also greater among older people.

People who injected street drugs and who died did so from infections unrelated to AIDS and from liver-related complications. These deaths were associated with low CD4+ counts and detectable viral loads.

Bear in mind

In this group of 13,011 participants 95% of whom survived their first decade on ART, it remains

important to monitor HIV-related lab tests such as CD4+ cell count and viral load because poor results are linked to reduced survival.

Some populations of HIV-positive participants had substantially elevated rates of death compared to HIV-negative people of the same age.

The researchers found that older age was "strongly associated" with an increased risk of dying, particularly from causes unrelated to AIDS. The researchers therefore made the following statements:

- This association with age "suggests that provision of both preventive and therapeutic care in older [HIV-positive] patients treated for many years will become increasingly important as the number of patients aged 60 [and older] increases."
- "The most common cause of death was non-AIDS-related cancer, implying a need for preventive and screening measures adapted for use with HIV-positive patients who have survived long-term treatment with ART to be incorporated into their routine health care."

The researchers noted that the drugs available for treatment of HIV in the mid-to-late 1990s, while lifesaving, were less effective and relatively toxic compared to regimens available today in high-income countries. Therefore, they stated that the risk of death in "patients starting ART today can be expected to be lower than those found in our study."

Substance use

The ART-CC researchers stated that people who inject street drugs need support for maintaining and improving their health and survival. At a minimum, such support would include opioid substitution and counselling, as well as screening for liver disease, including infection with hepatitis B and C viruses, and, when positive, treatment.

The researchers also noted that "alcohol misuse" might be another factor that unfavourably impacts the health of some people who use street drugs.

They also stated that people who smoke should be offered entry into smoking cessation programs.

Importantly, the researchers sought to underscore the drivers of addiction and substance use and noted that people who engage in such behaviours "may require interventions to address depression and social deprivation."

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Trickey A, May MT, Vehreschild J, et al. Cause-specific mortality in HIV-positive patients who survived ten years after starting antiretroviral therapy. *PLoS One*. 2016 Aug 15; 11(8):e0160460.

D. Dutch study examines aging and cardiovascular disease

Researchers in the Netherlands sought to measure and compare stiffening of the arteries (which is linked to cardiovascular disease) among 1,000 middle-aged people, half of whom were HIV positive. The researchers found that HIV-positive people had increased arterial stiffness. Overall, traditional cardiovascular disease risk factors—particularly smoking—were largely responsible for this increased risk. However, among a subset of HIV-positive people, those who had serious immune deficiency (100 CD4+ cells or less) were also at elevated risk for stiffening arteries.

About stiffer arteries

Every time the heart pumps blood, a wave-like movement of blood is pushed outward from the heart along the arteries. Flexible arteries are needed to help the wave of blood move. As arteries age they can become stiffer (arterial stiffness). When this happens blood does not travel as well from the heart, and the heart's pumping action intensifies as this organ attempts to compensate by pushing blood more forcefully. Over time, this intensified action can place a strain on the heart. Stiffer arteries have been linked to an increased risk for heart attack and stroke.

Study details

Dutch researchers have been trying to understand the impact of HIV on the aging process in a study called AGE_hIV. What is very useful about the Dutch study is that it enrolled both HIV-negative and HIV-positive people from the same communities who have similar socio-economic and behavioural factors. This greatly strengthens comparisons made within the study.

Researchers focused their analysis on the following groups:

- 566 HIV-positive people
- 507 HIV-negative people

The researchers made the following summary of the profile of participants when they entered the study:

> "…HIV-infected individuals were more often diagnosed with [higher-than-normal blood pressure], had generally less favourable [levels of cholesterol and triglycerides in their blood], and were more often smokers."

Additionally, the average profile of HIV-positive participants upon entering the study was as follows:

- age – 53 years
- 89% men, 11% women
- 32% currently smoked

The vast majority of participants were taking ART and had an undetectable viral load.

Results

Overall, HIV-positive people had a greater degree of arterial stiffening than HIV-negative people. According to the researchers, this was mainly due to smoking and elevated blood pressure.

Taking into account many factors (including gender, age, smoking), researchers found that some HIV-positive people, particularly those who had endured a high degree of immune deficiency in the past (that is, who had 100 or less CD4+ cells), were significantly more likely to have stiffer arteries.

Why the link with immune deficiency?

Immune deficiency is associated with heightened inflammation and immune activation. Such effects likely injure the arteries and increase the pace at which cardiovascular disease occurs.

It is also possible that, as the Dutch study suggests, having immune deficiency in the past leaves a lasting impact on the health of the arteries.

Researchers were not able to find any HIV-related factors that drove arterial stiffness, so they think that other factors may be continuing to incite inflammation within the arteries. One such possible factor is CMV (cytomegalovirus), a common sexually transmitted member of the herpes family of viruses. Other studies have found an association between CMV co-infection and a risk for increased inflammation in people with HIV.

Overall, the researchers concluded that arterial stiffening played a small role in the increased risk for cardiovascular disease in HIV-positive people. However, the study is important because it adds to the information known about the role of traditional cardiovascular disease risk factors and it has exposed the impact of a history of immune deficiency on arterial health. In this latter regard, the Dutch study provides yet another reason to start ART as early as possible.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

REFERENCE:

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E. U.S. researchers explore the impact of depression on heart attack risk

In Canada and other high-income countries, the widespread use of potent combination anti-HIV therapy (ART) has greatly decreased the risk of AIDS-related infections. As a result, ART users are living longer but are developing more health issues that are not related to AIDS. In the past 15 years researchers have found that these other health issues—such as cardiovascular disease, including heart attack and stroke—appear to be more common in HIV-positive people.

Part of the reason for the rise in heart attacks may be related to several factors, such as elevated rates of smoking, abnormal levels of cholesterol in the blood and elevated blood pressure. However, researchers suspect that there are other factors that can influence cardiovascular disease risk.

In a study with HIV-negative people who took part in a randomized clinical trial, researchers conducted long-term monitoring of a portion of participants and found that those who had depression and who were treated for it before cardiovascular disease occurred were significantly able to reduce their future risk of a heart attack.

Spurred by this finding (and results from other studies) researchers in the U.S. conducted a study to explore the impact that depression had on heart attack risk among HIV-positive people. Over the course of 11 years they found that adults with major depression (sometimes simply called depression) had a 30% elevated risk for developing a heart attack. This study was observational in nature and cannot prove that major depression caused a heart attack. However, its results are highly suggestive and add to the growing body of evidence that major depression plays a role in heart attack risk in HIV-positive people.

Study details

Researchers reviewed health-related data collected from 26,144 HIV-positive veterans in the U.S. Participants entered the study in 1998 and were monitored until the end of 2009.

Key average features of participants when they entered the study were as follows:

- age – 48 years
- 19% had major depression
- 9% had persistent low-grade depression

Results

After an average of six years of monitoring, 490 new heart attacks occurred. This is equivalent to saying that about 2% of study participants developed a heart attack.

Researchers found that participants with major depression had a 30% increased risk for developing a heart attack compared to participants without depression—a statistically significant difference.

The researchers arrived at this figure even after taking into account traditional cardiovascular disease risk factors (such as smoking) and HIV-specific factors.

The risk of a heart attack conferred by major depression fell to 25% (still statistically significant) when researchers took into account the following factors:

- co-infection with hepatitis C virus
- the presence of kidney disease
- alcohol and/or cocaine abuse or dependence

Mild but persistent depression was not associated with an increased risk for cardiovascular disease.

Potential explanations

Researchers are not certain precisely how major depression likely increases the risk for a heart attack in some people, but there may be several potential explanations as follows:

- Depression may increase inflammation in the body. As inflammation is already higher than normal among HIV-positive people, additional inflammation may hasten the development and onset of a heart attack
- Depressed people may engage in unhealthy behaviours, such as smoking, not exercising, not taking ART every day as directed. Any or all of these together could increase the risk of a heart attack. ART reduces (but does not eliminate) HIV-related inflammation, and a randomized study of treatment interruption found that such interruptions increase inflammation and the risk of a heart attack or stroke.

The use of the anti-HIV drug efavirenz (Sustiva and in Atripla) has been linked to an increased risk of depression and, in very rare cases, suicide. However, in this study, there was no clear connection between the use of efavirenz and depression. In part this likely occurred because doctors seemed to avoid prescribing efavirenz to people who became depressed.

Note that the present study is observational in design. Such studies are good at finding associations but cannot prove, for instance, that major depression caused heart attacks. However, because this study monitored a relatively large number of participants over a long period, its findings are highly suggestive.

For the future

The present study, like nearly all studies of HIV-positive veterans, was made up overwhelmingly of men. Studies are needed among HIV-positive women to assess the impact of major depression on their health, particularly for heart attack risk. Researchers also need to understand *how* major depression could eventually be linked to a heart attack in some people. As well, researchers should prospectively study the impact of interventions, such as counselling and the use of antidepressants, on the future risk of heart attack in HIV-positive people who have major depression.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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F. Saturn—final results of a study on rosuvastatin (Crestor)

In a trial called Saturn, researchers randomly assigned users of potent combination anti-HIV therapy (ART) to receive one of the following daily interventions:

- rosuvastatin 10 mg
- fake rosuvastatin (placebo)

Participants were mostly middle-aged men and had blood tests suggestive of heightened inflammation.

On average, levels of bad cholesterol (LDL-C) in blood samples of participants taking rosuvastatin fell between 20% and 25% during the first six months of the study. This was sustained for the duration of the trial. Furthermore, participants taking rosuvastatin developed only a very modest narrowing of their arteries compared to placebo users. In some assessments, rosuvastatin appeared to reduce HIV-related immune activation.

Study details

Researchers recruited HIV-positive adults taking ART who did not have coronary artery disease or uncontrolled diabetes. Blood tests revealed that participants had elevated levels of inflammation and immune activation. Participants also underwent high-resolution CT scans of the chest. This imaging technique can reveal deposits in arteries. Arteries that have more deposits become narrow and less flexible and less able to help blood flow. Narrowing of the arteries is a well-established measure of cardiovascular disease.

Researchers randomly assigned 72 people to receive rosuvastatin and 75 people to receive placebo.

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

- 78% men, 22% women
- age – 46 years
- CD4+ count – 620 cells/mm^3
- 78% had an undetectable viral load
- 50% were taking an HIV protease inhibitor
- 64% smoked tobacco
- 33% had a close family member who had a heart attack

In total, 28 participants prematurely left the study, distributed as follows:

- rosuvastatin – nine people
- placebo – 19 people

None of the 19 people left because of perceived or actual side effects. One person could not be assessed because of a poor CT scan. This left 118 people whose data could be assessed at week 96.

Results—Changes in lipid levels

On average, participants who took rosuvastatin had their levels of bad cholesterol (LDL-C) fall between 20% and 25%. This change was statistically significant compared to placebo users and was maintained throughout the study.

Changes in levels of good cholesterol (HDL-C) and triglycerides were not statistically significant between rosuvastatin and placebo users.

Results—Changes in arteries

Arteries carry fresh oxygen-rich blood to tissues and organs. In both aging and cardiovascular disease, arteries narrow as substances are deposited in them.

Participants who used rosuvastatin appeared to have only very minor and slow narrowing of the arteries over the course of the study compared to placebo users. This occurred regardless of age, gender, use of protease inhibitors or if participants had pre-diabetes or diabetes.

Results—Inflammation

According to tests that are generally used in studies of immune activation and inflammation in HIV, rosuvastatin did not reduce such activation on T-cells. However, it did reduce the level of activation on another group of the immune system's cells called monocytes. As these cells play a role in the formation of blood clots, their reduced activation by rosuvastatin may prove to be beneficial in the long term.

Bear in mind

Rosuvastatin was able to significantly reduce levels of bad cholesterol in ART users. Its impact on other lipids was relatively modest.

Rosuvastatin was able to reduce levels of some activated cells of the immune system.

There were no heart attacks in this study—it only lasted for two years and contained a relatively small number of participants, none of whom had a history of cardiovascular disease.

Other analyses from Saturn show that rosuvastatin has no harmful effect on bone density. It may help to slightly increase leg muscle mass.

The big question

A major question that remains unanswered is this: Will rosuvastatin significantly reduce heart attacks in the long term among HIV-positive people? Unfortunately, Saturn was not designed to answer this question; the study focused on lab and other test results rather than a hard endpoint such as heart attacks. The reason for this focus on lab and other tests is that heart attacks are not common events. A much larger and longer study is needed to provide answers about the use of a statin and hard endpoints such as heart attacks and stroke. Such a study (called Reprieve) has been designed and will take place in Canada using a different statin called pitavastatin. The next report in *TreatmentUpdate* focuses on the Reprieve study.

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1. Longenecker CT, Sattar A, Gilkeson R, et al. Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. *AIDS*. 2016 Sep 10;30(14):2195-203.

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G. The Reprieve study comes to Canada

HIV infection is associated with an increased risk for cardiovascular disease. Part of the reason for this is that, according to some studies, there are very high rates of smoking among HIV-positive people.

However, even after accounting for smoking, other studies have found that HIV-positive people tend to have a higher level of inflammation and immune systems that are chronically activated. Together, this inflammation and activation likely worsen the risk for injury to vital organs and systems, including the cardiovascular system. Initiating potent combination anti-HIV therapy (ART) early in the course of HIV disease and achieving and maintaining an undetectable viral load greatly reduces but does not eliminate HIV-associated immune activation and inflammation. Therefore, researchers are seeking other ways to reduce immune activation and inflammation as well as cardiovascular risk.

Small studies of lipid-lowering drugs called statins, such as atorvastatin (Lipitor) and rosuvastatin (Crestor), have shown that these drugs can significantly reduce levels of bad cholesterol (LDL-C). However, because these studies have been small and short in duration, they could not show any impact of statin therapy on heart attacks, stroke or death arising from complications of cardiovascular disease.

Enter Reprieve

Researchers in the U.S., Canada and Thailand are conducting a large study called Reprieve. Approximately 6,500 HIV-positive people will be recruited; half will receive a relatively new statin called pitavastatin 4 mg/day and the other half will receive placebo. Pitavastatin has been approved in the U.S. and Japan but not yet in Canada. Although it is not approved in Canada, pitavastatin can be used in clinical trials here. Reprieve is expected to last for up to six years.

Advantages of Reprieve

Reprieve is a large well-designed placebo-controlled study. As a result, researchers will be able to determine whether pitavastatin is able to reduce heart attacks, stroke, deaths related to cardiovascular disease and the need for cardiovascular surgery to improve the flow of blood. Researchers will also explore pitavastatin's ability to reduce inflammation and narrowing of the arteries.

Researchers enrolling participants for Reprieve will be seeking people who are at low or moderate risk for heart disease. For more information about Reprieve, see these links from the Canadian HIV Trials Network:

- Seeking a Reprieve for Heart Disease: CTN Partners with the ACTG (http://www.hivnet.ubc.ca/2016/03/seeking-a-reprieve-for-heart-disease-ctn-partners-with-the-actg/)
- CTN 293: REPRIEVE trial (http://www.hivnet.ubc.ca/clinical-trials/ctn-293-reprieve-trial/)

About pitavastatin

In clinical trials with HIV-negative people, pitavastatin has been found to be effective at reducing levels of bad cholesterol. The drug was also found to be generally safe. Some statins have been associated with a small but increased risk for developing type 2 diabetes. Pitavastatin does not appear to carry such a risk.

A placebo-controlled study of pitavastatin has been done with 24 HIV-positive people in Thailand. All participants entered the study with abnormal lipid levels and had been taking ART based on a combination of atazanavir (Reyataz) and ritonavir and nucleoside analogues. They took pitavastatin 4 mg/day or placebo for 12 weeks and then stopped. After two subsequent weeks participants who were taking pitavastatin were given placebo and vice versa for 12 consecutive weeks and then stopped. In this study, pitavastatin significantly reduced levels of total cholesterol and LDL-C. These changes were detectable in as little as four weeks after starting the drug.

No side effects were reported in that study.

There were no significant changes to liver enzymes or any lab test results suggestive of toxicity. There were also no significant changes to levels of atazanavir in the blood of participants. Previous studies had found that there are no significant interactions between pitavastatin and darunavir (Prezista), ritonavir or efavirenz (Sustiva and in Atripla).

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H. Improvements in survival after a heart attack

Researchers with a large study called DAD have reviewed cases of heart attacks that occurred between 1999 and 2014 among HIV-positive people. The proportion of participants who died within the first month of a heart attack decreased in the latter years of the study. This effect was likely due to the combination of surgery and prescription medicines to treat cardiovascular disease. Despite this trend in better survival, risk factors for cardiovascular disease remained relatively common throughout the span of the study.

Study details

The DAD study has accumulated health-related information on about 50,000 HIV-positive participants. Data are collected principally from clinics in Europe and also from some sites in the U.S., Argentina, Australia and Israel.

Results

A total of 1,008 heart attacks were recorded between 1999 and 2014—about 2% of participants had heart attacks.

The average profile of participants at the time they had a heart attack was as follows:

- age – 51 years
- 91% men, 9% women
- three common risk factors for heart attack were distributed as follows – 66% of participants had abnormal levels of cholesterol/triglycerides in the blood; 53% smoked tobacco; 43% had higher-than-normal blood pressure
- 36% were taking drugs for abnormal cholesterol levels and 27% were taking drugs to help reduce elevated blood pressure
- 90% were taking ART

Results—Trends

DAD obtained information on heart attacks from the clinical records of participants. A team of DAD researchers then reviewed the information on heart attacks and classified heart attacks in the following ways:

- a heart attack definitely occurred
- a heart attack possibly occurred
- unable to classify if a heart attack occurred

Focusing only on cases in which researchers were certain that a heart attack occurred, rates were stable throughout the study. When taking both definite and possible heart attacks into account, researchers found that rates of heart attacks decreased over the course of the study.

Here are some trends:

In the early years of the study, the average age at which a heart attack occurred was 48 years. By the latter years of the study, the average age for this event rose to 54.

Over time, more participants who had a heart attack also had elevated blood pressure and abnormal cholesterol levels in their blood. Also, scores from cardiovascular disease risk calculators, such as the Framingham risk score, rose. This suggests that, over time, the cardiovascular disease risk of participants in DAD was increasing.

Causes of death after a heart attack

On average, people who had a heart attack were monitored for four years. In total, 117 (12%) of 1,008 participants had a second heart attack.

Of the 1,008 participants who had at least one heart attack, 339 (34%) died. These deaths were distributed as follows:

- 43% of deaths occurred on the same day as the heart attack
- 11% of deaths occurred within the first month of the heart attack
- 46% of deaths occurred more than one month after the heart attack

The death rate within the first month of a heart attack changed according to different periods of the study, as follows:

- 1999 to 2002 – 27% died within the first month of a heart attack
- 2011 to 2014 – 8% died within the first month of a heart attack

The researchers also sought to assess the impact of a stroke on survival. They found that the proportion of participants dying from a heart attack or stroke fell dramatically from 73% in the period 1999 to 2002 to 41% in the period 2011 to 2014. In contrast, over time, deaths rose from the following causes:

- AIDS
- cancers unrelated to AIDS
- bacterial infections
- lung disease

After a heart attack

Only some participants underwent invasive cardiac surgery to help improve their flow of blood. Below are the proportions of participants who underwent specific procedures:

- 1% had endarterectomy – surgery to remove the deposits of plaque from the wall of an artery
- 9% had coronary bypass surgery – in this type of intervention, surgeons remove one or more blood vessels, usually from the legs, and insert them in the chest to help blood flow around blocked arteries
- 58% had angioplasty – surgery to widen arteries and keep them open

About two-thirds of these procedures were done on the same day that a heart attack occurred.

Doctors also prescribed the following categories of drugs for a majority of participants who were not already taking them:

- drugs to lower abnormal lipid levels
- drugs to decrease the formation of unnecessary blood clots
- drugs to lower blood pressure

Statistical analysis found that the combination of surgery and medications within the first month of a heart attack was associated with a significant reduction in the risk of short-term death.

Heart attacks and survival

Taking many issues into account, the researchers found that the following factors were associated with an increased risk of death after a heart attack even when interventions (surgery and/or drugs) were made):

- older age
- history of injecting street drugs
- type 2 diabetes
- history of a heart attack

Bear in mind

In this analysis from DAD, about 2% of 50,000 participants developed a heart attack between 1999 and 2014.

Overall, the risk of a heart attack seemed to decrease during the course of the study. A similar trend has been reported among HIV-negative people in high-income countries.

HIV-positive people who had a heart attack generally were at elevated risk for cardiovascular disease. This finding means that there are opportunities for doctors and their patients to help lower the risk for heart attacks.

Over the course of the study, there was an increase in the use of interventions shortly after a heart attack occurred and this reduced the short-term risk of death.

Toward the latter years of the study, the risk of death in the short term after a heart attack fell about threefold. According to the DAD team, this

improvement in survival "appeared to be largely driven by improved clinical management."

The researchers noted that "there is still a proportion of individuals surviving their heart attacks who do not appear to receive [cardiac surgery and cardiovascular medicines]." The DAD team is not certain why this is the case and advanced this explanation: "complicating [co-existing health conditions] influencing the eligibility of a person to undergo invasive cardiac procedures, the type of heart attack, and differences in clinical practices at different clinical centres may [explain why some people did not receive cardiac surgery and cardiovascular medicines]."

There are limitations to the ability of DAD to analyse the data, as it is an observational study. Also, DAD did not receive information from the clinics that supplied data on whether they provided smoking cessation services or advice about healthy changes to dietary habits or exercise. Hopefully, the clinics that provide care for HIV-positive people with heart attacks will be able to improve the survival of all of their patients in the future.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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I. Can the ratio of triglycerides to good cholesterol help predict diabetes?

Researchers in Italy have analysed health-related information collected from HIV-positive people between 1997 and 2013, focusing on new cases of type 2 diabetes. They found that rates of diabetes in HIV-positive people were not significantly different from those in HIV-negative people in northern Italy. However, they did find that a ratio of two fatty substances in the blood—triglycerides and good cholesterol (HDL-C)—was statistically linked to an increased risk for developing type 2 diabetes. Participants who had extensive liver injury (scarring of the liver) due to chronic viral hepatitis were also at increased risk for diabetes. Due to issues with the study's design its findings should be treated as interesting and preliminary until they can be confirmed.

Study details

Researchers with the ICONA foundation have been collecting health-related information from HIV-positive people for the past two decades. The latest analysis of this data focused on 3,546 participants, as researchers sought to help healthcare professionals find ways to predict which of their patients would be at high risk for developing type 2 diabetes.

Here is the average profile of participants upon entering the study:

- 74% men, 26% women
- age – 38 years
- duration of HIV infection – one and a half years
- CD4+ count – 286 cells/mm^3
- HIV viral load – 63,000 copies/mL
- ratio of triglycerides to HDL – 2.8

Researchers also used an indirect but useful assessment of liver injury called FIB-4. This is a score calculated using figures derived from a person's age, the levels of liver enzymes ALT and AST, and platelets in the blood. FIB-4 values greater than 3.25 suggest extensive scarring of the liver. This problem can occur as a result of chronic infection with hepatitis B or C viruses.

Results

Over the course of the study, 80 participants developed type 2 diabetes (herein after simply referred to as diabetes).

According to the researchers, analysis of a ratio of triglycerides to HDL that was high (greater than 4.5) was associated with a heightened risk for developing diabetes. Other factors associated with an increased risk for diabetes in this study were as follows:

- older age
- body mass index (BMI, a relative assessment of fatness) greater than 30

- use of the combination of two older anti-HIV drugs, d4T (stavudine, Zerit) and 3TC (lamivudine)
- use of the anti-HIV drugs atazanavir (Reyataz) and ritonavir
- FIB-4 scores greater than 3.25

Bear in mind

This study, which looked back upon previously collected data, is retrospective in design. While relatively inexpensive, such studies can sometimes arrive at inadvertently biased conclusions. However, it is likely that most of the findings from the present analysis are probably correct in their conclusions. Retrospective analyses are a first step in exploring an idea and their results can be used to seek funding for a study of a more robust statistical design. Indeed, the present study's main finding about using the ratio of triglycerides to HDL to help predict diabetes risk is interesting but requires confirmation in a study of a more robust statistical design.

The finding of an association between an increased risk for diabetes and the use of d4T and 3TC is probably due to the presence of d4T in a regimen. The drug 3TC is generally safe and in well-designed studies has not been associated with an increased risk for diabetes. On the other hand, d4T is an older drug that is seldom used in high-income countries today because it has many toxicities. Also, some studies have found an association between exposure to d4T and an increased risk of diabetes.

The link between the use of atazanavir (in combination with ritonavir) and an increased risk for diabetes is puzzling. There is no evidence from previous studies that atazanavir causes diabetes. Furthermore, compared to earlier protease inhibitors, atazanavir was found to be generally neutral when it comes to changes in cholesterol and blood sugar. It is possible that because atazanavir does not generally have an unfavourable impact on cholesterol and blood sugar levels, it may have been preferentially prescribed to patients who were already at elevated risk for diabetes, hence the apparent association found in this study.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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J. U.S. researchers find increasing cases of high blood pressure among HIV-positive people

Researchers at the University of North Carolina have been investigating cardiovascular disease risk among 3,612 HIV-positive people between the years 1996 and 2013. During that time they found that cases of higher-than-normal blood pressure increased threefold. Not surprisingly, people who were obese or who had type 2 diabetes or kidney dysfunction were at increased risk for developing elevated blood pressure. However, researchers also found an interesting association between the timing of initiating combination anti-HIV therapy (ART) and blood pressure. They found that participants who began taking ART *before* their CD4+ counts fell below the 500-cell mark were less likely to develop higher-than-normal blood pressure (hypertension).

Study details

Researchers reviewed health-related information collected from 3,612 participants. The average profile of participants upon entering the study was as follows:

- age – 36 years
- 71% men, 29% women
- lowest-ever CD4+ count – 173 cells/mm^3

- 41% were current or former tobacco smokers
- 18% were co-infected with hepatitis C virus

Results—Hypertension at the start of the study

After all participants underwent medical evaluation and tests, a total of 471 participants were diagnosed with hypertension at the beginning of the study. These participants were likely to have the following risk factors:

- obesity
- elevated levels of cholesterol and triglycerides in their blood
- type 2 diabetes

Results—Hypertension over the course of the study

The remaining 3,141 participants who did not have hypertension were monitored for an average of six years. In that time, a total of 756 new cases of hypertension were diagnosed. Over time, the rate of diagnoses of hypertension increased about threefold.

Risk factors for new cases of hypertension

Researchers found that the following factors were significantly associated with an increased risk for developing hypertension:

- older age (for every 10-year increase in age)
- obesity
- kidney dysfunction
- type 2 diabetes

An immunological connection

After researchers took into account the previously mentioned factors, they found that participants who had 500 or more CD4+ cells seemed less likely to develop hypertension. We say "seemed" because this was a statistical trend that approached but did not achieve significance. Participants who had an undetectable viral load were at decreased risk for developing hypertension, and this was statistically significant.

Experiments with mice suggest that there is a connection between a dysfunctional or depleted immune system and an increased risk for developing hypertension. However, well-designed studies in people are needed to prove a link between immunological issues and hypertension risk.

The researchers note that having a suppressed viral load may be a sign of "favourable health behaviours" and that such behaviours might lead to improved overall health and a reduced risk for hypertension. So this finding between a suppressed viral load and an apparent reduced risk for hypertension should be treated cautiously.

Why might rates of diagnoses of hypertension increase?

Part of the reason that hypertension rates increased over the course of the study is that participants were getting older. However, even after the research team adjusted their findings for the age at which hypertension was diagnosed, cases of hypertension seemed excessive. This likely means that there are factors other than age at play, and the researchers have advanced the following possible explanation:

> In the earlier part of the study, some participants were likely ill "with low body weight and generally poor health" and immune deficiency. Such people would have been likely to have low blood pressure. Once they initiated ART, people with severe immune deficiency experienced a return to health, "often presaged by a rapid gain in weight and other dynamic changes in metabolism that may unmask longstanding predilections (genetic, demographic or behavioural) towards hypertension."

There was no clear statistical link between an increased risk for developing type 2 diabetes and the following treatment-related factors:

- use of HIV protease inhibitors
- length of time on ART

The research team states that it will conduct other analyses in the future that attempt to assess the impact of specific anti-HIV drugs and an increased risk for hypertension.

Bear in mind

The present study is observational in design. Such studies can find associations but cannot, for instance, prove that a specific factor causes diabetes.

However, the study's findings with traditional risk factors (obesity, diabetes, kidney dysfunction) make sense and have been found in HIV-negative people.

The present study's finding about a link between maintaining the health of the immune system (having a high CD4+ cell count) and a reduced risk for hypertension are interesting. A Dutch study reported earlier in this issue of *TreatmentUpdate* has found a link between immune deficiency and a greater risk for stiffer arteries (a risk factor for cardiovascular disease). Together, the findings from the U.S. and Dutch studies underscore the importance of starting ART early in the course of HIV disease before immune deficiency has occurred. Both studies also point to the importance of screening HIV-positive people for risk factors for cardiovascular disease and, when found, reducing such risks.

Another analysis from the same team of Dutch researchers in the previously mentioned study (above) has found that hypertension was more likely to occur in HIV-positive people than in HIV-negative people. It found that "abdominal obesity" was associated with an increased risk for elevated blood pressure. In part, this increased risk association with abdominal obesity in some participants may have been due to exposure to the older anti-HIV drug d4T (stavudine, Zerit), which is now notorious for causing changes in body shape, including the fat deposits deep within the belly.

Resource:

HIV and cardiovascular disease – CATIE fact sheet

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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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