

CARDIOVASCULAR DISEASE *in People with HIV*



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In the past few years disturbing reports have begun to accumulate about young, relatively healthy HIV positive men who have developed heart disease or suffered heart attacks. Researchers and health-care providers treating people with HIV are taking these reports seriously and increasing attention has been devoted to cardiovascular disease at recent medical conferences.

It remains to be determined whether these cardiovascular manifestations are attributable to HIV infection itself, to antiretroviral drug therapy, to a high prevalence among HIV positive people of traditional risk factors that pose a danger for the population at large—such as tobacco smoking, older age, male sex, and family history—or to some other not-yet-known factors.

Heart disease in people with HIV remains poorly understood and continues to generate considerable fear and controversy. But there is good reason to believe that common-sense risk reduction strategies can help delay or prevent cardiovascular problems such as atherosclerosis, heart attacks, and strokes. (For an explanation of cardiovascular conditions, see the sidebar on page 12).

What's the Problem?

By 1998 health-care providers had begun to report on small numbers of young HIV positive people who had experienced coronary heart disease. Many researchers and advocates came to suspect that such events might be related to the elevated levels of blood fats—in particular cholesterol and triglycerides—that were being observed in people taking highly active antiretroviral therapy (HAART), especially the then-new protease inhibitor (PI) drugs. Numerous studies were undertaken in an attempt to understand the phenomenon.

Conflicting Results

Max David, MD, of the University of Cincinnati College of Medicine and colleagues reported in the January 1, 2002 issue of *Clinical Infectious Diseases* that duration of antiretroviral therapy was associated with ischemic heart disease in people with HIV. The researchers compared data from 16 HIV positive people with cardiovascular disease and 32 HIV positive people without heart disease. The group with cardiovascular disease had a lower mean CD4 cell nadir (lowest ever count) and longer exposure to nucleoside reverse transcriptase (NRTI) drugs; both factors may be markers for a longer duration of HIV infection. However, use of PI drugs was similar in both groups.

In contrast, M. Mary-Krause, MD, of INSERM in Paris and colleagues reported at the 8th Conference on Retroviruses and Opportunistic Infections (the Retrovirus conference) in February 2001 that in a French cohort, myocardial infarction rates increased with duration of PI use. Fifty-four heart attacks occurred among 19,795 HIV positive men who had taken PIs. The incidence rate was 8.9 per 10,000 person-years among those taking PIs for less than 18 months, 19.2 among those taking PIs for 18–29 months, and 34.7 among those taking the drugs for more than 30 months (although there were few people in the latter group); the expected incidence rate in the general population

(matched for age and sex) is 10.8 per 10,000 person-years. Unfortunately, this study did not control for additional cardiovascular risk factors.

Michel Duong, MD, of Hôpital du Bocage in Dijon, France, and colleagues presented a study of heart disease risk factors at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in December 2001. The researchers analyzed coronary heart disease risk factors in a group of 99 HIV positive people using HAART who had no known history of heart disease. Participants underwent an exercise stress test to detect silent myocardial ischemia. (In a stress test, a subject exercises on a treadmill while electrocardiogram and blood pressure tests are done.) The researchers found no statistically significant differences in type or duration of antiretroviral therapy, length of HIV infection, viral load, or CD4 cell count between those who had positive stress tests (that is, those with evidence of myocardial ischemia) and those with negative stress tests. Evidence of ischemia was statistically associated with older age, obesity, and elevated cholesterol level.

Retrovirus Conference Clarifies Little

The 9th Retrovirus conference in February 2002 did little to clarify matters, with different research teams presenting conflicting data. Scott Holmberg, MD, from the Centers for Disease Control and Prevention (CDC) and colleagues followed 5,676 HIV positive people at nine clinics (the HOPS cohort) from 1993 to 2001. Slightly more than half the group used PI-based regimens. Although uncommon overall, 13 of 3,013 participants taking PIs suffered myocardial infarctions during the study period, compared with just two of 2,663 participants not using PIs. Although people taking PIs were more than five times as likely to have a heart attack, no increased risk was observed for angina or strokes.

On the other hand, a study by Samuel Bozzette, MD, of the University of California at San Diego and colleagues detected what appears to be a slight

decline in heart disease and strokes since the advent of HAART. Dr. Bozzette's team examined the medical records of 36,766 HIV positive patients at U.S. Veterans Administration medical centers over the same eight-year period. During this time there were 1,800 hospital admissions and 500 deaths due to cardiovascular or cerebrovascular disease. Since 1997 rates of hospital admissions and deaths due to heart attack or stroke have fallen compared to the rates prior to the availability of PIs; over the course of the study period, heart attack and stroke admission and mortality rates declined 10–20%. The researchers concluded that their findings did not support an association between PI, NRTI, or non-nucleoside reverse transcriptase inhibitor (NNRTI) use and excess cardiovascular or cerebrovascular problems. However, the results of this study may reflect the fact that by 1997 health-care providers were prescribing statins and other lipid-lowering therapies for HIV positive people with high blood fat levels.

A smaller study by Daniel Klein, MD, and Leo Hurley, MPH, of Kaiser Permanente in Oakland, California, also did not detect an increase in cardiovascular events among 4,159 HIV positive men in the Kaiser health-care system since the introduction of PIs. Between 1996 and 2001 there were 72 hospitalizations for coronary heart disease, including 47 myocardial infarctions. Rates of cardiovascular problems did not differ significantly between those taking and not taking PIs, or between those taking and not taking any antiretroviral therapy. However, the researchers did find that cardiovascular events were almost twice as likely among HIV positive participants compared with HIV negative participants (6.5 vs 3.8 events per 1,000 person-years). The researchers found “no effect of treatment type” on heart disease, and suggested that the higher rate in people with HIV may be due to chronic infection or other cofactors.

Carl Fichtenbaum, MD, and colleagues from the Cincinnati College of Medicine in Ohio evaluated 111 HIV positive people and 25 HIV negative

Common Cardiovascular Conditions

Cardiovascular (heart and blood vessel) disease is the single largest cause of death for both men and women in the United States. Various cardiovascular manifestations are described below. Symptoms of cardiovascular disease may include shortness of breath, fatigue, dizziness, fainting, and chest pains (which may extend to the arms, shoulders, back, neck, or jaw), especially during exertion. People who experience these symptoms should seek prompt medical attention.

Atherosclerosis refers to narrowing and hardening of large and medium-sized arteries due to the buildup of plaques on blood vessel walls, a process that usually takes many years. Plaques are composed of material such as cholesterol, cellular debris, mineral deposits, and scar tissue. As plaques build up, the walls of the artery thicken while the open passageway (lumen) becomes narrower, allowing less blood to flow through. When this happens, the heart must work harder to pump blood. In addition, plaques may rupture or damage the endothelial lining of vessels, leading to the formation of blood clots. Such clots may further block the affected artery, and may break off and become lodged in vessels elsewhere in the body.

Coronary heart disease (CHD), also called **coronary artery disease (CAD)**, is atherosclerosis affecting the three coronary arteries that supply the heart. As these arteries become clogged, they are unable to deliver adequate oxygen and nutrients to the heart muscle, potentially leading to ischemia or heart attack. Artery

controls. They found that the ten-year risk of progression to coronary heart disease was 4% among HIV positive participants compared with 1% among HIV negative participants. Additionally, among the HIV positive participants, heart disease risk was 6% for those treated with PIs compared with 3% for PI-naive participants.

Finally, results presented at the XIV International AIDS Conference

eventually involved some 10,000 people over two generations. Using population data, researchers have developed calculations to show how various factors affect heart disease risk. (See sidebar on page 13 for a list of cardiovascular risk factors.)

Some heart disease risk factors are related to demographics. Because atherosclerosis develops over many years, older people (men over age 45 and

Some experts believe that the emergence of heart disease in people with HIV is due to a high prevalence of traditional risk factors.



held in Barcelona, Spain, in July 2002 offer perhaps the strongest evidence to date of an association between PIs and cardiovascular disease. Giorgio Barbarini, MD, of University La Sapienza in Rome and colleagues studied 1,200 HIV positive persons, half receiving regimens containing a PI and half taking PI-sparing combinations. After three years there were 23 new-onset cardiovascular events (12 heart attacks, 11 cases of angina) in the PI arm compared with two cases in the PI-sparing arm. The factors most highly associated with heart disease were elevated cholesterol and triglyceride levels, lipodystrophy, increased levels of fibrinogen (a protein that promotes blood clotting), and smoking; notably, all participants in this study were smokers.

Why Does It Happen?

Cardiovascular Risk Factors

Studies of the general population have provided a good understanding of the biology of cardiovascular disease and risk factors for problems such as atherosclerosis, heart attacks, and strokes. Prominent among these is the Framingham Heart Study, a 50-year longitudinal study begun in 1948 in Framingham, Massachusetts, that

women over age 55) are most likely to experience adverse cardiovascular events. In general, coronary heart disease is uncommon in young people unless they have a genetic predisposition or multiple risk factors. However, atherosclerosis may begin to develop in young adults well before obvious events such as ischemia or heart attacks occur. Men are more likely to develop heart disease than women. Estrogen has long been thought to play a protective role in women; however, the value of hormone replacement therapy to reduce cardiovascular disease in postmenopausal women is now disputed.

Other factors are related to lifestyle. Tobacco smoking is one of the clearest cardiovascular risk factors. In the Caerphilly Heart Study, which followed more than 2,500 men in a Welsh town between 1979 and 1983, smokers had a 2.3-fold increased risk of heart disease. Studies also have shown that cocaine use may cause more rapid cardiovascular disease progression, and the drug is known to trigger heart attacks.

Diet also plays a role. A diet high in saturated fat and/or cholesterol may predispose a person to atherosclerosis, while a diet high in sodium promotes

high blood pressure in some people. Obesity is associated with a greater risk of heart disease, especially excess abdominal fat (the so-called “pot belly” or “spare tire”). Sedentary people are more likely to develop cardiovascular disease; conversely, exercise has a protective effect.

High levels of blood fats—notably total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides—are a major cardiovascular risk factor. In the Caerphilly study, people with a total cholesterol level above 200 mg/dL had a 1.5-fold increased risk of heart disease, while those with a triglyceride level above 175 mg/dL had a 1.8-fold increased risk. LDL cholesterol contributes to the formation of plaques on artery walls (atherosclerosis). In contrast, high-density lipoprotein

(HDL) cholesterol protects against heart disease; in the Caerphilly study, HDL levels below 40 mg/dL were associated with a 1.4-fold increased risk. (See page 22 for more information on blood lipids.)

Other metabolic factors associated with increased cardiovascular risk include high blood glucose levels, insulin resistance (reduced sensitivity of cells to the action of insulin), and diabetes; in the Caerphilly study, people with diabetes had a 2.3-fold increased risk of heart disease. Hypertension also is known to predispose people to heart disease; those with blood pressure over 140/90 had a 1.5-fold increased risk in the Caerphilly study.

Finally, studies have shown that various biochemical factors including C-reactive protein (a chemical that signals

blockages may be treated with angioplasty (in which a device is inserted into an artery to open it up, for example by inserting a stent, inflating a balloon, or cutting out plaque with a laser) or bypass surgery (in which blood is routed around the blocked artery through a blood vessel graft).

Peripheral arterial disease refers to reduced blood flow through the arteries in the extremities (the arms and legs), which may be due to atherosclerosis or blood clots that block the vessels.

Ischemia refers to lack of oxygen. **Myocardial ischemia** (also called **ischemic heart disease**) is a condition in which the heart muscle does not receive enough oxygen. Typically this is due to atherosclerosis affecting the coronary arteries.

Angina pectoris (angina, for short) refers to chest pains, often a symptom of ischemia. People with angina may experience tightness, heaviness, pressure, or pain on the left side of the chest, which may extend to the arms, shoulders, back, neck, or jaw. Other symptoms may include shortness of breath, sweating, and a feeling of nausea, indigestion, or “heartburn.” Often angina is brought on by exertion. Angina may be a warning sign of an impending heart attack and should be promptly brought to the attention of a health-care provider. Sublingual (under the tongue) nitroglycerin may be used to quickly open blocked blood vessels in people experiencing angina.

Myocardial infarction (MI), also called a **heart attack** or a **cardiac or coronary arrest**, occurs when the coronary arteries serving the heart become completely blocked, often by a blood clot. This deprives the heart of oxygen and can lead to the death of heart muscle tissue. Heart attack symptoms are similar to those of angina, but may last longer; symptoms that persist for 30 minutes or more usually indicate a heart attack. About

CARDIOVASCULAR DISEASE



Risk Factors

- Male sex
- Older age (over age 45 for males, over age 55 for females)
- Family history of cardiovascular disease (heart disease in an immediate male relative—father or brother—under age 55 or an immediate female relative—mother or sister—under age 65)
- Tobacco smoking
- Obesity
- Abdominal fat accumulation
- High-fat diet
- Sedentary lifestyle
- “Type A” personality (impatient, competitive, easily irritated)
- High total cholesterol level
- High low-density lipoprotein (LDL) cholesterol level
- Low high-density lipoprotein (HDL) cholesterol level
- High triglyceride level
- High blood pressure (hypertension) above 140 systolic and/or above 90 diastolic
- Diabetes
- High blood glucose level
- Insulin resistance

25% of heart attacks are “silent” with few or no symptoms. A heart attack is a medical emergency that requires immediate attention.

A **cerebrovascular accident (CVA)**, better known as a **stroke** or **brain attack**, occurs when blood flow to the brain is interrupted. This can happen when a blood clot forms in a vessel supplying the brain (a thrombotic stroke), when a clot travels from somewhere else in the body and lodges in one of the brain’s small vessels (an embolic stroke), or when vessels in the brain rupture (a hemorrhagic stroke). When the brain is deprived of oxygen, cells in the immediate area die (called an infarct) and chemical changes occur that can injure surrounding tissue. Signs of a stroke may include sudden numbness, weakness, or paralysis of the face or extremities (especially on one side of the body); confusion, difficulty speaking, vision problems, or loss of balance and coordination; severe headache; and brief loss of consciousness. A stroke is a medical emergency that requires immediate attention. Rapid treatment—within about three hours—with a neuroprotective drug such as tissue plasminogen activator (TPA) can help limit long-term brain damage.

Congestive heart failure (CHF) refers to any condition in which the heart cannot properly pump blood. This may be due to a variety of causes including coronary heart disease, heart valve damage, cardiomyopathy, heart infection, or congenital heart defects. When blood is not pumped out of the heart efficiently, blood returning to the heart may back up, causing congestion in tissues and organs. Treatments for heart failure include daily aspirin to “thin” the blood and reduce clotting, angiotensin-converting enzyme (ACE) inhibitors to control blood pressure and reduce blood volume, beta blockers to slow heart rate and control arrhythmia,

inflammation), fibrinogen, plasminogen activator inhibitor (a chemical that interferes with tissue plasminogen activator, an enzyme that dissolves blood clots), and homocysteine (an amino acid) may play a role in the development of cardiovascular disease.

Some experts believe that the emergence of heart disease in people with HIV is due to a high prevalence of traditional risk factors. A majority of people with HIV and AIDS in North America and Europe are male, and as effective treatment delays HIV disease progression, an increasing proportion are approaching the age at which cardiovascular events typically occur in the general population. To combat wasting, some people with HIV consume high-fat diets, and others are sedentary due to fatigue and illness. In addition, several studies have shown that a higher percentage of HIV positive people smoke tobacco compared with the general population; for example, 50% of those in Rainer Weber’s DAD database (described below) were smokers. All of these risk factors may interact with metabolic side effects of antiretroviral therapy to increase cardiovascular risk.

HIV Infection and Heart Disease

In the early years of the AIDS epidemic, many people were afflicted with life-threatening opportunistic illnesses (OIs), and health-care providers and people with HIV tended to focus on immediate rather than long-term manifestations of the disease.

Even before the advent of HAART, it was clear that HIV positive people were prone to fat metabolism disorders. People with HIV—especially those with advanced immune deficiency—often were observed to have high triglyceride levels, particularly if they had wasting syndrome. But they tended to have low cholesterol levels, both LDL and HDL. Although HAART has been shown to increase total and LDL cholesterol levels (discussed below), currently approved antiretroviral drugs are not known to decrease HDL levels. Therefore, some degree of increased cardiovascular risk likely exists in HIV positive people regardless of treatment status.

Some experts believe that chronic HIV infection itself increases heart disease risk. For example, certain cytokines—such as interferon-alpha and tumor necrosis factor—that may be present at high levels in people with HIV appear to interfere with lipid metabolism. Chronic inflammation may contribute to atherosclerosis. In addition, HIV infection has been associated with heart muscle damage (cardiomyopathy). Also, people with compromised immune systems are more likely to develop heart infections, and injection drug users are particularly prone to endocarditis.

Finally, many people with HIV have taken androgens and anabolic steroids to combat conditions such as wasting and abnormal body fat redistribution. These hormones can increase blood viscosity (thickness), and may interfere with blood flow and increase the risk of high blood pressure.

Lipodystrophy and Metabolic Abnormalities

Beginning in 1998—two years after the advent of HAART—people with HIV and their health-care providers began to report unusual metabolic problems that appeared to be linked to the new drug combinations. Among these were body fat redistribution, fat accumulation (e.g., in the abdomen, back of the neck, and breasts), loss of fat in the face and extremities, elevated blood fat levels (hyperlipidemia), elevated blood glucose levels (hyperglycemia), and insulin resistance (a potential precursor to diabetes). These manifestations are sometimes collectively referred to as “lipodystrophy syndrome,” although experts have not agreed upon an exact definition.

To date lipodystrophy syndrome has most strongly been associated with PIs, but metabolic side effects also have been linked to NRTIs and NNRTIs. Fat abnormalities have even been seen in HIV positive people who have never taken antiretroviral therapy, lending weight to the theory that HIV infection itself contributes to such manifestations. Many experts believe that metabolic

changes in people with HIV are due to a combination of HIV infection, immune system recovery, antiretroviral side effects, and perhaps other not-yet-determined factors. (For more on lipodystrophy see “Body Fat Changes: More than Lipodystrophy,” *BETA*,

seen in people taking HAART, health-care providers and advocates worried that this might be a warning sign of an impending increase in cardiovascular problems among people with HIV.

Hyperlipidemia is quite common among people taking antiretroviral

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January 1999, page 23; and “HAART Attack: Metabolic Disorders during Long-Term Antiretroviral Therapy,” *BETA*, April 1999, page 10.)

Altered body fat metabolism may contribute in several ways to increased cardiovascular risk. Some people with lipodystrophy syndrome develop accumulations of fat around the midsection (the so-called “protease paunch”) and visceral abdominal fat surrounding the internal organs. Studies of the general population have shown that abdominal fat accumulation (indicated by a waist-to-hip ratio greater than 1) is a risk factor for heart disease.

Likewise, high blood glucose levels, insulin resistance, and diabetes are known risk factors for cardiovascular disease among the population at large. Different studies have detected varying increased rates of insulin resistance in people using PIs, although it is not yet known whether this is clinically relevant.

Hyperlipidemia

Among the side effects associated with antiretroviral therapy, high blood lipids are the most likely to lead to an increased rate of heart disease among HIV positive people. Because general population studies have shown that high total cholesterol and triglyceride levels are associated with increased risk, when hyperlipidemia began to be

drugs; some studies have found rates higher than 50% in people taking first-generation PIs. Total cholesterol levels as high as 1,000 mg/dL have been seen. (The National Cholesterol Education Program defines total cholesterol levels above 240 mg/dL as presenting a high risk for cardiovascular disease). High blood fat levels have been most clearly associated with PIs, but also are seen to a lesser extent in some people taking NNRTIs. PIs are believed to cause hyperlipidemia by interfering with proteins that regulate fat metabolism. All approved PI drugs have been linked to hyperlipidemia, with ritonavir (Norvir), saquinavir (Fortovase), and lopinavir/ritonavir (Kaletra) being the worst offenders.

In an attempt to better understand the relationship between antiretroviral therapy and heart disease, Rainer Weber, MD, of the University Hospital in Zurich, Switzerland, and colleagues looked at a database containing information on over 20,000 HIV positive participants in 11 large prospective cohort studies in North America, Europe, and Australia (the DAD study); results were presented at the December 2001 ICAAC. Elevated total cholesterol levels were least common in people who had never taken antiretroviral drugs. Increasing rates of elevated total cholesterol were observed in people

calcium channel blockers to reduce blood pressure and relax blood vessels, digitalis derivatives to increase the heart’s pumping efficiency, diuretics to eliminate excess fluid, and/or vasodilators to expand blood vessels.

Hypertension, or high blood pressure,

can be caused by a variety of factors. In the case of atherosclerosis, it is due to thickening of arterial walls, which forces the heart to work harder to pump blood through the narrowed vessels. Hypertension increases the risk of heart attack, stroke, and kidney failure. The so-called “silent killer,” hypertension often has no symptoms; if symptoms do occur they may include sweating, heart palpitations, headaches, and dizziness. Blood pressure is expressed as two numbers (for example, 120/80). The upper number is systolic pressure, measured while the heart is contracting; the lower number is diastolic pressure, measured while the heart is resting between beats.

Pulmonary hypertension (PH)

refers to high blood pressure in the pulmonary artery that carries blood from the heart to the lungs, typically due to narrowing of the pulmonary artery and associated vessels. The right ventricle of the heart must work harder to force blood through the narrowed vessels, potentially leading to right ventricle congestive heart failure or heart attack. Symptoms of PH may include shortness of breath, fatigue, dizziness, and fainting. While the condition is uncommon in the general population, studies show that HIV positive people are many times more likely to develop PH.

Thrombosis refers to the formation of a blood clot within a vessel. Clots often develop in the deep veins of the legs (**deep vein thrombosis**), but also may form in other parts of the body, including the heart. Deep vein thrombosis is most likely to occur when blood flow is restricted,

for example due to poor circulation, dehydration, or prolonged inactivity. If a blood clot breaks free, it can travel through the bloodstream and lodge in a distant vessel (**embolism**). A blood clot that lodges in the lungs is called a **pulmonary embolism**; blood clots that lodge in the brain are a major cause of strokes. A recent study indicated that HIV positive people under age 50 are at increased risk for thrombosis compared to HIV negative people of the same age.

Arrhythmia is a disturbance of the heart's normal rhythm. The heart may beat too rapidly (**tachycardia**), too slowly (**bradycardia**), or irregularly. Normally the heart's sinoatrial node emits a regular electrical impulse that causes the four chambers of the heart (two atria and two ventricles) to contract in an organized fashion. Heart rhythm disorders may have various causes. Although they are often harmless, certain types of arrhythmia can lead to heart attack. Arrhythmia may be treated with medication or a pacemaker, a device that provides regular electrical stimulation that mimics a properly functioning sinoatrial node.

Cardiomyopathy (or **myocardiodiopathy**) refers to disease of the heart muscle itself. The condition may be inherited or caused by a variety of factors such as thiamine (vitamin B1) deficiency, untreated hypertension, or a viral infection, which may damage heart muscle cells directly or trigger the body's immune system to attack the heart.

Carditis, pericarditis, and endocarditis are infections of the heart. Carditis is a general term for heart infection. Pericarditis affects the outer membrane covering the heart, while endocarditis affects the heart valves. People with compromised immune systems are more prone to heart infection. Pericarditis is more common in people who have autoimmune

who had taken only NRTIs, those who had taken NRTIs plus NNRTIs, and those who had taken NRTIs plus PIs; those who had taken drugs from all three classes had the highest incidence of elevated total cholesterol (44%).

HIV positive people with CD4 cell counts below 350 cells/mm³ (vs 500 cells/mm³ in the previous guidelines) and viral loads above 55,000 copies/mL by PCR or bDNA (vs 10,000 copies/mL previously).

While small, early studies have shown that blood fat levels decrease during periods off drugs, it is not known whether rising and falling lipid levels present less cardiovascular risk than consistently elevated levels.



Elevated total cholesterol levels were associated with higher CD4 cell counts and lower viral loads. Elevated triglyceride levels also were most often seen in people who had taken all three classes of drugs. In addition, 25% of participants had decreased HDL cholesterol. The same research team presented results at the February 2002 Retrovirus conference showing that while people taking either PI-based or NNRTI-based regimens had elevated total cholesterol levels, those taking NNRTI-based regimens had comparatively higher HDL levels, potentially protecting them against cardiovascular problems. Other studies have suggested that efavirenz (Sustiva) may increase HDL.

Switching and Substituting

Concern about the adverse metabolic side effects associated with HAART has led to some new approaches to anti-HIV therapy. Perhaps the most sweeping change is a shift away from early treatment in asymptomatic people with HIV. As reflected in the most recent treatment guidelines from the U.S. Department of Health and Human Services, antiretroviral therapy is now recommended for asymptomatic

Researchers also have explored the possibility of structured intermittent therapy or structured treatment interruption, in which anti-HIV therapy is taken on a cyclical basis with careful monitoring. While small, early studies have shown that blood fat levels decrease during periods off drugs, it is not known whether rising and falling lipid levels present less cardiovascular risk than consistently elevated levels.

Because different antiretroviral drug classes and different drugs within a class affect fat metabolism to different degrees, health-care providers have various options for attempting to minimize hyperlipidemia while maximizing therapeutic benefit. Numerous researchers have conducted "switch studies" in which protease-sparing regimens or new PIs with presumably milder side effects are substituted for older PIs.

An entire session at the February Retrovirus conference was devoted to switch studies. For example, C. Fisac from Hospital Bellvitge in Barcelona found decreased lipid levels after six months in 92 participants who switched from a protease-based regimen to one containing either abacavir (Ziagen, an NRTI), efavirenz (an

NNRTI), or nevirapine (Viramune, also an NNRTI). Total cholesterol decreased in all three groups, as did LDL cholesterol. HDL cholesterol increased significantly in the efavirenz and nevirapine groups, but decreased significantly in the abacavir group. Triglyceride levels decreased by 29.5% in the nevirapine group (a statistically significant decline), 9.9% in the abacavir group, and 4% in the nevirapine group.

Similar results for a larger group of 460 participants after one year on a new regimen were presented as a late-breaker at the same conference by Jose Maria Gatell, MD, also from the Barcelona team. This study—the largest switch study to date—showed that protease-sparing regimens were well tolerated and maintained good virological suppression; after 12 months viral load remained undetectable in 78% of the nevirapine group, 77% of the abacavir group, and 74% of the efavirenz group (using an intent-to-treat analysis). Although the rate of viral control was lower in the abacavir group, this was balanced by fewer people discontinuing the drug due to side effects.

In early studies the PI amprenavir (Agenerase) appeared to produce milder blood lipid increases, but this has not been consistently borne out in more recent, larger trials. Researchers are now holding out hope for the newest PI, atazanavir (Zrivada). Studies to date suggest that atazanavir does not increase LDL or triglyceride levels as much as other PIs, but does increase HDL cholesterol, leading to a more favorable LDL-to-HDL ratio. At the February Retrovirus conference Peter Piliero, MD, of Albany Medical College in New York and colleagues reported on two clinical trials of atazanavir in treatment-naïve participants. After 48 weeks, the lipid elevations seen in those taking nelfinavir were not seen in those receiving atazanavir. The researchers went so far as to conclude, “this suggests that atazanavir may reduce the risk of cardiovascular events in this population.” (For more information on atazanavir, see “The HIV/AIDS Drug Pipeline: A Status Report” on page 29.)

Arterial Dysfunction

In addition to hyperlipidemia, arterial dysfunction is another potential cause of increased cardiovascular risk in people with HIV. Impaired function of the endothelial cells lining blood vessels is known to play a role in the development of atherosclerosis. Previous studies have shown that PI-based regimens are associated with endothelial dysfunction. For example, James Sosman, MD, of the University of Wisconsin and colleagues reported results of a study of arterial function at the November 2001 meeting of the American Heart Association. They found impaired arterial vasodilation (expansion) as measured by ultrasonography in 21 of 28 HIV positive people using PIs.

At the February Retrovirus conference Michael Dubé of Indiana University in Indianapolis and colleagues presented data showing that indinavir (Crixivan) led to endothelial dysfunction in six HIV negative men (five of them smokers) as determined by measurements of blood flow in the legs. After four weeks of indinavir, blood flow was significantly impaired compared to baseline. The drug appeared to interfere with arterial production of nitrous oxide, which acts as a vasodilator (an agent that expands blood vessels and increases blood flow). The participants in this study did not experience significant lipid elevations, suggesting that arterial dysfunction is independent of high blood fat levels. The researchers speculated that insulin resistance, a side effect of indinavir, may play a role in endothelial dysfunction. Other research teams, however, have failed to find an association between HAART and endothelial dysfunction.

Other Biological Mechanisms

High blood pressure (especially systolic pressure) is a known independent risk factor for heart disease. Data are inconclusive as to whether HIV infection itself is associated with hypertension. However, there is evidence that some antiretroviral drugs increase the risk of high blood pressure. For example, Ross Hewitt, MD,

conditions and who have had certain viral infections. Endocarditis sometimes occurs in injection drug users due to bacteria injected into the bloodstream. People with congenital heart valve abnormalities or prior valve damage are more prone to endocarditis, and may be given prophylactic antibiotics before medical procedures such as surgery or dental work.

For more information on cardiovascular conditions see:

- www.americanheart.org
- www.cardiologychannel.com
- www.nhlbi.nih.gov/health/public/heart/index.htm

CARDIOVASCULAR RISK-REDUCTION MEASURES

Several measures can help prevent cardiovascular disease, including both lifestyle changes and medical interventions. The National Cholesterol Education Program recommends a Therapeutic Lifestyle Changes (TLC) program that includes a low-fat diet, weight control, and increased physical activity.

Monitoring

All adults should receive periodic blood lipid profiles; a profile done after fasting for 8–12 hours is most useful for determining the various types of lipids in the blood. (In people with a triglyceride level above 400 mg/dL, LDL should be measured separately rather than derived from an equation.) People starting anti-HIV therapy should have a fasting lipid profile done before treatment begins and every 6–12 months during treatment (or every 1–2 months if baseline lipid levels

are high or a person has other risk factors). Blood glucose also should be measured before antiretroviral therapy begins and periodically during treatment. A family medical history and questionnaire about lifestyle factors is important in helping assess cardiovascular risk.

Smoking cessation

Quitting smoking, or even cutting down, is one of the most important steps people can take to reduce their cardiovascular risk. In some cases nicotine patches or gum, or the antidepressant bupropion (Zyban) may be used to aid smoking cessation.

Heart-healthy diet

A healthy diet includes reduced amounts of fats and cholesterol. The NCEP recommends that 30% or less of total daily calories should come from fat. No more than 10% should come from saturated fat (7% or less if a person is at increased risk for heart disease). The diet should include no more than 300 mg cholesterol daily (200 mg for a person at increased risk for heart disease). Sodium consumption should be no more than 2,400 mg per day. The NCEP also recommends reduced alcohol consumption. (However, some studies suggest that a small amount of alcohol each day—especially red wine—may reduce cardiovascular risk).

Healthy weight

Weight loss can help lower LDL and triglyceride levels and increase HDL levels. However, if wasting is a problem it may be difficult to obtain adequate calories on a very low fat diet. It is important to consider the relative benefits and risks for each individual. If more calories are needed, it is better to obtain them in the form of unsaturated rather than saturated fat.

Increased physical activity Exercise can lower LDL and VLDL levels and raise HDL levels; it also can help lower blood pressure. Aerobic exercise works out the heart and lungs. Even moderate exercise—such as walking 30 minutes per day several times a week—can improve cardiovascular health. Note that anaerobic exercise such as weight lifting does not improve cardiovascular fitness.

from the State University of New York at Buffalo and colleagues analyzed data from 445 people treated with PI-based regimens. After 200 days of therapy, 32% of those taking indinavir had developed high blood pressure (140/90 or higher) compared with 19% of those taking nelfinavir and 18% of those not using PIs. After 600 days, the percentages were 53%, 36%, and 34%, respectively.

Fred Sattler, MD, from the University of Southern California at Los Angeles and colleagues compared data from 42 HIV positive individuals taking HAART who had lipodystrophy, 42 HIV positive people taking HAART who did not have lipodystrophy, and 13 HIV negative controls. After an average of 21 months, hypertension (over 140 diastolic, over 90 systolic, or both) was seen in 74% of those with lipodystrophy and in 48% of HIV positive people without lipodystrophy. Participants with an increased waist-to-hip ratio were significantly more likely to have high blood pressure. The authors suggested that elevated blood pressure may be linked to the constellation of metabolic disorders seen in people with HIV. They concluded that the occurrence of hypertension “portends an increased risk for myocardial infarction, stroke, renal failure, and peripheral arterial disease,” and recommended early identification and management.

Keith Henry, MD, of the University of Minnesota and colleagues reported at the February Retrovirus conference that HIV positive participants using indinavir were more likely than the general population to have high-risk levels of C-reactive protein, a chemical marker of chronic inflammation that is associated with increased cardiovascular risk.

Finally, Linda Bausserman, PhD, from Brown University in Providence, Rhode Island, and colleagues reported that HIV positive women had significantly elevated levels of cell adhesion molecules compared with HIV negative women, although there were no statistical differences in terms of type of antiretroviral therapy. Cell adhesion

molecules are believed to play a role in the development of atherosclerosis, and are associated with higher heart attack and stroke risk.

What Does It All Mean?

Practical Implications

What are the implications of the disparate and sometimes conflicting data on HIV disease, antiretroviral therapy, and cardiovascular disease? Will elevated blood fat levels, abdominal fat accumulation, diabetes, and high blood pressure in people taking HAART lead to an increased incidence of cardiovascular events, as is the case among those in the general population with similar risk factors? All evidence to date indicates that it is still too soon to know.

On the one hand, in the words of Pablo Tebas, MD, “there is not a very good biological reason to think that these elevations are not going to be associated with an increased risk of cardiovascular disease.” According to the Adult AIDS Clinical Trial Group (AACTG) Cardiovascular Disease Focus Group, “On the basis of precedent in other disease states, there is reason to believe that HIV treatment-associated changes in lipid levels are likely to result in some degree of increased cardiovascular risk. It appears likely that the chronic presence of traditional cardiovascular risk factors increases risk regardless of the etiology, and this same potential certainly exists during the long-term management of HIV-infected subjects.” As AACTG focus group members Oluwatoyin Falusi, MD, and Judith Aberg, MD, point out, “Even if [HIV positive] patients are not at increased risk for cardiovascular disease, they are at least at the same risk as HIV negative, age-matched persons with similar risk factors.”

Beyond studying risk factors, some researchers have looked for actual evidence of early cardiovascular disease in people with HIV. In the November 10, 2000 issue of *AIDS*, Paolo Maggi, MD, of

the University of Bari in Italy and colleagues reported that 29 of 55 study participants (nearly 58%) taking PIs showed evidence of carotid artery dysfunction compared with 7 of 47 PI-naïve participants (15%) and 7 of 104 HIV negative participants (7%). The carotid arteries in the neck supply blood to the brain, and plaques in these vessels are associated with strokes. In contrast, Michèle Depairon, MD, of CHUV University Hospital in

LDL—about 30%—was comparable to that in the population at large. The other participants with elevated total cholesterol had only high VLDL, which is believed to be less atherogenic (likely to lead to cardiovascular disease) because the particles are too large to deposit cholesterol in artery walls.

HAART has only been in use for six years, and cardiovascular disease generally takes years or decades to

“There is not a very good biological reason to think that these elevations are not going to be associated with an increased risk of cardiovascular disease.”



Lausanne, Switzerland, and colleagues found that while carotid and femoral (leg) artery plaques were significantly more common in HIV positive people (93 of 168, or 55%) compared with HIV negative people (26 of 68, or 38%), there was no independent association with PI use.

On the other hand, lipid level elevations in people taking HAART may not be quite as similar as many have assumed to hyperlipidemia in the general population. Stefan Mauss, MD, of the Center for HIV and Hepatogastroenterology in Düsseldorf, Germany, and colleagues presented results at the February Retrovirus conference suggesting that a closer look at cholesterol may be indicated. The researchers analyzed fasting blood samples from 187 HIV positive participants receiving different types of antiretroviral treatment. Overall, 45% had high total cholesterol levels; of these, 14% had elevated LDL levels, 16% had elevated LDL plus elevated very low-density lipoprotein (VLDL) levels, and 66% had elevated VLDL levels only. The rate of elevated

develop. The long-term impact of HIV infection and antiretroviral therapy on the heart and blood vessels is only beginning to be revealed. A majority of people receiving treatment for HIV still are relatively young. The complete picture may only emerge when larger numbers of people who have taken anti-HIV drugs for many years reach their fifties, the age at which cardiovascular problems typically begin to occur. Large, longitudinal cohort studies spanning many years will be needed to uncover definitive answers to the question of whether HIV infection and/or antiretroviral therapy increases the incidence of cardiovascular events in people with HIV.

Risk vs Benefit

Some researchers have attempted to quantify the increased risk of heart disease due to blood lipid elevations related to HAART, and to weigh this against the benefits of antiretroviral therapy. Using data from the Framingham Heart Study, Carl Grunfeld, MD, of the San Francisco Veterans Affairs Medical

Lipid-lowering drugs

Drugs that reduce high blood fat levels may be used if lifestyle modifications are not adequate. Studies in the general population have shown that cholesterol-lowering drugs successfully decrease total and LDL cholesterol levels and reduce the risk of cardiovascular disease. These drugs have not been thoroughly studied in people with HIV, but early results suggest they are effective. However, some lipid-lowering drugs can interact with antiretroviral drugs and should be used with caution.

- **Statins** are first-line therapy for high cholesterol in HIV negative people; they also may help reduce triglyceride levels. The Adult AIDS Clinical Trial Group (AACTG) Cardiovascular Disease Focus Group recommends starting with low doses of pravastatin (Pravachol) or atorvastatin (Lipitor), which are least likely to interact with PIs. Lovastatin (Mevacor), simvastatin (Zocor), and fluvastatin (Lescol) are metabolized by the same CP450 liver enzyme system as PIs, and concurrent use can lead to high drug levels and intensified side effects; these drugs are contraindicated with PIs. Statins may cause muscle toxicity; one drug in this class, cerivastatin (Baycol), was recently removed from the market for this reason.
- **Fibrates** are used to treat high triglycerides or hypercholesterolemia accompanied by high triglycerides. This class includes fenofibrate (Tricor) and gemfibrozil (Lopid). According to the AACTG focus group, these drugs are unlikely to interact with antiretroviral drugs, but this has not been well studied and they should be used with caution.
- **Bile sequestrants** such as cholestyramine (Questran) and colestipol (Colestid) are used to decrease cholesterol levels; however, in some cases these drugs have been associated with increased triglyceride levels, and their interactions with antiretroviral

drugs have not been well studied. The AACTG focus group discourages their use in people receiving HAART.

- **Nicotinic acid** (niacin) is also used to lower LDL cholesterol. Side effects include skin flushing and itching. The drug also can cause insulin resistance, and the AACTG focus group does not recommend it for people taking antiretroviral drugs that are themselves associated with insulin resistance.

Diabetes management

People taking HAART should have their blood sugar monitored regularly and be alert for early signs of diabetes such as frequent urination and increased hunger and thirst. To manage insulin resistance and diabetes, AACTG focus group members Oluwatoyin Falusi, MD, and Judith Aberg, MD, recommend that diet modification and increased exercise be tried first, followed by oral anti-diabetes agents such as the glitazone drugs and metformin (Glucophage). A recent study showed disappointing results for rosiglitazone (Avandia) in HIV positive people with lipodystrophy syndrome. Diabetes drugs should be used with caution in people taking antiretroviral drugs.

Blood pressure control

Diet modification and exercise should be the first steps in controlling hypertension. Sodium consumption can lead to high blood pressure, and the NCEP recommends no more than 2,400 mg per day. If these measures are inadequate, hypertension-reducing drugs—including ACE inhibitors, beta blockers, calcium channel blockers, diuretics, and vasodilators—may be used. According to the AACTG focus group, no class of antihypertensives is completely contraindicated with HAART, but calcium channel blockers should be used with caution due to potential interactions with PIs.

Complementary measures

Several dietary measures have been proposed to decrease cardiovascular risk, including increased consumption

Center calculated that cholesterol and triglyceride increases in people using PIs could be expected to lead to a small average increase in coronary heart disease—one case per 100 people over 10 years—but that this risk was outweighed by the benefits of HAART. However, in people with additional risk factors such as smoking, high blood pressure, male sex, age over 50 years, and/or family history of heart disease, the additional increase in cardiovascular events may be as high as 27 cases per 100 people over 10 years.

Matthias Egger, MD, of the University of Bristol in the UK also has attempted to predict the impact of HAART-related metabolic changes on heart disease risk. Dr. Egger applied relative risk figures from the Caerphilly Heart Disease Study to a cohort of 113 HIV positive people who had used PI-based regimens. After calculating absolute five-year cardiovascular risk for individuals with and without lipodystrophy, Dr. Egger estimated that anywhere between 10 and 200 people would have to be treated with HAART to produce a single additional case of coronary heart disease. He then compared this increase in relative risk to the benefits of HAART. In people with low CD4 cell counts and high viral loads, antiretroviral therapy greatly decreases rates of HIV disease progression and death. But in those with higher CD4 cell counts (over 350 cells/mm³) and lower viral loads (less than 5,000 copies/mL), the risk of HIV disease progression is already low, and HAART has less of an impact. Among the latter group, 100–200 people would need to receive treatment for three years in order for one person to benefit.

Putting it all together, Dr. Egger estimated, “For 30-year-old men who don’t smoke and have metabolic complications associated with lipodystrophy, 71 need to continue [antiretroviral] treatment for five years and only one of them will have a cardiac event. This will be an acceptable risk for most patients on HAART.” However, for older people with additional risk factors, the picture changes. For example, a 50-year-old HIV positive man who

smokes and has a high CD4 cell count and a low viral load may be more likely to develop coronary heart disease than to benefit from HAART. “While it’s clear that the benefits of HAART outweigh the risks of [coronary heart disease] for many patients, there are definitely some patients for whom the reverse may be true.”

While Dr. Egger concluded that, “the potential risk of long-term adverse effects, in particular coronary heart disease, cannot be ignored when making decisions on starting or delaying [antiretroviral] treatment,” others are more hesitant to consider forgoing HAART. According to Dr. Bozzette, “We don’t think fear of vascular complications should inhibit prescribing of antiretroviral medicines.” Although Dr. Holmberg believes that his findings in the HOPS study may reflect an early indication of a growing problem, he agrees that PIs should not be discarded due to worry about cardiovascular complications.

Prevention Is Key

As Dr. Egger’s estimates reveal, many factors besides drug-related metabolic abnormalities contribute to a person’s aggregate risk for cardiovascular disease. Studies in the general population have shown that elevated blood fat levels alone do not always lead to heart disease in people without other risk factors, and that people with several other risk factors may develop cardiovascular disease even in the absence of elevated blood lipids. And hyperlipidemia itself is much more likely to lead to cardiovascular disease in people with other risk factors such as older age, smoking, family history of heart disease, obesity, and sedentary lifestyle. In fact, several researchers including Drs. Depairon, Duong, and Fichtenbaum have concluded from their data that heart disease in people with HIV is more closely correlated with these traditional risk factors than with antiretroviral therapy. The more risk factors a person has, the more likely he or she is to experience cardiovascular problems—and the more likely to benefit from risk reduction measures (see sidebar on page 17).

Based on what is known to date, it appears that for many people using HAART the short-term risk of developing cardiovascular disease is relatively low. But as effective antiretroviral treatment extends the life expectancy of people with HIV, preventive measures become increasingly important. In the words of Marshall Glesby, MD, PhD, of Cornell University's Weill Medical College, "With the prolongation of survival associated with potent antiretroviral therapy, clinicians and patients now have the luxury of worrying about longer-term complications and comorbidities associated with HIV infection, such as chronic hepatitis and cardiovascular disease."

Although much remains to be learned about heart disease in people with HIV, experts agree that there are several steps that can be taken to decrease the likelihood of cardiovascular problems. Health-care providers should carefully monitor their patients' cholesterol, triglyceride, and blood glucose levels; regularly check blood pressure; and be on the lookout for manifestations that signal increased cardiovascular risk. People with HIV should make every effort to quit smoking, eat a healthy diet, lose excess weight, and exercise regularly. When appropriate, medications should be used to control elevated blood lipids, diabetes, and high blood pressure. If these measures are inadequate, people with HIV and their health-care providers may consider switching to a protease-sparing regimen or a newer PI that is less likely to cause metabolic abnormalities.

As Dr. Depairon notes, addressing modifiable risk factors has led to a significant decline in the incidence of heart disease among the general population, and "there is no evidence that HIV-infected individuals may benefit less from these interventions."

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of garlic, oats, soy products, brewer's yeast, calcium, niacin, and fish oils containing omega-3 fatty acids. These interventions are not well studied, but they present little risk if used as part of a healthy diet. Some research suggests that B vitamin supplements can help reduce blood levels of homocysteine, which is associated with increased cardiovascular risk. Studies suggest that another supplement, Cholestin, may work like a statin drug. Herbal remedies that may help lower cholesterol include red yeast rice, green tea, and guggal (a plant extract used in traditional Indian Ayurvedic medicine). Dietary supplements, herbs, and unusual diets should be discussed with a health-care provider. (Be aware that garlic supplements are known to interfere with certain PI drugs.)

Changes in antiretroviral therapy

Switching to a protease-sparing regimen or to a PI that is less likely to cause metabolic abnormalities may be done in conjunction with or instead of lipid-lowering drugs. Drs. Falusi and Aberg recommended that providers initially attempt to manage hyperlipidemia without switching HAART regimens, especially if the person is adherent, is otherwise tolerating their drugs, and has good virologic control. In people with existing cardiovascular risk factors, however, it may be prudent to start with or switch to a regimen with fewer metabolic side effects.

Blood Lipids

Cholesterol is a waxy, fatty substance that circulates in the blood. It is an important component of cell membranes, certain hormones, vitamin D, and bile acids that help digest fat. Cholesterol is produced by the liver and also is present in foods such as organ meats and egg yolks. Elevated total cholesterol (hypercholesterolemia) is known to increase the risk of cardiovascular disease. However, it is more useful to look at the individual components that make up total cholesterol:

- **High-density lipoproteins (HDL)**—so-called “good cholesterol”—help clear cholesterol from the body and reduce the risk of cardiovascular disease.
- **Low-density lipoproteins (LDL)**—so-called “bad” cholesterol—carry cholesterol in the bloodstream, where it may be deposited in the walls of the arteries leading to atherosclerosis.
- **Very low-density lipoproteins (VLDL)** appear to be less atherogenic (likely to promote atherosclerosis) than LDL cholesterol.

Triglycerides are another type of fat in the blood. After eating, energy that is not needed immediately is converted into triglycerides and transported to fat cells for storage. An elevated blood triglyceride level (hypertriglyceridemia) has been associated with increased cardiovascular risk, especially when high cholesterol is also present; however, it is not clear whether high triglycerides are an independent risk factor in the absence of other factors. Very high triglyceride levels can cause pancreatitis (inflammation of the pancreas).

The National Cholesterol Education Program (NCEP) has set forth levels of cholesterol and triglycerides that are associated with heart and circulatory disease. Studies have shown that people who have a total cholesterol level of 300 mg/dL or higher are about five times more likely to have a fatal heart attack than those who have a total cholesterol level below 200 mg/dL. The 1984 Lipid Research Clinics-Coronary Primary Prevention Trial showed that lowering LDL cholesterol significantly reduces the occurrence of heart disease.

For more information on high cholesterol see:
www.nhlbi.nih.gov/health/public/heart/chol/wyntk.htm

CHOLESTEROL AND TRIGLYCERIDE LEVELS

Total cholesterol

less than 200 mg/dL	desirable
200–239 mg/dL	borderline high
240 mg/dL or greater	high

LDL cholesterol

Less than 100 mg/dL	optimal
100–129 mg/dL	near or above optimal
130–159 mg/dL	borderline high
160–189 mg/dL	high
190 mg/dL or greater	very high

HDL cholesterol

Less than 40 mg/dL	low
40–60 mg/dL	normal (acceptable)
60 mg/dL or greater	high (desirable)

Triglycerides

Less than 150 mg/dL	normal
150–199 mg/dL	borderline high
200–499 mg/dL	high
500 mg/dL or greater	very high

NCEP RECOMMENDATIONS

The NCEP recognizes LDL cholesterol as the primary target for interventions aimed at reducing cardiovascular risk. The more additional risk factors people have, the more likely they are to benefit from cholesterol reduction. The NCEP offers the following recommendations for reducing LDL cholesterol:

Status	LDL goal	Make lifestyle changes if:	Consider treatment if:
Prior heart disease	less than 100 mg/dL	greater than 100 mg/dL	greater than 130 mg/dL
No heart disease and 2 or more risk factors	less than 130 mg/dL	greater than 130 mg/dL	greater than 160 mg/dL
No heart disease and 1 or no risk factors	less than 160 mg/dL	greater than 160 mg/dL	greater than 190 mg/dL