A bizarre and unexpected set of vascular and lipid syndromes appears to afflict an as-yet-undetermined percentage of HIV-infected patients taking what is called highly active antiviral therapy. The syndromes, the subject of several presentations at the 12th World AIDS Conference in Geneva, Switzerland, were among the most serious side effects of the therapy that has revolutionized AIDS treatment in industrialized nations.

HAART, as the treatment is more generally known, usually consists of 2 nucleoside reverse-transcriptase inhibitors and a protease inhibitor. Usually, 1 of the reverse-transcriptase inhibitors crosses the blood-brain barrier. These drugs interfere with the life cycle of the retrovirus at the point at which RNA is translated into the DNA that can be incorporated into the genetic blueprint of the cell. Protease inhibitors work later in the life cycle of the virus, preventing release of virions from the cellular machinery that has been subverted into a virus factory.

The syndrome consists of a lipodystrophy, with fat disappearing from the limbs and distant areas of the body while concentrating in the trunk. There are often unusual fat deposits in the abdomen and a “buffalo hump” of fat in the upper shoulders. There were also some levels of serious insulin resistance and, in some cases, frank diabetes mellitus associated with the syndrome. Of even greater concern are high cholesterol and triglyceride levels—above where most physicians in the world would begin to treat, said David Cooper, MD, immediate past president of the International AIDS Society and a practicing physician at St Vincent’s Hospital in Sydney, Australia.

The nucleoside reverse-transcriptase inhibitors block the action of the retroviral enzyme that translates the RNA of the virus into DNA that can integrate into the genome of the cell. But the protease inhibitors, only recently approved for general use, are the reason that AIDS treatment has gone from abysmal to fairly effective in those patients who can follow the complicated and often onerous regimens. However, the protease inhibitors are also the source of the lipid problems seen in HAART-treated patients.

Protease inhibitors interfere with the end of the viral life cycle, when the virus is ready to release virions from the cells. It seems bizarre that they are somehow also involved in lipid changes that have, at times, been life threatening in the 2 years since they came into widespread use.

Cooper said that about 60% of his patients have suffered the syndrome in some form but that it is severe in only 10% to 20%. The factors most often associated with the syndrome are the length of time the patient has been taking a protease inhibitor and the type of protease inhibitor. Ritonavir, 1 of the first protease inhibitors developed, is probably 1 of those most likely to be associated with the problem, although all are to some degree, Cooper said.

“Only 7% of patients taking protease inhibitors had normal lipid values,” said Andrew Carr, MD, one of Cooper’s colleagues. In describing 116 patients taking the protease-containing regimen, Carr said only 18% reported lipodystrophy 22 months after beginning the therapy. Of 76 patients who received glucose tolerance tests, 23% had abnormal values, he said.

Before treatment, 59% of the patients who had never before received a protease inhibitor had cholesterol and triglyceride values below the normal, healthy value, said Carr. After treatment, only 7% of protease patients had normal lipid values.

Krista Dong, MD, of Brown University said 20 women in her study reported changes in their bodies, with some developing truncal obesity and a buffalo hump. However, she said, levels of cortisol were found. “In HIV-negative persons, this body habitus is associated with dyslipidemias and cardiovascular mortality,” she said. “Most studies have reported these effects exclusively in men.”

Although some women had changes in cholesterol and triglyceride levels, “the most frequent changes in habitus were increases in stomach and breast size. The gains in breast size were big enough to cause 1 woman to have to purchase dresses that were 2 sizes larger than she usually wore,” said Dong. The waist-to-hip ratio was still 0.8%, she said. “Many had a BMI [body mass index] associated with obesity.”

Cholesterol levels were elevated in most patients, and HDL levels were lowered, said Dong. Triglycerides were elevated 33%. Dong said the serum lipid abnormalities and body fat changes are apparently a frequent side effect of HAART therapy. “In non–HIV-infected people, these levels have been associated with risk of angina, stroke, and diabetes,” she said. She advised long-term studies to determine if these kinds of sequelae can be expected in people taking these therapies as well.

Although no one knows how serious these changes are or if they will have the same effect that increased values have in normal people, some physicians have reported anecdotal cases of serious problems. In a recent issue of The Lancet, Bruno Gallet, Marc Pulik, Philippe Genet, Pierre Chedin, and Michel Hiltgen, of the departments of cardiology, hematology, and AIDS and endocrinology at Victor Dupouy Hospital in Argenteuil, France, reported 2 cases of heart attack and angina while patients were receiving HAART treatment.
One was a 33-year-old HIV-infected man who was admitted to the hospital because of inferoposterior wall myocardial infarction. He had been taking the protease inhibitor ritonavir for 14 months previously, along with stavudine and didanosine—a typical 3-drug cocktail. However, he also smoked 1 pack of cigarettes daily.

Cholesterol and triglyceride levels were elevated, and coronary arteriography showed a subtotal occlusion of the right coronary artery. PTCA was successful, but 4 months later, the patient had a recurrent myocardial infarction. Coronary arteriography showed reocclusion, and a second PTCA was done with coronary stenting.

Case 2 involved a 32-year-old HIV-infected man who was admitted because of anterolateral wall myocardial infarction. He had been treated for 18 months with indinavir, lamivudine, and stavudine. Plasma HIV RNA was 649 copies per milliliter 5 months before admission. He smoked 40 cigarettes daily. On admission, cholesterol and triglyceride values were normal. Peak serum creatine kinase was 290 U/L. Coronary arteriography showed a 90% stenosis of the left anterior descending artery, and PTCA with coronary stenting was successful.

A 54-year-old HIV-infected man presented with angina. He had been treated for 21 months with lamivudine and ritonavir, and saquinavir was added 13 months before he arrived at the hospital. Initiation of protease inhibition was followed by a striking rise in cholesterol and triglyceride levels 11 months before presentation, leading to treatment with fenofibrate. An exercise test induced chest pain with ischemic ST-segment depression. When the patient declined coronary arteriography, acebutolol, transdermal nitroglycerin patches, and aspirin were started. Angina resolved, and an exercise test while the patient was taking medication was negative. (Lancet. 1998;351:1958–1959.)

Although the news of the side effects of the treatment was greeted with alarm at the conference, Cooper warned that what he has seen does not warrant the removal of patients from protease-containing therapy. More research needs to be done into why patients are suffering cardiovascular-related complications, he said.

He said the cardiovascular complications need to be treated, but the mechanism of the problem must be completely elucidated before a determination can be made about which drugs should be used. There is some indication that the statins are not effective and might act synergistically with the protease inhibitors.

“It’s risk-benefit,” said Cooper. “These drugs [protease inhibitors] stopped people from checking out of the planet.” It’s a matter of treating the problems, according to Cooper, not a matter of taking people off life-saving treatment.

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Circulation Newswriter
Vascular and Lipid Syndromes in Selected HIV-Infected Patients
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Circulation. 1998;98:829-830
doi: 10.1161/01.CIR.98.9.829

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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