Understanding Lipodystrophy

Abnormal body fat distribution includes visceral fat and a hard belly.

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People living with HIV—nearly half are now 50 or older—are prone to a variety of health conditions as they age. Research has shown that HIV-positive people may experience problems such as cardiovascular disease and non-AIDS-related cancers as much as a decade earlier than their HIV-negative peers.

One of these problems is lipodystrophy, or abnormal body fat distribution. Although not limited to older people, the chances of developing lipo increase with age. These days, lipodystrophy is most often seen among long-term survivors who took older antiretroviral drugs with more side effects.

Lipodystrophy is often accompanied by metabolic complications, such as diabetes, high cholesterol and hypertension, which raise the risk of cardiovascular disease and other health problems. What's more, it can lead to emotional distress, reduced adherence to HIV treatment and poorer quality of life. (See "The Stigma of Lipo," for more.)

What Is Lipo?

Lipodystrophy is an umbrella term that covers both fat loss (known as lipoatrophy), especially in the face, limbs and buttocks, and fat accumulation (known as lipohypertrophy), especially in the belly and breasts. Lipodystrophy was once thought of as body fat redistribution, but it is now understood that these conditions are independent—rather than reflecting a shift of fat from one area to another—and have different causes.

"While an individual may experience both, they are almost certainly separate processes," says Marshall Glesby, MD, PhD, a professor of medicine and health care policy and research at Weill Cornell Medical College in New York City.

A gaunt face with sunken cheeks was once a common sign of AIDS, attributable both to overall wasting and the side effects of certain early medications. Although these drugs are no longer widely used and are not recommended in the United States, the facial fat loss they caused may never be fully reversed.

The advent of protease inhibitors and modern combination antiretroviral therapy in the mid-1990s finally enabled people to maintain control of their HIV. But soon after the new drugs arrived, many people who took them started seeing unexpected new health problems, including unusual body

shape changes.

People with HIV may experience weight loss as their immune function declines, followed by weight gain as they return to health after starting treatment. But HIV-related fat accumulation goes beyond that. (See "Standing Up," for more.)

Some people with HIV experience a buildup of fat around the midsection that may have little connection with how much they eat or exercise. Both women and men may experience breast growth (known as gynecomastia when it occurs in men), or they may develop a fat pad on the upper back known as a "buffalo hump." A combination of fat loss and gain can give the appearance of a potato on toothpicks.

"Lipoatrophy is generally something that we see in people who were treated with older drugs like stavudine [Zerit, or d4T] and zidovudine [Retrovir, or AZT]. It is rarely seen in people who have never been on these older drugs but is also not a problem that typically goes away," Glesby explains. "Lipohypertrophy, in contrast, is something that still occurs and in many cases may be similar to the abdominal obesity and metabolic syndrome that is relatively common in the general population."

In recent years, there's been a growing recognition that weight gain—often as much as several pounds—is common among people starting treatment with modern meds. Black women living with HIV appear to be particularly susceptible. Although this can occur after starting any type of antiretroviral drug, integrase inhibitors and the newer form of tenofovir (tenofovir alafenamide, a component of Descovy and other combination pills) are frequently implicated.

But general weight gain and normal obesity are not the same as lipohypertrophy.

Fat buildup can occur in two different patterns, one of which is linked to more health risks than the other. Subcutaneous fat builds up beneath the skin, often around the abdomen, hips, buttocks and thighs. It is soft and squishy, hence the nickname "love handles." People with mostly subcutaneous fat often have a pear-shaped body.

Visceral fat builds up inside the abdomen and surrounds the internal organs. This extra fat pushes up against the muscles of the abdominal wall, resulting in a taut, hard belly. People with mostly visceral fat typically have an apple-shaped body and a larger waistline in relation to the size of their hips. This type of fat can be harder to reduce with diet and exercise.

While obesity and lipo both lead to large abdomens, people with normal obesity usually have pinchable fat under the skin and rolls of soft fat on their belly. HIV-associated lipohypertrophy, in contrast, is distinguished by the kind of fat that causes a hard belly.

In some cases, fat buildup can be severe enough to cause pain, limit movement or interfere with sleep. A protruding hard belly is especially worrisome because of its link to other health problems, including heart disease. And along with its physical effects, lipo can also lead to a poor body image and loss of self-esteem.

What Causes Lipo?

Four decades into the HIV/AIDS epidemic, experts still do not fully understand the causes of lipodystrophy or the best ways to manage it.

Older individuals are more likely to develop lipo. Women more commonly have fat buildup in the belly or breasts. People who have lived with HIV or used antiretrovirals longer, those who have a high viral load before starting treatment and those with low CD4 counts—especially if they ever had advanced immune suppression with very low CD4s—are also at greater risk.

Fat buildup was initially blamed on early protease inhibitors—it was once dubbed "Crix belly" after Crixivan (indinavir), one of the first drugs in this class—which can cause metabolic abnormalities that contribute to fat gain. But it soon became clear that this was not the whole story.

"We do not fully understand the causes of lipohypertrophy," Glesby says. "Unlike lipoatrophy, there are not clear associations with use of specific antiretroviral drugs or classes of drugs. There are multiple hypotheses about the causes."

HIV infection itself can lead to body fat changes. The virus can trigger chronic inflammation, raising the risk of health conditions including heart, liver and kidney disease. Inflammatory cytokines, or chemical messengers produced by immune cells, can alter metabolism in ways that promote fat buildup.

Fat doesn't just take up space in the body. Rather, it is active tissue that produces cytokines and hormones of its own. Hormones made by fat tissue include estrogen, adiponectin (which regulates glucose and fat metabolism) and leptin (which controls appetite). Some of the cytokines released by fat cells can cause further inflammation, which, in a vicious cycle, can lead to more fat buildup.

HIV-related lipo often goes hand in hand with other metabolic abnormalities, such as insulin resistance, diabetes, high cholesterol and hypertension, collectively known as metabolic syndrome. It has been linked to health problems ranging from cardiovascular disease to dementia as well as to a higher risk of death. Visceral fat can sometimes accumulate inside the liver and other organs. Over time, fatty liver disease can lead to cirrhosis and liver cancer.

HIV can also affect hormones. For example, it has been linked to lower production of growth hormone by the pituitary gland in the brain or reduced responsiveness to it. This hormone helps build muscle and break down fat, and low levels can lead to excess belly fat.

Some experts think the seesaw effect of immune system damage caused by HIV, followed by immune reconstitution after starting treatment, also contributes to lipo—which helps explain why it occurs more often in those who have had low CD4 counts. Alterations in the gut microbiome related to HIV or antiretroviral drugs may also play a role, according to Glesby.

In addition, genetic traits, lifestyle factors such as diet and exercise, and being overweight or having normal obesity can affect the likelihood of developing lipodystrophy. But for reasons that

remain unclear, many people with HIV who appear to be at risk never develop lipo.

Managing Lipo

Suppressing HIV viral load, getting CD4 counts back into normal territory and adopting a healthy lifestyle are great for overall health, but they may not fully reverse body fat changes due to lipo.

People starting antiretrovirals for the first time or switching regimens should have their body weight and fat distribution monitored regularly, as it's easier to address lipo early rather than trying to reverse belly fat buildup later.

The first step in managing lipodystrophy is a comprehensive checkup and discussion with your doctor. This can help determine which specific factors are contributing to your body fat changes and distinguish lipo from other conditions, including normal obesity. Your clinician will want to know about your HIV treatment history, diet, exercise, sleep, smoking, alcohol consumption and recreational drug use.

Your doctor will likely feel your belly to see whether it's hard or soft and measure your waist and hips to calculate your waist-to-hip ratio. Having a bigger waistline relative to the size of the hips can be a sign of lipo. CT, MRI or DEXA imaging scans may help show how fat is distributed in the body.

Your clinician may run blood tests for metabolic or hormonal abnormalities. These include tests for blood sugar (glucose), lipids such as cholesterol and triglycerides, and certain hormones. A sluggish thyroid can cause weight gain. Cushing syndrome, caused by high levels of the stress hormone cortisol, can lead to body fat changes that look like lipo. These conditions can be treated with medications.

Your provider will likely suggest lifestyle changes, such as improving your diet, getting more exercise, getting enough sleep and quitting smoking. A combination of regular cardiovascular exercise and strength training to build muscles is key. Experts recommend at least 30 minutes of moderate-intensity activity at least five times a week. Stick with a diet and exercise program for at least six months to give it time to work.

"Dietary modifications and exercise are important as general health measures to reduce cardiovascular risk, and they may specifically have an impact on lipohypertrophy, though there is a shortage of good data on this," Glesby says. "Those with access to a registered dietitian could benefit from devising a tailored, balanced diet to reduce calories."

However, lifestyle changes alone are often not enough to alleviate lipodystrophy. If that's the case, adding medical treatments might help.

The medications Egrifta (tesamorelin) and Serostim (somatropin) may be helpful, especially if lipo is related to low growth hormone levels.

The Food and Drug Administration (FDA) approved Egrifta in 2010 to reduce excess belly fat in

HIV-positive people with lipodystrophy. It’s self-administered as an injection under the skin of the belly, usually once daily. The newer formulation approved last year, Egrifta SV, is easier to prepare, does not require refrigeration and can be administered with a smaller needle.

Egrifta is a growth hormone–releasing factor analogue, meaning it mimics a natural hormone produced in the brain that triggers the release of growth hormone. Clinical studies showed that it reduced visceral hard belly fat by up to 18%, on average; some people have a better response than others. However, lost belly fat usually returns within a few months after stopping treatment. Recent research has shown that Egrifta can also reduce liver fat in HIV-positive people with non-alcoholic fatty liver disease, but it is not approved for this purpose.

The older drug Serostim is a synthetic version of growth hormone approved by the FDA in 1996 to treat HIV-related wasting. Studies suggest it may also reduce visceral abdominal fat. Like Egrifta, it is administered as a daily injection.

Other medications may be used to manage the metabolic problems that often accompany lipodystrophy and reduce the risk of cardiovascular disease and other health problems. For example, Glucophage (metformin) may be prescribed to control blood sugar, and statins may be used to lower cholesterol levels. Some studies have found that Glucophage may help reduce visceral belly fat as well.

Surgical approaches such as liposuction, which uses a suction technique to remove fat tissue, may be an option for reducing excess breast fat or a buffalo hump. But it is not a safe way to remove visceral fat deep within the abdomen. Breast reduction surgery is another option for those whose breasts have swelled enough to cause pain or limit movement.

The cost of medications and surgery can be a barrier, as many insurers consider them to be cosmetic. The manufacturers of Egrifta and Serostim offer patient assistance programs to help cover medication costs and insurance co-pays.

Managing lipodystrophy can be challenging, and you and your doctor may have to try a variety of approaches—or a combination of them—before finding a solution.

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