Can lipodystrophy improve over the long term?

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Shortly after highly active antiretroviral therapy (HAART) became available in high-income countries in the mid-to-late 1990s, reports emerged of strange changes in body shape among some HAART users. These changes can be divided into two basic types:

- lipoatrophy – loss of the fatty layer just under the skin (subcutaneous fat). This can cause the cheeks to have a sunken appearance and veins can appear to bulge in the limbs
- lipohypertrophy – buildup of fat in the belly, breasts (in women) and, in rare cases, the back of the neck.

Some people may experience one of these fat-related problems while others may have both processes taking place at the same time. Additionally, inside the body, other changes, such as problems managing blood sugar levels and increased cholesterol and other fatty substances in the blood, are taking place. Together, all of these physical and biochemical changes are called the HIV lipodystrophy syndrome.

When HIV-related lipoatrophy first appeared, it was blamed on the newest family of anti-HIV drugs at the time —protease inhibitors. However, much research in the past 10 years suggests that exposure to two drugs in particular, d4T (stavudine, Zerit) and, to a lesser extent, AZT (zidovudine, Retrovir and in Combivir and Trizivir), is linked to the problem of fat wasting.

Nowadays, the use of d4T is generally shunned in high-income countries and instead other drugs are preferred, such as the following:

- Truvada – (tenofovir + FTC)
- Kivexa – (abacavir + 3TC)

Researchers in France have been analysing long-term data collected from men with HIV-related lipodystrophy. Their findings suggest that lipodystrophy can improve for some men. However, the improvement is generally slow and modest.

Study details

Researchers in Southern France at hospitals in Cahors and Toulouse have been collecting health-related information from HIV-positive men who were patients at local clinics. As part of regular care, these men received occasional low-dose X-ray scans called DEXA. This type of scan is useful for objectively assessing changes in body composition—fat, muscle, bone and so on. Using the results from DEXA scans and other information in the medical charts of the men, the research team assessed changes in body composition that occurred over an average of four years.

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

- age – 46 years
- length of time HIV positive – 10 years
- current CD4+ count – 495 cells
- lowest-ever CD4+ count – 206 cells
- body mass index (BMI), a simple way of assessing a person’s weight relative to their height – 23

Results—four years later
In analysing the DEXA scans and other tests over four years, here are some of the changes researchers found:

- total body fat increased by 1.3 kg (almost 3 pounds)
- fat in the trunk of the body increased by a bit more than a half-kilo (600 grams or 1.3 pounds)
- fat in the lower limbs increased by 300 grams (more than half a pound)
- BMI was stable
- the density of bones decreased

Before participants had their first DEXA scan, 85% had received AZT and 79% had received d4T. But over the course of the study, 55% of participants used AZT and 23% used d4T.

In comparing data from everyone, researchers found that some participants had improvements in lipodystrophy (58%) but others did not. So they conducted further analyses to find possible reasons for this.

Taking many factors into account, researchers found that the following factors were statistically linked to improvements in lipodystrophy:

- having a high CD4+ cell count
- having a high ratio of the proportion of trunk fat to the proportion of lower limb fat
- a greater interval between DEXA scans

The longer AZT was used in this study, the greater the risk for lipodystrophy worsening.

**Putting it in perspective**

1. In this French study, a shift away from the use of thymidine analogues (d4T and AZT) was linked to increased fat in the limbs in some participants. According to the researchers, this fat was very likely subcutaneous fat. It suggests that in some HIV-positive people lipoatrophy may be partially reversed. However, the average person is not likely to notice an increase of 300 grams (less than one pound) of fat distributed over two legs over a period of four years. This change also suggests that any improvement in fat is a slow process.

2. The sooner doctors switched patients from thymidine analogues to safer nukes, the greater the likelihood that an increase in subcutaneous fat occurred.

3. The researchers also found that lipoatrophy and lipohypertrophy occurred together. This goes against previous findings that suggested that these two events are separate.

4. A large proportion of participants (40%) had thin bones—osteopenia or its more severe form, osteoporosis. Decreases in bone density occurred whether or not lipodystrophy improved.

**Bear in mind**

The French study had several important limitations, as follows:

- It was a retrospective study, meaning it looked back on already collected data. Such studies are prone to cause biased interpretation of events. Retrospective studies may be faster and cheaper to conduct than other study designs but their findings need to be confirmed in a clinical trial of a more robust design.
- The prescription of nukes in this study was not randomly assigned or in any way controlled, as it would be in a prospective clinical trial. This lack of randomization adds another layer of potential bias when interpreting results.
- Only adult males were enrolled in this study, so its conclusions may not apply to women and children.
- There was no information provided about co-infections such as hepatitis C and the study’s findings may not apply to co-infected people.

Despite all of these potential weaknesses, the French study appears to be the longest published review of DEXA scans used for assessing changes in HIV-related lipoatrophy. Its findings will hopefully stimulate other researchers to conduct a different study to confirm and extend the French findings over a longer period.

**Surprising results from trial ANRS 136**

In France, an ongoing study called ANRS 136 (Monoi) randomly assigned participants to darunavir-ritonavir-based HAART or darunavir-ritonavir monotherapy. Darunavir is sold under the brand name Prezista.
After 48 weeks, 8 out of 74 people assigned to HAART developed fat wasting (lipoatrophy) vs. 1 out of 67 people assigned to darunavir-ritonavir monotherapy. Among participants who received HAART, the following nukes were used:

- tenofovir + FTC (Truvada) - 5 people
- 3TC + abacavir (Kivexa) - 1 person
- AZT + 3TC (Combivir) - 2 people
- 3TC (lamivudine) + ddI (didanosine, Videx EC) - 1 person

Although the number of people with lipoatrophy in the Monoi study is small, the finding with Truvada and Kivexa is surprising because these nuke combinations are generally perceived as safe and not associated with lipoatrophy. Longer results from ANRS 136 are awaited to see if there continues to be a difference between participants who use nukes and those who do not.

—Sean R. Hosein

REFERENCES:


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