Leading to lipodystrophy

In high-income countries, many anti-HIV therapies are available for sale. These can be divided into four classes as follows:

Nukes (nucleoside analogues):

- 3TC – lamivudine (Epivir)
- ABC – abacavir (Ziagen)
- AZT – zidovudine (Retrovir)
- ddI – didanosine (Videx)
- d4T – stavudine (Zerit)
- FTC – emtricitabine (Emtriva)

Nucleotide analogue:

- tenofovir (Viread)

Although tenofovir is a nucleotide analogue, it is usually regarded as another nuke.

Nukes are often co-formulated into combinations that are together in one pill, such as the following:

- AZT + 3TC – Combivir
- 3TC + ABC – Kivexa
- AZT + 3TC + ABC – Trizivir
- FTC + tenofovir – Truvada

Non-nukes:

- efavirenz (Stocrin, Sustiva)
- nevirapine (Viramune)

Under development are the following non-nukes:

- TMC125 (etravirine)
- TMC278 (rilpivirine)

Protease inhibitors:

These days, most protease inhibitors are taken together with a small dose of another protease inhibitor, ritonavir (Norvir). The reason for this is that ritonavir helps delay the breakdown of the other protease inhibitor (PI), leading to high and prolonged levels of this other drug in the blood. In practice, this means that most PIs can be taken once or twice daily. The following PIs are generally available in high-income countries:

- fosamprenavir (Telzir)
- atazanavir (Reyataz)
- darunavir (Prezista)
- indinavir (Crixivan)
- lopinavir + ritonavir (Kaletra, Aluvia)
- nelfinavir (Viracept)
- ritonavir (Norvir)
- saquinavir (Invirase)
tipranavir (Aptivus)

**Fusion inhibitor:**
So far only one fusion inhibitor is available and it is injected twice daily.

- T-20 – enfuvirtide (Fuzeon)

**From AZT to HAART**
The first anti-HIV drug, AZT, was introduced in the late 1980s. In the early to mid-1990s, several other nukes were released, including ddi, d4T and 3TC. In that time, these drugs were used either on their own, as monotherapy, or together with another nuke. Compared to the combinations used today, monotherapy with a nuke was mildly useful for a short period of time. Indeed, before HAART became available, survival with AIDS was relatively short and deaths from life-threatening infections were common.

However, around 1996 a new class of drugs called protease inhibitors became available. When PIs and other anti-HIV drugs are used to treat HIV/AIDS (often a combination of at least three drugs), this is called highly active antiretroviral therapy (HAART). For the first time, prolonged recovery from previously hard-to-treat infections was possible.

**Enter lipodystrophy**
In the late 1990s, as more PHAs began to live longer, a strange collection of signs and symptoms called the lipodystrophy syndrome emerged. Features of this syndrome involve changes in body shape as well as changes to the biochemistry of the blood. These changes can include the following:

- lipoatrophy – loss of subcutaneous fat (the fatty layer under the skin). Lipoatrophy causes a sunken appearance in the face, while the arms and legs also lose fat and can look thinner. Also, veins in the limbs appear to bulge because the subcutaneous fatty layer has disappeared.
- lipohypertrophy – fat gain. Lipohypertrophy can make women’s breasts larger and can cause both men and women to have bigger bellies.

Biochemical changes in the blood can also occur as a result of lipodystrophy, including the following:

- increased levels of sugar (glucose)
- increased levels of insulin

These changes suggest that the body is having difficulty keeping blood sugar within its normal range and that cells are beginning to resist the effects of insulin (insulin resistance). Left unchecked, these changes can lead to diabetes.

Other changes in blood include the following:

- increased levels of fatty substances, such as cholesterol and triglycerides
- increased levels of so-called “bad” cholesterol (LDL-c)
- decreased levels of so-called “good” cholesterol (HDL-c)

These changes in lipids increase the risk of cardiovascular disease.

Most distressing for many PHAs are the changes in appearance caused by lipoatrophy. At first, this was blamed on the use of protease inhibitors, as these drugs were introduced shortly before lipodystrophy in general and lipoatrophy in particular became noticeable. However, after much research, it became clear that fat wasting was linked to exposure to d4T and, to a much lesser extent, AZT. Both of these drugs are called thymidine analogues.

Treatment guidelines, first in the UK and then later in the US, now suggest that, at least for initial therapy, use of d4T be avoided so as to minimize the likelihood of lipoatrophy developing.

**An unexpected result**
At the 14th CROI, an unexpected development occurred. Results from two long-term clinical trials suggest that exposure to the non-nuke efavirenz can increase the risk of lipoatrophy.

The fact that two separate studies, one of which was relatively large, have found this result is disturbing and suggests that the relationship between efavirenz and fat wasting is not a statistical error or related to a fluke. Details about these studies as well as possible reasons that efavirenz might affect the health of fat cells appear later in this...
REFERENCES:


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