Efavirenz and fat wasting—what might be happening?

Until very recently, fat wasting in HAART users was blamed on exposure to the drugs d4T and/or AZT, prolonged HIV infection or a combination of these. However, clinical trial results from the 14th CROI as well as test-tube studies conducted in France raise concerns about an additional drug—efavirenz—when it comes to the loss of subcutaneous fat.

According to laboratory experiments from France, efavirenz impacts the health of fat cells in a number of ways. This drug profoundly affects the ability of fat cells to produce some proteins that they need in order to grow and mature. Efavirenz does this by apparently suppressing the activity of key genes inside fat cells that produce these proteins.

In ACTG trial 5142 (reported earlier in this issue of TreatmentUpdate) there were three regimens tested as follows:

- lopinavir/r + efavirenz
- lopinavir/r + 2 nukes
- efavirenz + 2 nukes

Severe fat loss after two years was found in the following proportion of participants:

- efavirenz + 2 nukes – 32%
- lopinavir/r + 2 nukes – 17%
- lopinavir/r + efavirenz – 9%

A question that immediately arises is: Why did the combination of lopinavir/r + efavirenz result in the lowest level of lipoatrophy? Part of the answer may be that no nukes, particularly thymidine analogues such as d4T or AZT, were present. Also, test-tube research done in Canada and France suggests that ritonavir may be able to stimulate the growth of fat cells and, perhaps, counter the effect of efavirenz. This requires further laboratory study with experiments on fat cells, comparing the effect of lopinavir, ritonavir and efavirenz.

Nevirapine, the other licensed non-nuke, does not appear to cause any increased lipoatrophy, at least in one study.

Hopefully, investigations will begin looking into the effect of the experimental non-nukes TMC125 and TMC278 on fat wasting.

The fact that two clinical trials have found a significant loss of subcutaneous fat associated with the use of efavirenz is not a chance finding. The next step is unclear. Efavirenz is a potent and popular part of HAART, so the findings from ACTG 5142 may not be readily accepted by some physicians and their patients. Regulatory and research agencies could do the following:

- Convene an expert panel to assess the findings from ACTG 5142 and other studies on lipoatrophy and efavirenz.
- Initiate laboratory research to further study the underlying basis for the findings from ACTG 5142.
- Consider another clinical trial to confirm or refute ACTG 5142’s results.

REFERENCES:


2. Cameron DW, da Silva B, Arribas J, et al. Significant sparing of peripheral lipoatrophy by HIV treatment with LPV/r
+ ZDV/3TC induction followed by LPV/r monotherapy compared with EFV + ZDV/3TC. Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections, February 25–28, 2007, Los Angeles, USA. Abstract 44LB.


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