Author's response to reviews

Title: Persistence of lipoatrophy after a four-year long interruption of antiretroviral therapy for HIV1 infection: case report

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Reply to referees' comments

Referee ndegrees 1

1. Minor Essential Revisions at Abstract line 3: "t is it" and Reference 12: "cells/ml is cells/microl" were performed as recommended.
2. We agree with the Discretionary revision at Background line 7. The previous sentence "Objective measurements of fat deposits at affected sites by dual-energy X-ray absorptiometry or computerized tomography lend little support to clinical evidence; the diagnosis of lipodystrophy relies essentially on concordant patient's and physician's evaluation [3-5]." was therefore changed with this new sentence: "Complex methods for objective measurements of fat deposits at affected sites involve use of Dual-energy X-ray absorptiometry, Magnetic Resonance Tomography or CT scans. These methods, however, are costly and not always feasible in routine clinical practice. Moreover, they lack adequate standardization, so that the diagnosis of lipodystrophy more frequently relies on concordant patient's and physician's evaluation [3-5]."
3. Discretionary revisions at Background line 16 and 17 were agreed. The sentence in the text: "Combined or severe abnormalities, however, develop only in 5 to 20% of affected patients [3-5, 6], more frequently in older patients, females, patients starting therapy for advanced HIV infection and in patients taking stavudine and/or indinavir as components of HAART [6-8]." was accordingly changed with this new sentence: "Combined or severe abnormalities, however, develop only in 5 to 20% of affected patients [3-5, 6], more frequently in older patients, females, patients with more advanced HIV disease and a longer exposure to antiretroviral drugs, especially stavudine and/or indinavir [6-8]. As to the evolution over time of the body fat abnormalities, evidence has been gathered that once body changes become clinically evident, they generally tend to remain or worsen, and improve in only a small minority of cases [9]."
4. In Discretionary revision on case presentation line 28, Dr. Galli stated: pictures 1a and 1b showing the reversion of pads of fat accumulation do not give visual evidence of modifications since previous pictures were not performed. Therefore they should be left out. We agree on this comment. As a consequence, we removed picture 1a, which actually provides a poor pictorial evidence; we asked our patient to give us a picture of her breasts she took at a time shortly before starting HAART, and introduced that as an insert for figure 1b, which is now picture 1a, to allow visual comparison of breasts' size; we gave more space to the image of her buttocks, previously put in the insert, which is now picture 1b, and left without further modifications pictures 1c and 1d.
5. In discretionery revisions on case presentation lines 32 and 46, Dr. Galli asked us to specify further about the evolution of triglycerides during treatment interruption and to comment about their possible liaison with lipodystrophy. We accordingly added the sentence: "Her metabolic parameters, including triglycerides, remained within the normal range at all further checks." We do not feel, however, we should comment further on that, as triglycerides were normal throughout follow up but in one case. Further speculation would add to the risk of over-generalization raised by the second referee.
6. We agree on the Discretionary revision on line 50 of case presentation. The sentence: "probably because of persistent interference with lipid metabolism caused by the change of HAART regimes [3-5]." was changed with the sentence: "probably because of persistent interference with lipid metabolism caused by the new antiretroviral drugs [3-5]."
7. We agree on the Discretionary revisions on line 51 and 56 of case presentation. The sentence: "our observation seems to lend support to the idea that the loss in peripheral adipose tissue cells caused by HAART [3-5, 15] may not be fully reversible, even in the long run." was changed with the new sentence: "our observation suggests that the loss in peripheral adipose tissue cells caused by HAART [3-5, 15] may not be fully reversible after treatment interruption, even in the long run."
8. Finally, the last sentence in the case presentation was deleted according to the suggestion of Dr. Galli.

Referee ndegrees2.

1. In his general comment, Dr. Brian Boyle states: "It would be good, if available, to include objective studies (e.g., CT scan or DEXA scan) or findings (e.g., fat measurements such as anthropometry, waist-hip ratio) to support conclusions". This kind of investigations were not available at our site until recently; as a consequence, prospective evaluation of our patient by such tools was not performed. We feel that performing a Dual-energy X-ray absorptiometry, a Magnetic Resonance Tomography or a CT scan of legs' fat right now, with our patient on a second line treatment, wouldn't be appropriate.

2. Again in his general comment, Dr. Boyle states: "authors should verify that during the therapy interruption the patient was not on any other medications or treatments that could have affected either visceral or subcutaneous fat." We agree with this point: we helped our patient to recall about, and we modified the sentence: "She practiced sports on a regular basis and ate a balanced diet." with the new sentence: "She did eat a light and balanced diet; she reported taking L-carnitine (5 grams/qd) since June, 2000, until June, 2001, whereas she denied taking any other drug or supplement possibly interfering with lipid metabolism thereafter."

The paper was again revised by an English speaking native expert. We hope that our manuscript may be acceptable in its present form.

Sincerely, Dr. Giustino Parruti