Author's response to reviews

Title: Carotid intima media thickness is associated with body fat abnormalities in HIV-infected patients

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Author's response to reviews: see over
Dear Editor,

Please find in attach the answers and amendments according to the reviewers comments, the changes were made in the manuscript according the suggestions of the reviewers and we answered each individual comment.

Best regards,

Paula Freitas

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**Answers to the reviewers**

We thank the reviewers for the pertinent observations. We made the changes suggested in the manuscript and we'll answer it point by point.

**Reviewer's report**

**Title:** Carotid intima media thickness is associated with body fat abnormalities in HIV-infected patients

**Version:** 1  **Date:** 17 November 2013

**Reviewer:** Giovanni Guaraldi

**Reviewer's report:**

Dr. Freitas and co-authors evaluate the association of lipodystrophy with cIMT. Regardless the association between lipodystrophy and subclinical or clinical CVD is not original this is one of the first report in which IMT was used as an outcome, and I hope this paper will contribute to include lipodystrophy among the risk
factors for CVD in HIV infected patients.
We appreciate the reviewer comments and we decided to include this in the highlights.

**My major concerns are the followings:**

1. In the paper is not clear if authors want to describe the association between IMT and clinical diagnosis of lipodistrofy or objective measures of lipodistrophy. In my view the availability of objective measured of fat distribution is an advantage therefore the clinical description of lipodistrofy should just be mentioned but not be the criteria of diagnosis.
   We agree with the reviewer suggestion and remove the clinical description and we included in the results the CT scan data of the table 1.

It is said that pts were categorized into one of 4 groups according to the presence or absence of either lipoatrophy or abdominal prominence using FMR assessed with DXA. I suggest that table 1 should use these 4 group categories to describe population characteristics. This table should incorporate VAT data (specify how many pts have VAT measurement).

According to the previous suggestion of the reviewer we decided to eliminate data of clinical definition of lipodystrophy. Since the categorization of the 4 groups is clinical based (despite the only objective parameter is waist circumference) we present only objective parameters (CT data about adipose tissue distribution). All patients did VAT measurement.

2. The objective of the study should be rephrased in consideration of the choice of patient categorization.
   We agree and reformulated.

3. If you use HOMA, there is no need to use QUICKI. I suggest to remove this variable.
   We agree and removed.

4. “The presence of subclinical carotid atherosclerosis was defined as IMT > 0.80 mm”. Please describe in your data set to what percentile of IMT distribution this correspond.
   We included in the results the percentile of IMT distribution (70th percentile).

5. “Carotid IMT was higher in patients with lipodystrophy than patients without lipodystrophy [mean (SD) 0.81 (0.24) vs. 0.76 (0.25); p=0.037)). I suggest this data to be drown in a box plot figure. We performed the box plot figure (Figure1).

6. “Using generalized linear models, cIMT means were adjusted for age and body fat distribution measured by central vs. peripheral fat ratio estimated by
quantitative CT. No significant differences remained after this adjustment when patients with and without lipodystrophy were compared”. Of course body fat measures and lipodystrophy diagnosis are collinear: for this reason should not be placed in the same model.
We agree and we reformulated.

7. “It was our aim to evaluate the association of lipodystrophy per se in cIMT.”
I suggest to attenuate this sentence because you cannot exclude an indirect asociacion.
We reformulated the sentence.

8. Other studies have analysed the association between lipodystrophy and body fat measurement (VAT and SAT) and subclinical cardiovascular disease, former CVD event and at Lipodistrophy meeting this year with future CVD. Authors should discuss to what extent the use of IMT as an end point add significant information. We discussed the role of cIMT as predictor of CV events.
We included this aspect in the discussion.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician

Reviewer's report
Title: Carotid intima media thickness is associated with body fat abnormalities in HIV-infected patients
Version: 1 Date: 21 February 2014
Reviewer: Francesc Vidal

Reviewer's report:
General comment
Paula Freitas, et al. present here a study which deals on the relationship between HIV-related lipodystrophy and atherosclerosis in treated HIV-infected patients with several types of fat redistribution. The study group is made of 199 treated infected patients. Main findings of the study are that lipohypertrophy is associated with increased cIMT. The relationship between the lipodystrophy syndrome and accelerated atherosclerosis is not on fully established, since previous research show inconsistent results. Hence, this investigation offers information that should be welcome. There are however some aspects in the paper that need further clarification before a definitive recommendation is made.

Specific comments
Major comments
1. A common (and unresolved) problem when evaluating the effect of (or the relationship between) lipodystrophy and atherosclerosis is to assess the differential effects of antiretroviral drugs, of the own HIV, of the lipodystrophy syndrome itself, and of the different traditional risk factors such as insulin resistance, dyslipidemia, hypertension or smoking. In this paper a more accurate evaluation of smoking history would be of interest (quantitative, not simply qualitative). The qualitative assessment used by the authors provides uncomplete information. As example, we are not certain that patients with greater values of cIMT had heavier smoking habits than patients with lower cIMT. Unfortunately, regarding smoking habits only this information was collected. We include this in the study limitations.

2. Another confounding factor in your study is that patients with lipodystrophy were significantly older that patients without lipodystrophy. Age per se is a risk factor for atherosclerosis, as you correctly show in Table 2. We agree with the reviewer, we reformulate the discussion.

3. Results section, page 11, top: after adjustment for some confounding variables, mean cIMT values were NS different in patients with and without lipodystrophy. This recommends that your affirmation that cIMT is associated with lipodystrophy should be toned down. We agree and we reformulate.

4. Discussion is too large, there are many generalisation and commentaries regarding articles published elsewhere. It should be focused to discuss the authors’ findings regarding their interesting investigation. In my opinion it can be reduced to one half. We agree and we reformulated.

Minor comments
1. Please spell out several abbreviations (CV, cART, CV, CVD on page 4; FMR on page 5) We agree and we reformulated.

2. Discussion, page 11, first paragraph. The comments to Coll and Mercié papers should be reduced to a minimum. We agree and we reformulated.

3. Limitations: the qualitative assessment of smoking habits could be placed here. We agree and included in that section.

Since you investigated the effect of environmental variables on cIMT (HIV, lipodystrophy, age, etc...), the comment with respect to genetic determinants is not necessary. We agree and remove.
4. Table 1 is large and heterogenous (clinical, analytical, drug use, metabolic data put together). Could you subdivide and categorize? We agree that the table is huge but if we subdivided in clinical, analytical, drug use, and metabolic data will stay with a large number of tables.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I have no competing interests