Reviewer's report

Title: The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials

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Reviewer: Shelley Salpeter

Reviewer's report:

Comments for the authors

1. Is the question posed by the authors well defined?
   Yes. HIV-associated lipodystrophy syndrome is a clinically important side effect of anti-retroviral therapy. This meta-analysis reviews the effect of insulin sensitizing agents on the components of HALS, including insulin resistance, lipid abnormalities and body fat redistribution.

2. Are the methods appropriate and well described?
   Adequate detail is provided in the methods section and supplemental appendices on search criteria, study inclusion, and data extraction. I recommend some changes in data synthesis and reporting.
   - Fasting insulin and fasting glucose were measured and reported. However, it would be helpful to also calculate insulin resistance, with is related to the product of insulin and glucose levels. The standard method used is the homeostatic measurement of insulin resistance, or HOMA-IR. This can be calculated from the mean fasting insulin and fasting glucose from each trial, and then pooled across studies.
   - The weighted mean difference for continuous variables was measured using RevMan 4.2. However, I cannot see in the text or figures whether the random-effects method or fixed-effects method was used. Evidence of potential inter-study heterogeneity was noted in some of the analyses. The random-effects method should be used in cases with inter-study heterogeneity. This could be used for all analyses, or the fixed-effect method could be used, and then compared with the random-effects method in cases with potential heterogeneity.

3. Are the data sound?
   It appears that adequate attempts were made to include the available randomized trials, and to contact investigators to obtain more information, in needed. Suggestions for improvement of data synthesis are made above.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Standard techniques were used for meta-analytic research. I have some recommendations to improve the reporting of results.
- The study durations ranged from 2-12 months. It would be helpful to provide the mean trial duration, to understand the benefits in treatment seen.

- The assessment of inter-study heterogeneity is difficult to follow in the text. The methods state that when heterogeneity was evident, a sensitivity analysis was performed to investigate how removal of apparent outliers affected the results. These results are shown in the figures, but are not consistently described in the text. For example, when a “heterogeneous” trial is removed, is the evidence for inter-study heterogeneity eliminated and do the results change significantly? In addition, some of the results in the heterogeneity analysis are reported in the Results section and others are reported in the Heterogeneity section.

- The outcomes measured for each of the drug comparisons are shown in the forest plot figures. However, it is difficult to follow the results clearly in the results section. The significant results are presented, which is helpful. However, nonsignificant results are variably reported. For example, a favorable trend for metformin and visceral fat is mentioned, although the p value was 0.8, while the favorable trend for metformin and HDL is not mentioned, even though the p value is 0.16. In addition, rosiglitazone had an unfavorable trend for triglyceride, with a p value of 0.09, but this is not mentioned.

- For serious adverse effects, it should be clarified that there was no significant increase in lactate levels with metformin in any of the trials. The statement that “there were elevated lactate levels with metformin in both the intervention and control arms” should be clarified.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

I have recommendations for changes in the discussion and conclusions, in order for it to adequately address the issues.

- The adverse effects of rosiglitazone are adequately described, and the conclusion that it should not be given to patients with HIV lipodystrophy is well supported by the data.

- Pioglitazone did not significantly improve insulin, glucose, LDL, triglycerides, waist-to-hip ratio or visceral fat, and significantly worsened body mass index. In my opinion, that is sufficient evidence at present to conclude that pioglitazone should not be used to treat HIV-lipodystrophy. I recommend that it be clarified that we have no evidence of benefit or even a trend to benefit with this drug, while showing a significant adverse effect.

- It is reported that metformin, in contrast, favorably impacted outcomes across all three areas of interest, including statistically significant reductions in insulin, triglycerides, BMI, and waist-to-hip ratio. I believe it is important to add that, in fact, there was a trend to improvement compared with placebo for all outcomes measured. I suspect that when insulin resistance is calculated using HOMA-IR, there will be a significant reduction in insulin resistance with metformin, as well. It appears to me that we have adequate data to support the conclusion that metformin should be used in the treatment of HIV lipodystrophy syndrome.
The conclusion that was stated concerning metformin was that it is unclear whether changes in these short-term surrogate markers would translate into long-term benefits. The purpose of the meta-analysis was to evaluate the effect of this agent on HIV-associated lipodystrophy syndrome, which is defined by these surrogate markers. Therefore, there is a benefit of metformin in treating this syndrome. Whether improvement in the syndrome will result in long-term clinical benefits is not being addressed by the study at all, and should not be in the conclusion. This can be discussed in the limitations section and applicability of evidence.

Of note, the trial durations ranged from 2-12 months, which indicates that the benefits seen with metformin are maintained over time. It would be helpful in the discussion to compare the results with metformin seen here to results in patients without HIV. For example, a meta-analysis of 31 trials in patients without diabetes, that had an average trial duration of 2 years, found significant long-term improvements in insulin resistance, lipids, and body composition (Salpeter et al, Am J Med 2008).

6. Are limitations of the work clearly stated?

Yes.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

The methods and results are similar to a previous meta-analysis of metformin treatment in non-diabetic patients without HIV, as mentioned above. The results found for patients with HIV could be compared to those seen in patients with similar metabolic derangements without HIV, especially because so many more studies have evaluated non-HIV patients. Are the results similar to those with true metabolic syndrome?

8. Do the title and abstract accurately convey what has been found?

I do not see an abstract, only an introduction. I believe an abstract summarizing the results would be helpful.

9. Is the writing acceptable?

Yes.

Please make your review as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- Major Compulsory Revisions (which the author must respond to before a
decision on publication can be reached)

O I have made specific recommendation, noted in my comments above. I would like each of these comments to be addressed by the authors before it be accepted. I would be happy to review the revised manuscript.

**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 declare that I have no competing interests.