Author's response to reviews

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

Authors:

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Version: 2 Date: 9 December 2009

Author's response to reviews: see over
To the BMC ID Editors and Reviewers:

We thank you for the close review and helpful feedback of our manuscript, “The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials”. We have enclosed a revised manuscript with updated tables and figures. We have provided a point-by-point response to the reviewers’ comments. With the incorporation of the reviewer revisions, we feel that our manuscript is substantially improved and our findings will remain of high interest to your readership.

Below you will find our replies to the reviewer’s reports and the editorial requests.

REPORTS:

Referee 1:
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.

Thank you.

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.
We appreciate the desire for more formal measures of insulin resistance and initially hoped to report HOMA as an outcome. Unfortunately very few studies reported the measure. While the recommended approach to calculating mean HOMAs for each trial might provide a reasonable estimate, we are concerned that without matching insulin and glucose results at the patient level, we might introduce error. We are hoping that the fasting insulin and glucose outcomes will be adequate.

- 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.

We used random effects models for calculating all summary estimates. We have clarified the point in the Methods section on page 7.

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.

Thank you.

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.

Here is the data you requested:

<table>
<thead>
<tr>
<th>Comparison</th>
<th># of trials</th>
<th># of subjects</th>
<th>mean duration f-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosi v pl</td>
<td>9</td>
<td>470</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Pio v p</td>
<td>2</td>
<td>144</td>
<td>50 weeks</td>
</tr>
<tr>
<td>Met v p</td>
<td>6</td>
<td>287</td>
<td>27 weeks</td>
</tr>
<tr>
<td>Rosi v Met</td>
<td>3</td>
<td>152</td>
<td>29 weeks</td>
</tr>
</tbody>
</table>

We have added this information to the opening sentence of each relevant section of the Results.
- 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.

We have clarified the Heterogeneity section which hopefully will be easier to follow.

- 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.

We agree with your suggestion and have accordingly have removed references to nonsignificant results in the text to keep each section consistent.

- 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.

Changes in lactate were surprisingly poorly reported. As such, we can not comment on whether increases from baseline were significant within study arms. In the studies that provided data, any increases in lactate that occurred were not statistically significantly different between study arms.

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.

Thank you.
- 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.

*We feel the available data is limited and with three more RCTs currently underway, we believe more conclusive judgment of the use of pioglitazone should be reserved until these studies have been completed.*

- 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.

*We agree that there is adequate data to support the use of metformin in HALS, though its role in patients with lipoatrophy is not clear. In order to avoid mentioning non-significant findings, we have only listed the significant ones.*

- 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 results 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.**

*We seem to agree that our study does not address the long term effects of insulin-sensitizers. However, we respectfully disagree that this point does not belong in the Implications for Practice.*

- 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).
Thank you for this suggestion. We have included a sentence in the discussion addressing this topic.

6. Are limitations of the work clearly stated?
Yes.

Thank you.

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?

As state above, we have added a sentence in the discussion.

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.

We agree! Our abstract is now included at the beginning of the manuscript.

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).
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.
Referee 2:
Reviewer's report

1. Major compulsory revisions (the author must respond to these before a decision on publication can be reached).
- None

2. Minor essential revisions (the author can be trusted to correct).
- None.

3. Discretionary revisions (recommendations for improvement which the author can choose to ignore).
- Although the authors present, in some extent, the limitations of their work, I think it would be important, to include, in more detail, the following aspects in their discussion:

(1) **Since the study subjects were predominantly males in their forties the data cannot be generalized to children, adolescents and young adults.** This is important due to the variability in insulin sensitivity, especially when comparing pre-pubertal and pubertal children;

*Thank you for your suggestion. We agree and have accordingly added a statement in the discussion.*

(2) As stated, the wide range of HIV-associated lypodystrophic syndrome (HALS) population, do not allow to precisely assess the impact of its individual components on the response to the insulin sensitizing agents; (3) Only measures of central obesity (body mass index [BMI], waist to hip ratio [WHR]), visceral abdominal fat [VAF]) were analyzed. The assessment of peripheral wasting could not be assessed. This does not allow the clinical practioner, to verify if their current use of metformin for the lypohtertrophic pattern and thiazolidinediones for the lypoatrophic pattern has scientific validity. 4) The type and dose of the ART (e.g., NRTIs and PIs) could not be adequately assessed, therefore it was not possible to evaluate the impact of these drugs in the insulin resistance; (5) Although the standardization of the measures of insulin sensitivity (e.g., euglycemic clamp, HOMA [homeostasis model assessment]) could be important, in clinical practice the fasting insulin and fasting glucose are the parameters more frequently used. Therefore they have some clinical validity;
Thank you. We are interpreting this list to include both new items to be addressed (#1, #6, and #7) as well as items we have already touched on in the original manuscript.

(6) If possible, information of the impact of leptin in insulin sensitivity would be important due to the known association of hypoleptinemia and insulin resistance and due to the ongoing trials using leptin to improve this metabolic derangement.

We have reviewed the data of all included studies and there is not adequate information to provide the impact of leptin on insulin sensitivity.

(7) Although the short term effect of the insulin sensitizing drugs are described, their long term effects on cardiovascular risk still needs to be evaluated.

We agree and have indicated this point in the discussion.

Level of interest an article of importance in its field
Quality of written English Acceptable
Statistical review Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests I declare that I have no competing interests.

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Editorial Requests:
Although you have provided detailed description of the methods we feel it would be helpful to include the keywords you used for your searches.

We agree and have accordingly added a list of keywords in the methods section.

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Thank you again for reviewing our manuscript and providing helpful feedback. Please feel free to contact us with any additional questions.

Sincerely,

Siddharth Sheth, MPH
Robin Larson, MD MPH