Author’s response to reviews

Title: Associations between human leukocyte antigen polymorphisms and hypersensitivity to antiretroviral therapy in patients with human immunodeficiency virus: a meta-analysis

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Author’s response to reviews:

Chuanyi Ning, PHD
Academic Editor
BMC Infectious Diseases

RE: Manuscript “Associations between HLA polymorphisms and hypersensitivity to antiretroviral therapy in patients with HIV: a meta-analysis”.

Dear Prof. Chuanyi Ning, PHD:

“Associations between HLA polymorphisms and hypersensitivity to antiretroviral therapy in patients with HIV: a meta-analysis (INFD-D-18-00881)”. We would like to thank BMC Infectious Diseases for giving us the opportunity to revise manuscript. We have carefully taken
the comments into consideration in preparing our revision, which has resulted in a paper that is more clear and compelling. The point-by-point responses are attached after this letter. The revisions were highlighted to the text in “RED” print, have been prepared.

The manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere. None of the authors have any competing financial interest to report.

Thank you for considering our manuscript for publication in your esteemed journal.

Point-By-Point Response

Comments to the Author

Reviewer #1:

Comment: This study explored the association between HLA polymorphisms and hypersensitivity to antiretroviral therapy in patients with HIV using meta-analysis methods. I have several questions and comments on this study.

Response: It is pleasing to have acknowledged our diligence in conducted this manuscript. We appreciate the reviewer’s constructive suggestions. We have already made these changes in the revised manuscript and marked “RED”.

Comment 1: Since hypersensitivity to antiretroviral therapy was the primary outcome of the study, it is important to give a clear definition of it. My concern is whether all study included in the meta-analysis have clear and consistent definition on hypersensitivity? Or the authors defined by themselves? If it is the later one, how the authors identified it is hypersensitivity symptoms?

Response: Thanks for this suggestion, and the definition of hypersensitivity was determined by individual study. Moreover, the details of hypersensitivity definition have already listed in Table 1 and marked “RED”. Moreover, we have already addressed this point in Limitation section.

Comment 2: The authors stated that this study is following the STROBE checklist. I think it is better to provide the checklist form in the supplementary materials.

Response: Thanks for this suggestion. The current study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement. Moreover, the PRISMA Checklist have already added in Supplemental files.

Comment 3: Random-effects models were employed in the meta-analysis regardless of the heterogeneities of the study. Could you please explain why do you choose random-effects model instead of fixed effects model?
Response: Thanks for this suggestion. All of summary results are calculated using random-effect models due to it assume the true underlying effect varies among included studies.

Reference:


Comment 4: The authors stated that they conducted sensitivity analysis and publication bias analysis, but no related results were shown in tables or figures, except for a sentence reporting "a sensitivity analysis indicated that the conclusion was not altered..." Could you please provide more details (statistics, figures or tables) about the results?

Response: Thanks for this suggestion, we have already added Supplementals 4-6 to address these questions, and the results of sensitivity, subgroup, and publication bias have already added in the revised manuscript. All of changes in text have already marked “RED”.

Comment 5: One of my concerns regarding the results is that some of the meta-analysis results were from a single study, it is not very conclusive. Additionally, we don't know which studies the results are from? Could you please provide information about source of the study? For example, provide reference in Table S2-S5. Or give more detail about which allens were reported in each reference in table 1.

Response: Thanks for this suggestion. We have already used “association” replaced causal relationship throughout the manuscript. Moreover, the the reference in Tables S2-5 have already added and marked “RED”.

Comment 6: When the results were insignificant, it should be cautious to have a conclusion. We would not conclusive to say that one factor/allen did not affect hypersensitivity risk. It is possible that current studies did not have enough power to find the association.

Response: Thanks for this suggestion. We have already used “association” replaced causal relationship throughout the manuscript.

Minor revisions:

Comment 7: Some typos exist. eg. Talbe etc.

Response: Thanks for this suggestion, and we have already made these changes in the revised manuscript and marked “RED”.

Comment 8: Please avoid to use abbreviations in title
Response: Thanks for this suggestion, and we have already made these changes in the revised manuscript and marked “RED”.

Comment 9: The figure legends might be wrong (Fig 4).

Response: Thanks for this suggestion, and we have already made these changes in the revised manuscript and marked “RED”.

Reviewer #2:

Comments: The manuscript discusses the association between HLA polymorphism and hypersensitivity to antiretroviral drugs. This important and has a lot of practical implication in selecting appropriate regimen for patients.

Unfortunately the paper is fatally flawed as it uses references that are old and do not reflect current practices in ART service delivery (Check references 1 to 6). Furthermore, the relationship between risk of hypersensitivity and antiretroviral drugs is meaningful only if it addresses specific drugs. Whilst the introduction and discussion mention specific drugs eg. abacavir the results of the metanalysis are very generic and not specific to any drug.

It is unclear why the authors used only March 2018 and not the period before it. The paper in its current form does not advance scholarship.

Response: Thanks for this suggestion, the results at Background have already updated and marked “RED”. Moreover, subgroup analyses were conducted based on the type of specific drugs and added in Supplemental Table S5. Finally, the last searching data have already updated in April 2019, and the flowchart have already updated.

Reviewer #3:

Comments: The paper is a meta-analysis for the association between HLA and drug hypersensitivity, and it is considered design and analyses are appropriate. The limitation of this paper is small sample size and authors could not discuss about ethnicity. Since it is well known that there found strong ethnic influence in drug hypersensitivity, readers are interested in the aspect. I suggest to add more explanation for ethnicity, just the information reported in other papers will do. Also, the data from 2 drugs are pooled in the analyses. Did you analyze the data for each drug? If exists, the information in discussion will be better for readers.

Response: Thanks for this suggestion, subgroup analyses based on ethnicity were not conducted due to mostly studies involved mixed ethnicity, and the results of stratified by ethnicity from individual study were not available. However, we added the results of subgroup analyses based on study conducted country (Eastern, Western, and Africa). Moreover, the results of subgroup analyses based on country and the type of drugs have already added in Supplemental Table S5.