PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Host blood transcriptomic biomarkers of tuberculosis disease in people living with HIV: a systematic review protocol
AUTHORS	Mendelsohn, Simon; Mulenga, Humphrey; Mbandi, Stanley; Darboe, Fatoumatta; Shelton, Mary; Scriba, Thomas; Hatherill, Mark

VERSION 1 – REVIEW

REVIEWER	Tornheim, Jeffrey Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases
REVIEW RETURNED	24-Mar-2021

GENERAL COMMENTS	This manuscript presents the design and protocol for a planned systematic review to evaluate and synthesize the evidence supporting the use of existing host-response signatures for the diagnostic and prognostic ability of these signatures. They have appropriately identified an area of great need and present a thoughtful methodology that is highly likely to succeed at their stated goals. This project is expected to provide useful guidance to the research community, and the publication of this protocol will likely support the planning and research activities of others around the world who are working to identify and translate biomarkers of tuberculosis for this population. Once completed, this protocol will also allow for future studies to optimize globally relevant signatures to other special populations.

REVIEWER	Turner, Carolin University College London
REVIEW RETURNED	22-May-2021

GENERAL COMMENTS	This is a well-designed study with a clear and detailed study protocol. The authors aim to systematically review performance of blood transcriptomic biomarkers for tuberculosis in people living with HIV. This builds on their previous work on people without HIV infection. The research question is clear, important, and has not been addressed previously. Comments: 1) Could the authors please clarify the rationale for excluding studies that do not stratify results by control group? Ultimately, biomarkers need to perform well in realistic cohorts where the control group is likely a mix of people with latent infection, other diseases and perhaps even healthy individuals whose symptoms might clear in the time between referral and test.

	2) Could the authors please clarify whether the control group in included studies can encompass HIV-infected and -uninfected individuals? 3) Table 3, Cohort identification: include ArrayExpress next to GEO as data are not synced between the two databases

REVIEWER	Rakotosamimanana, Niaina Institut Pasteur de Madagascar
REVIEW RETURNED	27-May-2021

GENERAL COMMENTS	I confirm the interest of such a systematic review on transcriptomic signatures addressed for TB and PLHIV as already briefly mentioned by the authors in their LGH article published in April 2021. Given the heterogeneity of the data anticipated for this systematic review, please ensure in the data analyzes that the Ziehl-Neelsen microscopy used as reference standard for TB endpoints is associated or confirmed with a second test or is to be considered in separate data analyses to avoid any confusion with infections due to atypical or non- tuberculosis Mycobacteria. Moreover, defining latent TB endpoints is tricky. Same cautions has to be taken with using the TST for latent TB status, especially with PLHIV where the test can be affected by other opportunistic infections. To my best of knowledge, there is no data yet about any transcriptomic signatures related to infections due to atypical mycobacteria or other HIV-associated opportunistic infections that might be seen at higher proportions in PLHIV compared to non-PLHIV. Minor: Please tick “yes” in the PRISMA-P checklist for the sections 15a and 15b

VERSION 1 – AUTHOR RESPONSE

We are grateful to the editorial team and peer reviewers for the positive comments and constructive feedback. We appreciate the opportunity to strengthen our paper further and submit a revised manuscript with careful consideration of the issues raised. We provide a response to each of the reviewers’ comments and indicate the changes we have made below.

(C1) Could the authors please clarify the rationale for excluding studies that do not stratify results by control group? Ultimately, biomarkers need to perform well in realistic cohorts where the control group is likely a mix of people with latent infection, other diseases and perhaps even healthy individuals whose symptoms might clear in the time between referral and test.
(R1) We agree with the reviewer and have now removed this exclusion criteria from Table 1, section 5.

(C2) Could the authors please clarify whether the control group in included studies can encompass HIV-infected and -uninfected individuals?
(R2) We have clarified this in the “*Study participants and setting*” section (Lines 149-150): “If the study encompasses both PLHIV and HIV-uninfected individuals, the study will only be included if the data are stratified by HIV subgroups.”

(C3) Table 3, Cohort identification: include ArrayExpress next to GEO as data are not synced between the two databases
(R3) We have added ArrayExpress next to GEO database in Table 3.

(C4) Given the heterogeneity of the data anticipated for this systematic review, please ensure in the data analyzes that the Ziehl-Neelsen microscopy used as reference standard for TB endpoints is associated or confirmed with a second test or is to be considered in separate data analyses to avoid any confusion with infections due to atypical or non- tuberculosis Mycobacteria.
(R4) We agree with the reviewer and state the following (lines 173-175): “Studies which use smear microscopy as a reference standard will be reported separately due to reduced diagnostic certainty.”

(C5)Moreover, defining latent TB endpoints is tricky. Same cautions has to be taken with using the TST for latent TB status, especially with PLHIV where the test can be affected by other opportunistic infections.
(R5) We agree with the reviewer, and will report the method of latent *Mtb* infection diagnosis (TST >5mm, TST >10mm, IGRA: T-Spot.TB or QuantiFERON) used in each study (see Table 3; “Cohort identification and methodology”).

(C6) To my best of knowledge, there is no data yet about any transcriptomic signatures related to infections due to atypical mycobacteria or other HIV-associated opportunistic infections that might be seen at higher proportions in PLHIV compared to non-PLHIV.
(R6) We are not aware of any human transcriptomic signature data related to infections due to atypical mycobacteria or other non-tuberculous HIV-associated opportunistic infections.

(C7) Please tick “yes” in the PRISMA-P checklist for the sections 15a and 15b
(R7) Done

VERSION 2 – REVIEW

REVIEWER	Turner, Carolin University College London
REVIEW RETURNED	28-Jun-2021

GENERAL COMMENTS	Thank you for addressing my comments. Good luck with the study, and I'm looking forward to seeing the results.

REVIEWER	Rakotosamimanana, Niaina Institut Pasteur de Madagascar
REVIEW RETURNED	21-Jun-2021

GENERAL COMMENTS	The previous comments were well integrated in the revised manuscript. This systematic review protocole deserves to get published with its current version.