PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Testing and treatment for latent tuberculosis infection in people living with HIV and substance dependence: a prospective cohort study
AUTHORS	Runels, Tessa; Ragan, Elizabeth; Ventura, Alicia; Winter, Michael; White, L; Horsburgh, C; Samet, Jeffrey; Saitz, Richard; Jacobson, Karen R.

VERSION 1 – REVIEW

REVIEWER	Winje, Brita Norwegian Institute of Public Health, Department of Infection Control and Vaccine
REVIEW RETURNED	01-Dec-2021

GENERAL COMMENTS	This is a well-written and nicely presented study on completion of the full LTBI care-cascade among high-risk groups for reactivation of latent TB. It is an important topic which is relevant in many settings. The authors have carefully assessed risk factors for TB using validated bio-behavioral instruments. Information on LTBI was obtained from medical records with fewer details. The limitation of the study is the low number of individuals with LTBI, and then the possibility to evaluate the full care cascade, specifically on how to improve acceptance and completion of LTBI treatment. Only 11 tested positive, five started treatment and three completed treatment. Thier finding that completion of testing is higher for IGRA than TST is well accepted and not new. Comments: The LTBI diagnosis is difficult and the interpretation is not straight forward. This may play a role in the physicians decision to prescribe treatment and the patients willingness to accept it. This group already have complex health challenges. Is it possible to add more information from medical records on TB exposure history, TST induration, reasons for prescribing or not prescribing preventive treatment, side-effects (as a reason to not complete treatment). What kind of follow-up is offered to patients starting a nine months treatment? Overall, the participants HIV-infection seemed to be well controlled; all were on ARV treatment at enrolment, more than half had undetectable HIV viral load and median CD4 count was 549. This could be better reflected in the discussion (although they also have other risk factors).

	Some of the references are old, i.e. no 10 from 2016 – including publications only up until 2015. Newer publications are available with higher completion rates. The link for reference 4 is not correct.

REVIEWER	Auguste, Peter University of Warwick Warwick Medical School
REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	The authors aimed to quantify the percentage of participants with HIV that completed each stage of the LTBI care cascade. The authors also aim to discuss the differences between participants who tested with IGRA versus TST. The authors found that majority of participants completed testing but further research is needed to investigate the reasons /challenges associated with initiation of TB-preventative treatment and completion. The manuscript was well written, but there were some concerns: Page 5 line 120 states that 'In this retrospective study of a well-characterized…' Are the authors referring to the current study? It was stated in the abstract that the study design is prospective. Authors provided details about definitions substance dependence and homelessness but less so about LTBI testing. It is unclear in this section what threshold is being used for a positive result on TST and IGRA. It is common to report the threshold for positive results. What do current testing guidelines state for this patient population? The authors should state early in the manuscript the TB-preventative treatment that is current practice. Which IGRA was used to test for LTBI? Did any participants receive both IGRA and TST? Were there any indeterminate results, and were these participants re-tested? The authors state that they found that a high proportion of participants received testing, higher than previously reported in two other studies. Can the authors elaborate why there is this discrepancy? Given that this study was retrospective, I presume that participants were not randomised. Could this be a limitation of the study?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. The LTBI diagnosis is difficult and the interpretation is not straight forward. This may play a role in the
physicians decision to prescribe treatment and the patients willingness to accept it. This group already have
complex health challenges.
We agree, and added the following sentence to the Discussion (starting Line 265) to elevate this: "Interpretation
of LTBI test results can be challenging and may ultimately impact likelihood of providers recommending and

patients subsequently initiating treatment."
2. Is it possible to add more information from medical records on TB exposure history, TST induration, reasons
for prescribing or not prescribing preventive treatment, side-effects (as a reason to not complete treatment).
These additional data points were not all systematically captured nor available as part of our chart review. We
were able to add additional information in the Results on TST induration, retesting, and reported side effects or
provider rationale for halting treatment for a number of patients (starting Line 226).
3. What kind of follow-up is offered to patients starting a nine months treatment?
We added additional information about standard practice clinical follow-up in the Study Setting and Population
section of Methods (starting Line 141).
4. Overall, the participants HIV-infection seemed to be well controlled; all were on ARV treatment at enrolment,
more than half had undetectable HIV viral load and median CD4 count was 549. This could be better reflected in
the discussion (although they also have other risk factors).
We added a sentence to better highlight this to the first paragraph of the Discussion (starting Line 239).
5. Some of the references are old, i.e. no 10 from 2016 – including publications only up until 2015. Newer
publications are available with higher completion rates. The link for reference 4 is not correct.
Reference 4 has been updated. We've added a number of more contemporary references, including Stockbridge et
al. 2020 and Bastos et al. 2021.
Reviewer 2:
1. Page 5 line 120 states that 'In this retrospective study of a well-characterized…' Are the authors referring to the
current study? It was stated in the abstract that the study design is prospective.
Thank you for raising this typo to our attention. This has been corrected to read "prospective study."
2. Authors provided details about definitions substance dependence and homelessness but less so about LTBI
testing. It is unclear in this section what threshold is being used for a positive result on TST and IGRA. It is
common to report the threshold for positive results. What do current testing guidelines state for this patient
population?
Information on how both TST and IGRA were interpreted was added to the Definitions section of Methods
(starting Line 178).
3. The authors should state early in the manuscript the TB-preventative treatment that is current practice.
We added information on current standard regimens to the Introduction (starting Line 109).
4. Which IGRA was used to test for LTBI? Did any participants receive both IGRA and TST? Were there any
indeterminate results, and were these participants re-tested?
We added clarification that QuantiFERON TB-Gold was used. In the results, we now describe that one patient
was initially tested with IGRA, then retested with TST.
5. The authors state that they found that a high proportion of participants received testing, higher than previously
reported in two other studies. Can the authors elaborate why there is this discrepancy?
We added a sentence to the first paragraph of our discussion describing that high testing adherence may be a
result of our cohort being well-engaged in HIV care (starting Line 239).
6. Given that this study was retrospective, I presume that participants were not randomised. Could this be a
limitation of the study?

We added this to the strengths and limitations section.
Thank you again for the opportunity to respond to the above feedback and revise our manuscript accordingly. We
look forward to hearing next steps.

VERSION 2 – REVIEW

REVIEWER	Winje, Brita Norwegian Institute of Public Health, Department of Infection Control and Vaccine
REVIEW RETURNED	25-Jan-2022

GENERAL COMMENTS	The authors have responded well to the comments from the previous review. My only suggestion is to refrain from using % when number are low, As an example, authors report 60% when 3 out of 5 respondents had information available (page 9, line 226). Then numercial data speeks for themselves.

REVIEWER	Auguste, Peter University of Warwick Warwick Medical School
REVIEW RETURNED	04-Feb-2022

GENERAL COMMENTS	Many thanks for considering the comments/queries raised. No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

The authors have responded well to the comments from the previous review. My only suggestion is to refrain from using % when number are low, As an example, authors report 60% when 3 out of 5 respondents had information available (page 9, line 226). Then numercial data speeks for themselves.

Thank you. We removed percentages for low numbers.

Reviewer 2:

Many thanks for considering the comments/queries raised. No further comments.

Thank you.

Thank you again for the opportunity to respond to the above feedback. We look forward to hearing next steps.