Author's response to reviews

Title: Psychological distress and its relationship with non-adherence to TB treatment: findings from a multicentre clinical trial

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Author's response to reviews: see over
Reviewer #1:

C1. Clarify what was controlled in multivariate analysis, especially effect on alcohol and HIV on gender.

R1. We controlled for multiple covariates in each multivariable analysis. The analysis tables in Tables 2-4 and Tables S4-S7, which are in the supplement, list each factor that was controlled for. Alcohol, HIV, gender were all included as possible confounders.

C2. Did all 1502 participants qualified to be called patients?

R2. Yes. The 1502 participants had symptoms of pulmonary TB, which was one of the eligibility criteria for entry into the parent study. As these individuals were investigated by medical staff for possible TB as well as other diseases, we believe the term “patient” is appropriate in this context.

C3. Address all shown in tracked changes.

R3. We have done so, where appropriate. Thank you for your comments.
Reviewer #2:

Major comments

C1. My single major inquiry has to do with the definition of non-adherence. Granted that no single accepted definition exists, use of one missed DOTS visit seems to lack clinical significance. The fact that some allowance for intermittent dosing has been acceptable in WHO guidelines suggests a certain degree of flexibility in dosing schedules. Most desirable would be to look at treatment default, or adherence as a continuous measure (proportion of doses taken). If these options are not feasible, sensitivity analyses using greater cut points could be an alternative.

R1. We agree that examining adherence as a continuous measure or with different cut-points for the proportion of doses taken would be useful. However, we unfortunately did not collect data on this. A binary “yes” or “no” question was asked at two- and six-months about adherence, and no further data are available. We have described this limitation in the Discussion:

We also recorded whether patients were compliant, but did not capture data about the proportion of doses taken. Consequently, we were unable to discriminate between patients who only missed a few doses and those who were completely non-compliant and had defaulted (which is defined as no treatment for a continuous period of two months\(^1\)).

Minor comments

C2. Non-specific psychological distress is less compelling than well-validated psychiatric diagnoses. I believe the authors should do a better job in the Introduction of making the link between the K-10 and actual DSM diagnoses (as in the Myer Soc Science and Med 2008 citation).

R2. Thank you. We agree and have added the following text to the Introduction:

The Kessler K-10 questionnaire, which has been validated in a variety of settings as part of population-level mental health surveys\(^2\), is a tool for population-level screening of people who are likely to meet formal DSM-IV definitions for anxiety or depressive disorders, and those who have sub-clinical psychiatric illness\(^3\).

C3. It would be great if the study hypothesis could be clearly stated in the Introduction. Was the primary aim to examine covariates associated with K-10, or predictors of non-adherence, or correlates of improvements in morbidity?

R3. This is a helpful suggestion. Our primary hypothesis was that patients who were non-adherent were more likely to be psychologically distressed at diagnosis. We have added the following text to the last paragraph of the Introduction:

We primarily hypothesised that patients who had higher levels of psychological distress would be more likely to be non-adherent to their anti-TB treatment. We also explored the association between psychological distress and adverse clinical- and economic outcomes, such as TB-related symptoms and unemployment, and the duration of symptoms before patients sought care.
C4. Should multivariate analyses account for clustering in the data? There is evidence that the sites are quite different (in particular with respect to psych distress), and therefore I might be cautious about interpreting the observations as independent. On the other hand, there are few clusters and adjustment for site may do nearly as well. Do the authors have thoughts on why reported distress is much higher in Harare and Mbeya, even after adjustment for other pertinent covariates?

R4. Thank you for this comment. Patients at some of the sites had, overall, higher levels of psychological distress, and this appears to be due to higher levels of covariates associated with high psychological distress (e.g., HIV-infection, heavy alcohol use). We detail this phenomenon further in the Discussion:

Our study showed approximately half of patients presenting to our primary care TB clinics in Harare and Mbeya to have a severe level (K-10≥30) of psychological distress, similar to that previous reported amongst Ethiopian patients infected with HIV or TB or both\(^4\). The high level of psychological distress likely resulted from the high local prevalence of associates of psychological distress compared to the other sites in our study. For example, Harare had the highest rate of HIV-infection out of the five sites, whereas patients in Mbeya were more likely to consume alcohol regularly than at any other site.

Due to these site differences, we included “site” as a variable in each multivariable analysis (each of the analysis tables lists the estimate or odds ratio and p-value for each site) as a fixed effect in order to account for variability.

We have now, however, also consulted with a biostatistician, so as to explore how clustering in the data can be accounted for further. We explored using mixed effects models with site as a random effect, but ultimately felt that small number of sites (and the small patients numbers are stratification – e.g., culture-positive, and non-adherent) preferred the fixed effect approach that we have taken.

C5. Line 228 on page 12: although the difference is statistically significant, some indication of the minimally important clinical difference in K-10 should be noted.

R5. We agree that this could potentially be useful, however, after scouring the literature and speaking to a senior psychiatrist with experience in the K-10 questionnaire, there appears to be little consensus about what the minimally important clinical difference in K-10 score is. Furthermore, because the K-10 is a screening tool for risk-stratifying participants for formalised screening for psychiatric disorders, rather than a tool used to directly diagnose patients, describing a minimally important clinical difference is arguably of limited utility. K-10 score strata have however been defined in a South African context, which correspond with different levels of distress (10-19 = low, 20-24 = moderate, 25-29 = high, ≥30 = severe)\(^5\). Thus, if a score difference results in a change in risk level, we would argue that that could be considered clinically important. Therefore, in reference to the text referred to by the reviewer (where K-10 scores across different subgroups are described), we have added the following text to the Discussion:
We found women and patients living with HIV to have a significantly higher level of psychological distress than men or HIV-uninfected patients. However, according to stratifications of the K-10 score previously performed in South Africa (where a score of 20-24 was graded as moderate), these differences, although significant, would not constitute an overall increase in risk classification level.

C6. I may have missed it, but do the authors define delay in seeking care? This is mentioned in the Discussion.

R6. We did not explicitly define it in the manuscript. When mentioned in the Discussion, this is in reference to the analysis under the “Cough duration” subheading of the Results (also Table S6), where we examined, in patients who have a cough for at least two weeks, what was associated with the duration of time that had passed before they presented to the clinic. This was possible because, in the original case record form, patients who had had a cough longer than two weeks were asked this information. We agree that this link (duration of symptoms as a proxy of delay in seeking care) could be made more prominent, and have made the following edit in the Results:

Patients with TB who reported themselves to have been coughing for at least two weeks prior to presenting to the clinic (n=1402) (and whom are hence likely to have transmitted more disease than those who had not coughed for as long) may have experienced a delay in seeking care.

And the following edits in the Discussion:

(iv) HIV-infection and heavy alcohol usage are associated with a delay in seeking care (defined as duration of coughing before presentation) amongst patients with a cough and culture-confirmed TB;

We found HIV-infection and heavy alcohol usage to be associated with a longer duration of cough before in presentation to the clinic, which is suggestive of a delay in seeking care and that these patients with a delayed presentation may be responsible for more transmission than those who present earlier.

C7. With these data, could the authors posit that mental health treatment could potentially improve patient outcomes, as has been shown for HIV? Or not? Should advocating for mental health treatment be imperative in its own right given the authors’ findings of a high prevalence of psychological distress?

R7. We do advocate for such interventions, including better mental health treatment as a whole. Furthermore, our research suggests that TB control programmes could themselves potentially screen for psychological distress, and use this to identify patients who are at a high risk of treatment non-adherence. Indeed, we conclude our manuscript on this note:

Screening for psychological distress could, together with counselling to reduce alcohol consumption and improve patients’ knowledge about TB, reduce treatment non-adherence.
We however wish to refrain from making stronger conclusions than this, because our study was descriptive in nature. Before such strong recommendations can be made, a trial of an intervention to alleviate psychological distress or encourage compliance in individuals with a high level of psychological distress should be conducted. Our data indicate that such a trial should be conducted, and provide preliminary evidence that such interventions may work.
References