

Baseline Radiographic and Microbiologic Predictors of Treatment Outcomes in a Shortened All-Oral Regimen for MDR/RR-TB

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Thank you for the opportunity to review this well-written and interesting manuscript. The authors used data from the End TB trial to identify radiographic features predictive of poor MRD-RR TB treatment outcomes in Lesotho, the majority of which were deaths. The authors found that certain radiographic abnormalities, alone and in combination with sputum smear grade, were associated with longer time to culture conversion (bilateral disease in unstratified analyses; amongst those without HIV, fibrosis and cavitory disease; amongst PLHIV, bilateral disease; cavitory-smear positive and fibrocavitory). For end of treatment unfavourable outcome — which was mostly death— bilateral disease (amongst those without HIV) and fibrosis (amongst PLHIV) were predictive; as were combinations of cavitory-smear positive and fibrocavitory disease.

I had the following questions:

Can the authors please describe in the Methods how CXR reading was performed: by who, how many readers, the readers' experience/training, whether a standard form was used to classify the abnormalities or was classification done retrospectively using the prose of the radiologist reports? Were all cavity sizes reported initially or retrospectively? I appreciate that the Discussion addresses limitations with respect to single person reading and potential inter-reader variability.

What was used to determine severity of fibrocavitory disease (severe fibrocavitory disease mentioned on page 7)?

The association between reported fibrosis on CXR and outcomes is interesting. Has it been described elsewhere? Bronchiectasis can sometimes have the appearance of fibrosis on Xray- did any patients have CT scans where one could assess whether fibrosis was interstitial thickening versus actually bronchiectasis?

The authors rightfully raise the question about whether some pts had silicosis. Silicosis is known to be associated with poor TB treatment outcomes. It would be of interest to see data on n% of population with history of mining work.

Can the authors report in a supplemental table the characteristics of participants, other than radiographic abnormalities, that were associated with time to conversion and unfavorable outcome? Could they also report what patient characteristics were associated with radiographing findings (cavities, fibrosis, bilateral disease, severe fibrocavitory disease)? Could there be confounding of associations between CXR abnormalities and conversion/unfavorable outcome due to the other characteristics? I understand the number experiencing outcomes is low which limits the number of variables that can be included in multivariable analyses, but I would be interested to see impact on associations in models adjusting for age, sex, prior TB, and HIV status.

It strikes me that the radiographic abnormalities associated with the outcomes of interest are all suggestive of substantial delays between disease onset and diagnosis/treatment. Might the study findings further emphasize the importance of screening?

I appreciate the practice impact suggested: that radiographic disease might be used for targeting clinical care measures to reduce mortality amongst those at greatest risk rather than to identify amongst whom could treatment be shortened.

Given the low rate of unsuccessful bacteriological outcomes, I am concerned that some of the phrasing in the abstract may be interpreted by readers as indicating associations between CXR abnormalities and failure/recurrence. As such, could the abstract Results section include the distribution of unfavourable outcomes (n deaths, n failure etc) and mention death in the conclusion? Eg. ... unfavorable outcomes, mostly death, ...

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)

General Comments

Shen and colleagues present the results of a prospective observational study examining the association between baseline clinical predictors and three key treatment outcomes – time to culture conversion, treatment failure, and recurrence – among adults in Lesotho receiving all-oral regimens for MDR/RR-TB between 2020 and 2025. The authors report favorable outcomes in about 90% of participants, with more abnormalities on baseline chest radiography and higher bacillary loads linked to less favorable clinical outcomes. They conclude that future studies should explore risk-adapted treatment strategies to improve outcomes among individuals with these high-risk features.

Major Comments

This analysis of a recent real-world cohort with MDR/RR-TB is welcome in light of the evolving treatment options that are more accessible and better tolerated. A strength of the analysis is the a priori designation of the hypothesized high-risk clinical phenotypes of interest, based on the prior literature, and the comprehensive outcome data across the study population. It's particularly encouraging to see the high rates of treatment success given what was reported from this region just a few short years ago.

That high level of success, unfortunately, greatly limits the statistical power of this study to identify predictors of adverse outcomes. As a result, a significant limitation of this analysis is that adverse outcomes were detected in only 6 persons for time to culture conversion, 22 persons for adverse end-of-treatment outcomes, and 5 persons for post-treatment outcomes. This makes the conclusions at high-risk of frailty. In addition, there is missing data in several key predictors, which while modest for programmatic data, does introduce substantial risk of residual confounding and selection bias, especially when participants are excluded via complete-case analysis.

There are numerous additional methodological or reporting concerns outlined below that the authors may hopefully be able to address and clarify, especially with the additional application of a reporting summary/checklist. Two of the most important questions about potential weaknesses are mentioned immediately below, and the remainder are included in the Minor Comments section further down.

What was the study base and sampling strategy? It's unclear whether the population is a selected or more generalizable set of patients representative of the study's target population.

What was the duration of the follow-up period for post-treatment outcomes? It seems that it may have been variable. If so, using logistic regression to analyze data with variable follow-up times could introduce bias, as the model cannot account for differences in patient exposure times. Because participants with shorter observation windows have less time to experience the outcome, ignoring the time-at-risk component can distort the adjusted effect estimates.

Minor Comments:

As noted above, the manuscript would benefit from using a reporting guideline, such as STROBE, to enhance reporting rigor and, in turn, the reader's assessment of the likely reproducibility of the findings.

Abstract

Please include the study design in the title and abstract.

Intro

An important aspect of the stated scientific premise is that there is a lack of data on the association between baseline predictors and treatment outcomes among persons with MDR/RR-TB treated with all-oral regimens as compared to older regimens that included injectables. Can the authors further elaborate on why they might expect this to differ for oral regimens, for example, given their hypothesis that bacillary load and chest radiograph severity predict treatment outcomes?

Methods

Line 143: How was the inclusion criterion of confirmed MDR/RR-TB defined and operationalized? How were patients identified and approached, and were participants recruited consecutively, or was this a convenience sample?

Line 148: Loss to follow-up is a WHO-defined treatment outcome, as outlined in the 2013 guidelines mentioned later, yet these individuals are excluded from the primary analysis.

Line 156: Please clarify for readers the specific indication for extending treatment at 4 months.

Line 158: What were the sources of data, and how were the data collected and recorded?

Line 168: Which individuals performed formal interpretation of chest radiography, and what was their training?

Line 219: How was the sample size determined?

Line 227: The bias referred to here is not quite clearly explained. Specifically. It's not clear how the small number of deaths relates to the selection bias that arises when culture conversion is misclassified.

How many sites were included in the study? Did the authors explore or account for potential correlation within these sites (e.g., due to within-site similarities among patients or practices)? Assuming that such observations are independent may inflate the Type 1 error rate.

In the Cox time-to-culture conversion analyses, the proportional hazards assumption was not assessed. This may lead to an overestimation of the influence of baseline characteristics on treatment outcomes, particularly when key time-varying factors, such as ART usage (or timely refills and adherence to TB medications), are unmeasured and not incorporated into the prediction model.

Results/ Discussion

Line 264: Please report how many had pulmonary vs extrapulmonary TB, and state how many diagnosed

The authors note that the amount of missing baseline data is modest, which they use as justification for the missing-indicator approach. However, this missingness is amplified for the predictor data for the clinical phenotypes, reaching around 20-25%. Given the modest size of these subgroups, this introduces substantial risk of residual confounding and selection bias when participants are excluded via complete-case analysis.

Figures and Tables

Please define the STEM-TB Lesotho Cohort, which is used as a header for many of the tables but not otherwise mentioned.

What proportion of persons living with HIV were receiving ART, and what proportion of those not receiving ART were initiated on ART, and at what time points? Given the favorable impact of ART on TB treatment outcomes, this represents a potentially significant unmeasured confounder.

Supplement

AI Declaration

The author of this review acknowledges the use of the following AI tools, with direct oversight:

- 1) Grammarly, to improve the wording and clarity of the review.
- 2) ChatGPT, to assist with clarification and articulation of core epidemiological and biostatistical comments

In no case was manuscript text or data shared with the AI tool or review text autonomously generated.

(Remarks on code availability)

While I was not able to provide a detailed review of the code, what was presented appears appropriate and strengthens the ability of readers to assess the rigor and reproducibility of the analysis.

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Response to Reviewers, *Nature Communications*

Article: Radiographic and Microbiologic Predictors of Treatment Outcomes in Patients Treated with a Shortened All-Oral Regimen for Multidrug- or Rifampicin-Resistant Tuberculosis (MDR/RR-TB): A Prospective Cohort Study in Lesotho

Dear Reviewers,

We thank you for your thoughtful and constructive comments regarding our manuscript. We have carefully considered all suggestions, and have revised the submission accordingly. The following pages provide a point-by-point response to each your individual comments. For clarity, we reproduce each comment, followed by our response and a description of the corresponding changes made to the manuscript.

Reviewer #1

COMMENT 1: Can the authors please describe in the Methods how CXR reading was performed: by who, how many readers, the readers' experience/training, whether a standard form was used to classify the abnormalities or was classification done retrospectively using the prose of the radiologist reports? Were all cavity sizes reported initially or retrospectively? I appreciate that the Discussion addresses limitations with respect to single person reading and potential inter-reader variability.

RESPONSE 1: We have added these details to Lines 209-211 of the Methods section:

“A team of MDR-TB physicians with specialized training in radiographic interpretation prospectively reviewed chest X-rays. Each radiograph was read by a single specialist physician, and findings were recorded in a standardized form.”

COMMENT 2: What was used to determine severity of fibrocavitary disease (severe fibrocavitary disease mentioned on page 7)?

RESPONSE 2: We have included the definition of severe fibrocavitary disease on Lines 223-226:

“...defined here as baseline radiographic evidence of both cavitary disease and fibrosis, with presence of both: (a) at least one cavitary lesion ≥ 5 cm in diameter, and (b) multi-lobe involvement of fibrotic lesions.”

COMMENT 3: The association between reported fibrosis on CXR and outcomes is interesting. Has it been described elsewhere? Bronchiectasis can sometimes have the appearance of fibrosis on Xray- did any patients have CT scans where one could assess whether fibrosis was interstitial thickening versus actually bronchiectasis?

RESPONSE 3: Chest CT scans were not routinely performed in this setting. CT imaging was obtained selectively for patients who were more severely ill and required hospital admission, where it served to guide clinical management rather than for research classification purposes. We have clarified this detail on Lines 217:

“Chest CT scans were not routinely performed.”

We have also added additional sentences addressing this as a limitation on Lines 510-513 of the Discussion:

“While thoracic CT would offer increased resolution and capacity for differentiation, it was not routinely conducted in this cohort. Future studies employing such modalities may further clarify the role of radiographic features requiring CT identification, such as bronchiectasis.”

COMMENT 4: The authors rightfully raise the question about whether some pts had silicosis. Silicosis is known to be associated with poor TB treatment outcomes. It would be of interest to see data on n% of population with history of mining work.

RESPONSE 4: We collected occupational history from all individual patients, and have added this description to Lines 312-314:

“Fifty-two (21.8%) reported an occupational history of mining; 29 (12.2%) additional participants reported other forms of exposure to industrial or construction work.”

COMMENT 5: Can the authors report in a supplemental table the characteristics of participants, other than radiographic abnormalities, that were associated with time to conversion and unfavorable outcome? Could they also report what patient characteristics were associated with radiographing findings (cavities, fibrosis, bilateral disease, severe fibrocavitary disease)? Could there be confounding of associations between CXR abnormalities and conversion/unfavorable outcome due to the other characteristics? I understand the number experiencing outcomes is low which limits the number of variables that can be included in multivariable analyses, but I would be interested to see impact on associations in models adjusting for age, sex, prior TB, and HIV status.

RESPONSE 5: We have added a supplementary table (Supplementary Table 1) of baseline radiographic characteristics, stratified by baseline clinical characteristics of interest. We have also added a supplementary table (Supplementary Table 2) of results of cox hazards and logistic regression analyses of non-radiographic baseline characteristics on time-to-conversion and treatment outcomes. We describe these tables in Lines 324-327:

“Those with radiographic abnormalities were more likely to be male, older, have low BMI, hospitalized at treatment initiation, and have previous history of TB therapy (Supplementary Table 1); however, only hospitalization was associated with study outcomes (end-of-treatment and final post-treatment outcomes; Supplementary Table 2).”

Based on these results, we have also included a separate supplementary table of logistic regression results when models included variables that were both associated with radiographic abnormalities and the outcome. The following descriptions of these data were added on Lines 387-388 and Lines 416-417 for end-of-treatment and final post-treatment outcomes, respectively:

“Models of radiographic features adjusted for hospitalization at start of TB therapy yielded similar findings to those without adjustment (Supplementary Table 3).”

“Models of radiographic features adjusted for hospitalization at start of TB therapy yielded similar findings (Supplementary Table 3).”

COMMENT 6: It strikes me that the radiographic abnormalities associated with the outcomes of interest are all suggestive of substantial delays between disease onset and diagnosis/treatment. Might the study findings further emphasize the importance of screening?

RESPONSE 6: We agree, and have added several sentences addressing this in the Discussion section on Lines 496-502:

“The radiographic features associated with poor outcomes in our cohort are each also suggestive of advanced or chronic progressive disease. This pattern likely reflects delays between disease onset and diagnosis or treatment initiation. As such, our findings also underscore the continued importance of MDR/RR-TB case-finding strategies. Opportune diagnosis and treatment through systematic screening and expanded access to rapid molecular diagnostics may decrease the frequency of high-risk presentations, thereby improving treatment outcomes.”

COMMENT 7: Given the low rate of unsuccessful bacteriological outcomes, I am concerned that some of the phrasing in the abstract may be interpreted by readers as indicating associations between CXR abnormalities and failure/recurrence. As such, could the abstract Results section include the distribution of unfavourable outcomes (n deaths, n failure etc) and mention death in the conclusion? Eg. ... unfavorable outcomes, mostly death, ...

RESPONSE 7: We agree, and have added the following to the abstract:

“...(20 deaths, 3 treatment failure, 4 recurrence)...” (Line 69)

“...unfavorable outcomes—primarily death—...” (Lines 82)

Reviewer #2

Overall

COMMENT 1: What was the study base and sampling strategy? It's unclear whether the population is a selected or more generalizable set of patients representative of the study's target population.

RESPONSE 1: During the study period, all patients with microbiologically confirmed MDR/RR pulmonary tuberculosis were referred for treatment at the Botsabelo Hospital and invited to participate in the study if they met eligibility criteria. Patients were enrolled from all ten districts of Lesotho, including both rural and urban communities. We have added the following details to Lines 165-169 of the Methods:

“Between September 2020 and October 2023, we consecutively enrolled patients (age ≥ 15 years) who were referred to the Botsabelo National MDR-TB Hospital for treatment of microbiologically-confirmed pulmonary MDR/RR-TB. All patients who met eligibility criteria were invited to participate in the study”

COMMENT 2: What was the duration of the follow-up period for post-treatment outcomes? It seems that it may have been variable. If so, using logistic regression to analyze data with variable follow-up times could introduce bias, as the model cannot account for differences in patient exposure times. Because participants with shorter observation windows have less time to experience the outcome, ignoring the time-at-risk component can distort the adjusted effect estimates.

RESPONSE 2: We agree with this point in principle. Participants were followed for 12 months following treatment completion or cure. Because nearly all participants completed the entire post-treatment follow-up (only 2% were LTFU), we elected to use logistic regression rather than a time-at-risk approach. We have included the following additional details regarding post-treatment follow-up to Lines 394-395:

“Nearly all participants with treatment success completed post-treatment follow-up: only 4 (1.9%) were lost to follow-up.”

COMMENT 3: As noted above, the manuscript would benefit from using a reporting guideline, such as STROBE, to enhance reporting rigor and, in turn, the reader's assessment of the likely reproducibility of the findings.

RESPONSE 3: We have submitted a copy of the completed STROBE checklist along with this revision.

Abstract

COMMENT 4: Please include the study design in the title and abstract.

RESPONSE 4: We have added “Prospective Cohort Study” to the title, and “prospective cohort study” to Line 59 of the abstract.

Intro

COMMENT 5: An important aspect of the stated scientific premise is that there is a lack of data on the association between baseline predictors and treatment outcomes among persons with MDR/RR-TB treated with all-oral regimens as compared to older regimens that included injectables. Can the authors further elaborate on why they might expect this to differ for oral regimens, for example, given their hypothesis that bacillary load and chest radiograph severity predict treatment outcomes?

RESPONSE 5: We have included additional context addressing this in Lines 116-145 of the introduction, and have also reformatted these paragraphs for clarity:

“While associations between bacillary burden, radiographic severity, and poor outcomes have been described for injectable-containing and longer oral regimens, it remains unclear whether such relationships translate to shortened, all-oral regimens, which differ in fundamental pharmacological respects. The aminoglycosides used in older regimens are concentration-dependent bactericidal agents which require aerobic intracellular transport and exhibit limited activity in regions of low-oxygen fibrotic or necrotic tissue [15, 16]. Core agents of contemporary all-oral regimens—including bedaquiline, linezolid, and fluoroquinolones—exhibit distinct pharmacokinetic and pharmacodynamic profiles and do not have the same aerobic dependency, such that the relationship between radiographic burden and impaired microbiological clearance may differ meaningfully from that observed with injectable-based regimens. Furthermore, durability of treatment response and patterns of relapse may differ between regimen types (injectable versus all-oral, prolonged versus shortened), given differences in total treatment time and each regimen’s sterilizing activity within anatomically-complex lesions.

To-date, patient-level factors associated with unfavorable outcomes for those who are treated with shortened, all-oral regimens remain incompletely characterized, with existing evidence limited by heterogeneous regimens and endpoints, and limited evaluation of detailed radiographic features and key subgroups. Prolonged time to culture conversion associated with the cavitary disease/high smear grade phenotype was observed in a small prospective cohort of patients treated with a shortened all-oral regimen [9], but whether additional radiographic features—such as baseline presence of fibrosis, bilateral pulmonary involvement, or the relative size and number of cavitary/fibrotic lesions—may further improve prediction of poor outcomes among patients with pulmonary MDR/RR-TB remains largely unknown. The prognostic utility of these features among patients with HIV co-infection—which has been associated with atypical radiographic presentation [17, 18]—also requires further investigation. These considerations underscore the importance of characterizing whether baseline bacillary load and radiographic severity similarly predict unfavorable on-treatment outcomes and post-treatment relapse specifically in the context of shortened, all-oral regimens.”

Methods

COMMENT 6: Line 143: How was the inclusion criterion of confirmed MDR/RR-TB defined and operationalized? How were patients identified and approached, and were participants recruited consecutively, or was this a convenience sample?

RESPONSE 6: We describe inclusion and exclusion criteria in the follow sections:

“We conducted a prospective observational study within the Lesotho National Tuberculosis and Leprosy Program as part of STEM-TB (NCT05871489), an operational research study of novel all-oral, shortened regimens for MDR/RR-TB. Between September 2020 and October 2023, we consecutively enrolled patients (age ≥ 15 years) who were referred to the Botsabelo National MDR-TB Hospital for treatment of microbiologically confirmed pulmonary MDR/RR-TB. All patients who met eligibility criteria were invited to participate in the study; a full list of exclusion criteria can be found in the Supplementary Material (Appendix A).” (Lines 163-169)

“All patients were enrolled and initiated on treatment at Botsabelo MDR-TB Hospital in Maseru, which served as the sole centralized MDR-TB treatment facility in Lesotho throughout the study period. Patients were drawn from all ten districts of Lesotho, encompassing both urban and rural settings. Following enrollment, Botsabelo clinicians maintained active monthly follow-up of all patients through structured visits to their home communities and districts for the duration of treatment. A program for decentralization of MDR-TB care commenced during the study period, resulting in a small number of patients transitioning their care to one district-level health facility following initial evaluation at Botsabelo.” (Lines 176-184)

COMMENT 7: Line 148: Loss to follow-up is a WHO-defined treatment outcome, as outlined in the 2013 guidelines mentioned later, yet these individuals are excluded from the primary analysis.

RESPONSE 7: We discuss the analysis for the very few ($n=2$) individuals who were lost to follow-up in this cohort in the Methods on Lines 246-249 and Lines 298-300:

“A very small proportion of participants ($n=2$, 0.8%) were lost-to-follow-up. Given this, and because we hypothesized that radiographic characteristics would be predictive of death and treatment failure (but not LTFU), we excluded losses to follow-up from the primary analysis and included them in a separate sensitivity analysis.”

“...sensitivity analyses including the two participants who were lost to follow-up as having unfavorable end-of-treatment and final post-treatment outcomes.”

COMMENT 8: Line 156: Please clarify for readers the specific indication for extending treatment at 4 months.

RESPONSE 8: We have added these details to Lines 191-194:

“Treatment could be extended up to 12 months based on clinical discretion, considering (1) microbiologic and radiographic evolution after 4 months of initial therapy, (2) presence of pulmonary lesions ≥ 2 lung fields, and (3) pertinent comorbidities including HIV and diabetes mellitus.”

COMMENT 9: What were the sources of data, and how were the data collected and recorded?

RESPONSE 9: We have added the following description on Lines 200-202:

“Demographic, clinical, and laboratory data were prospectively collected by clinicians

on standardized clinical forms as part of routine care and entered into an electronic medical record.”

COMMENT 10: Line 168: Which individuals performed formal interpretation of chest radiography, and what was their training?

RESPONSE 10: We have added these details to Lines 208-211 of the Methods section:

“MDR-TB physicians with specialized training in the interpretation of radiographic findings prospectively reviewed radiographs and recorded findings using a standardized form.”

COMMENT 11: Line 219: How was the sample size determined?

RESPONSE 11: We have included the following additional detail in the Methods section on Lines 184-186:

“The parent study was descriptive in nature, and no formal sample size calculation was conducted. All eligible consecutive individuals initiating treatment at during the study period were included.”

COMMENT 12: Line 227: The bias referred to here is not quite clearly explained. Specifically. It's not clear how the small number of deaths relates to the selection bias that arises when culture conversion is misclassified.

RESPONSE 12: We have clarified this and replaced “selection bias” with “survival bias” on Lines 271-272. We have also provided a reference which describes this phenomenon, ie. how extension of baseline sputum culture window beyond the date of treatment initiation may introduce bias. (*Rodriguez et al, PLOS One 2022*):

“Although extending the baseline window beyond treatment initiation can introduce survival bias in culture conversion analyses...”

COMMENT 13: How many sites were included in the study? Did the authors explore or account for potential correlation within these sites (e.g., due to within-site similarities among patients or practices)? Assuming that such observations are independent may inflate the Type 1 error rate.

RESPONSE 13: We have clarified these details on Lines 176-184 of the Methods. Because there was only one primary recruitment and care delivery site, we did not explore site-specific correlation:

“All patients were enrolled and initiated on treatment at Botsabelo MDR-TB Hospital in Maseru, which served as the sole centralized MDR-TB treatment facility in Lesotho throughout the study period. Patients were drawn from all ten districts of Lesotho, encompassing both urban and rural settings. Following enrollment, Botsabelo clinicians maintained active monthly follow-up of all patients through structured visits to their home communities and districts for the duration of treatment. A program for decentralization of MDR-TB care commenced during the study period, resulting in a small number of patients transitioning their care to one district-level health facility following initial evaluation at Botsabelo.”

COMMENT 14: In the Cox time-to-culture conversion analyses, the proportional hazards assumption was not assessed. This may lead to an overestimation of the influence of baseline characteristics on treatment outcomes, particularly when key time-varying factors, such as ART usage (or timely refills and adherence to TB medications), are unmeasured and not incorporated into the prediction model.

RESPONSE 14: We have added details regarding the proportional hazards assumption to Lines 343-345:

“We found no evidence of violations of the proportional hazards assumption (Schoenfeld Residual $p > 0.05$ for all univariable models; $p = 0.63$ for four-factor multivariable model).”

Results/ Discussion

COMMENT 15: Line 264: Please report how many had pulmonary vs extrapulmonary TB, and state how many diagnosed

RESPONSE 15: All participants included in the cohort had pulmonary TB. Additional extra-pulmonary involvement was observed in a small minority. We have added these details to Lines 311-312:

“...5 (2.1%) had concurrent extra-pulmonary disease.”

COMMENT 16: The authors note that the amount of missing baseline data is modest, which they use as justification for the missing-indicator approach. However, this missingness is amplified for the predictor data for the clinical phenotypes, reaching around 20-25%. Given the modest size of these subgroups, this introduces substantial risk of residual confounding and selection bias when participants are excluded via complete-case analysis.

RESPONSE 16: We have included the results from complete case analysis only as a set of supplementary tables (discussed on Lines 420-422) to demonstrate that the results from the MIM and CCA approaches were similar, and thus that concern for residual confounding due to exclusion of those missing clinical phenotype data is minimal.

“Sensitivity analyses using a complete-case approach and including the two participants lost to follow-up as ‘unfavorable’ outcomes yielded similar findings (Supplementary Tables 4-8).”

Figures and Tables

COMMENT 17: Please define the STEM-TB Lesotho Cohort, which is used as a header for many of the tables but not otherwise mentioned.

RESPONSE 17: We have added the following details to Lines 163-165 of the Methods:

“We conducted a prospective observational study within the Lesotho National Tuberculosis and Leprosy Program as part of STEM-TB (NCT05871489), an operational research study of novel all-oral, shortened regimens for MDR/RR-TB”

COMMENT 18: What proportion of persons living with HIV were receiving ART, and what proportion of those not receiving ART were initiated on ART, and at what time points?

Given the favorable impact of ART on TB treatment outcomes, this represents a potentially significant unmeasured confounder.

RESPONSE 18: We have added these details to Lines 320-322 of the results:

One-hundred thirty-six (91.9%) were on antiretroviral treatment (ART). Of those not initially on ART, all were started on a dolutegravir-based regimen. Median time between start of TB therapy and ART initiation was 15 days (IQR: 11.5-21 days).