

## Reporting Summary

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### Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- |                                     |                                     |                                                                                                                                                                                                                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | Estimates of effect sizes (e.g. Cohen's $d$ , Pearson's $r$ ), indicating how they were calculated                                                                                                                                                         |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

### Software and code

Policy information about [availability of computer code](#)

Data collection

Demographic, clinical, and laboratory data were prospectively collected by clinicians on standardized clinical forms as part of routine care. Data were entered into an electronic data system, which was based on the Bahmni open-source medical-record system (<https://www.bahmni.org>) and administered by Partners In Health.

Data analysis

Data analysis was conducted using STATA BE version 18

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

### Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

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. Data were entered into an electronic data system, which was based on the Bahmni open-source medical-record system (<https://www.bahmni.org>) and administered by Partners In Health. Data quality checks were performed on a bimonthly basis.

The data reported in this text include protected clinical and patient information managed under the purview of the Lesotho National Tuberculosis Program; raw data containing patient identifier codes are protected and not available due to data privacy restrictions. A de-identified minimum source dataset containing the raw data underlying the main figures and tables has been provided in the Source Data file. To researchers with a methodologically sound proposal, pseudo-anonymized individual participant data that underlie the results reported in the text and tables of this article and a corresponding data dictionary may be made available upon request to Molly F. Franke (molly\_franke@hms.harvard.edu), with an expected response within one month. Data may be shared following joint discussion with the Lesotho National Tuberculosis Program, and upon execution of a data sharing agreement or alternate means that allows assurance that principles of Lesotho regulations will be met.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

### Reporting on sex and gender

Assigned biological sex was collected as a patient baseline clinical characteristic variable. Sex was not specifically considered as part of the study design, given that this was a prospective cohort study which consecutively enrolled patients (age  $\geq 15$  years) who were referred to the Botsabelo National MDR-TB Hospital for treatment of microbiologically-confirmed pulmonary MDR/RR-TB, regardless of sex. As with all other baseline clinical / demographic characteristics reported in Table 1, sex was evaluated for potential inclusion in multivariable models (see Supplementary Tables 1 and 2). However, we observed no significant association between sex and the outcomes of-interest in this study, namely time to culture conversion and end-of-treatment outcomes. Sex was thus not included as a covariate in adjusted/multivariable analyses, which were primarily for evaluation of associations between baseline radiographic features and our clinical outcomes of-interest.

### Reporting on race, ethnicity, or other socially relevant groupings

Race and ethnicity were not collected or reported variables within this study.

### Population characteristics

See above

### Recruitment

Between September 2020 and October 2023, we consecutively enrolled patients (age  $\geq 15$  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).

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.

### Ethics oversight

This study was approved by the Lesotho Ministry of Health National Ethics Committee and the Harvard Longwood Campus Institutional Review Board.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

## Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

### Study description

Quantitative prospective cohort study

### Research sample

We consecutively enrolled patients (age  $\geq 15$  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).

Identifying microbiological and radiographic characteristics that distinguish individuals at high risk for unfavorable outcomes may also permit further optimization of therapeutic strategies. This is particularly pertinent in high-burden, resource-limited settings of sub-Saharan Africa, where timely identification of patients at risk for poor outcomes may help to improve treatment success and enhance resource allocation. Lesotho, which has one of the highest TB incidence rates globally, high rates of HIV co-infection, and a high prevalence of MDR/RR-TB, represents a priority setting for such analyses

### Sampling strategy

All patients who met eligibility criteria were invited to participate in the study. 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.

### Data collection

Demographic, clinical, and laboratory data were prospectively collected by clinicians on standardized clinical forms as part of routine

care. Data were entered into an electronic data system, which was based on the Bahmni open-source medical-record system (<https://www.bahmni.org>) and administered by Partners In Health. More than 100 data quality checks were performed on a bimonthly basis to identify data that were potentially missing or erroneous; data were corrected as needed.

|                   |                                                                                                                                                                                                                                                                                                    |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Timing            | Between September 2020 and October 2023, we consecutively enrolled patients (age $\geq 15$ years) who were referred to the Botsabelo National MDR-TB Hospital for treatment of microbiologically-confirmed pulmonary MDR/RR-TB.                                                                    |
| Data exclusions   | For this analysis, we excluded participants if they were withdrawn from the study (e.g., late exclusion due to baseline drug resistance, or severe extra-pulmonary disease) (n=11), lost to follow-up (n=2), or were not evaluated due to transfer to a non-study site (e.g., South Africa) (n=4). |
| Non-participation | See above                                                                                                                                                                                                                                                                                          |
| Randomization     | This was a prospective observational cohort study; participants were not randomized.                                                                                                                                                                                                               |

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a                                 | Involved in the study                                  |
|-------------------------------------|--------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Clinical data      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

|                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical trial registration | STEM-TB (NCT05871489)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Study protocol              | Study protocol details relevant to the analyses of this manuscript have been reported in either the Methods or Supplementary Material. Further details regarding the full study protocol are included in a separate manuscript reporting the safety and overall effectiveness of the five-drug regimen in Lesotho--this manuscript is currently under revision.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Data collection             | <p>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 <math>\geq 15</math> 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).</p> <p>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. 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.</p> |
| Outcomes                    | <p>We considered three primary outcomes: time to culture conversion, end-of-treatment outcome, and final post-treatment outcome. Culture conversion was defined as two consecutive negative sputum cultures obtained at least 7 days apart, with the specimen collection date of the first negative result used as the date of conversion.</p> <p>Study clinicians determined end-of-treatment outcomes, based on definitions provided by the 2013 WHO reporting framework for tuberculosis. Participants were considered 'cured' if treatment was completed without evidence of failure, with three or more negative consecutive cultures taken at least 30 days apart at the end of treatment. The outcome of 'completed' was assigned if treatment was completed without evidence of failure, but there was no record of obtaining three or more consecutive negative cultures at least 30 days apart by the end of treatment. Treatment failure was defined as a permanent regimen change of at least two initial agents due to lack of conversion, bacteriological reversion, evidence of acquired resistance, or adverse drug reactions. End-of-treatment outcome was deemed overall 'favorable' if a participant was assigned the status of 'cured' or 'completed' and</p>                                                                                                                                                                                                                                                                                                                                        |

deemed 'unfavorable' if treatment failed (based on outcomes reporting definitions described above) or if the participant died during treatment.

## Plants

Seed stocks

n/a

Novel plant genotypes

n/a

Authentication

n/a