BMJ Public Health

Protocol for the effectiveness of multimonth refill of antituberculosis drugs (MORAD) on treatment success among people with drug-susceptible tuberculosis in rural eastern Uganda: a non-inferiority randomised trial

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To cite: Izudi J, Bajunirwe F, Cattamanchi A. Protocol for the effectiveness of multimonth refill of antituberculosis drugs (MORAD) on treatment success among people with drug-susceptible tuberculosis in rural eastern Uganda: a non-inferiority randomised trial. *BMJ Public Health* 2024;**2**:e001136. doi:10.1136/bmjph-2024-001136

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjph-2024-001136).

Received 6 March 2024
Accepted 6 August 2024

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ABSTRACT

Introduction Multimonth dispensing of antituberculosis (TB) drugs reduces frequent visits and costs associated with longer travel distances to a TB clinic. We will evaluate the effectiveness of multimonth dispensing of anti-TB drugs on treatment success in individuals with drug-susceptible TB in rural eastern Uganda, and explore its relevance and appropriateness from the stakeholders' perspectives.

Methods and analysis In this open-label, non-inferiority, individually randomised trial, we will randomise 260 participants to either the intervention (multimonth dispensing of anti-TB drugs) or control arm (routine care) and follow-up for 6 months. Intervention participants will receive monthly anti-TB refills for 2 months then a 2-month refill for 4 months, totalling four visits. Control participants will receive routine care comprising biweekly anti-TB refills for 2 months and monthly refills for 6 months, totalling eight visits. The primary outcome will be treatment success (treatment completion or cure) at month 6. Secondary outcomes will include adherence to anti-TB treatment over 6 months measured by self-report and pill counts, and sputum smear conversion at months 2 and 6 defined as a change in sputum smear status from positive to negative among bacteriologically confirmed individuals. Data will be analysed using a generalised linear mixed model at a 5% significance level, reported as a risk difference with a 95% CI. A formative qualitative study will be conducted among stakeholders at the national, district and health facility levels and people with TB including their treatment supporters to inform the intervention's relevance, appropriateness and implementation. Qualitative data gathered through focus group discussions and in-depth and key informant interviews will be transcribed and analysed using content analysis.

Ethics and dissemination The Infectious Diseases Institute Research Ethics Committee and the Uganda National Council for Science and Technology approved the protocol. Findings will be disseminated to all stakeholders through presentations, synthesised reports and manuscript publication.

Trial registration number PACTR202403586718783.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Frequent health facility visits and longer travel distances to tuberculosis (TB) clinics contribute to suboptimal treatment success among people with TB due to direct and indirect costs leading to missed TB clinic visits and compromised treatment adherence.

WHAT THIS STUDY ADDS

⇒ We will implement multimonth dispensing of anti-TB drugs as a novel and innovative approach to reducing frequent health facility visits and overcoming physical and economic barriers that deter people with TB from picking up their medications at a TB clinic. We hypothesise that multimonth dispensing of anti-TB drugs will be non-inferior to routine care in improving TB treatment success rate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Evidence from this study will inform policy and guideline changes by the Uganda National TB Control Programme and similar settings, including providing preliminary data needed for the design of a large-scale interventional study.

BACKGROUND

The global treatment success rate for people with drug-susceptible tuberculosis (TB) is 88%,[1] and the WHO has set a target of ≥90%.[2] Uganda's treatment success rate was 88% in 2022,[3] falling short of the global target, which is crucial for preventing TB transmission at the household and population levels, including morbidity and mortality at the individual level. Frequent health facility visits and longer travel distances to TB clinics contribute to suboptimal treatment success among people with TB due to both direct and indirect costs, missed visits and compromised

treatment adherence. Under routine care, individuals with drug-susceptible TB require eight visits to a TB clinic for medication collection, starting biweekly for the first 2 months and then monthly for the next 4 months.[4] Under routine care, TB clinic visits are frequent and studies have shown that people with TB who live distant from a TB clinic frequently miss scheduled visits as long travel distances pose an economic and physical barrier to medication pick-ups.[5] For example, a ≥5 km travel distance from home to a TB clinic is associated with a reduced chance of treatment success and a higher chance of mortality among people with TB.[6] Residing ≥2 km from a TB clinic has been reported to be associated with an increase in the likelihood of unfavourable treatment outcomes, namely death, treatment failure and loss to follow compared with residing within a 2 km radius of a TB clinic.[7] Interventions that improve access to medication pick-ups and minimise frequent health facility visits are urgently needed to optimise treatment success among people with TB.

In this study, we propose to implement multimonth dispensing of anti-TB drugs as a novel and innovative approach to reducing frequent health facility visits. This approach might overcome the physical and economic barriers that deter people with TB from adhering to scheduled medication pick-ups at a TB clinic. The Uganda Ministry of Health under the differentiated antiretroviral therapy (ART) delivery models has recommended multimonth dispensing for people living with HIV (PLHIV) regardless of their TB status provided that an individual is stable on ART.[8] Furthermore, the guideline permits a ART refill of 3–6 months for high-risk individuals in whom frequent drug pick-ups compromise adherence.[8] Multimonth dispensing of ART has shown promising results among PLHIV in recent years. Studies that have evaluated the effect of the COVID-19 pandemic restrictions on treatment outcomes among PLHIV in Uganda have found that multimonth dispensing of ART was extensively used for PLHIV regardless of TB status[9] including ensuring the continuity of ART delivery.[10]

Improvements in viral load suppression and reduction in mortality among PLHIV during the COVID-19 pandemic compared with the prepandemic period have been attributed to the multimonth dispensing of ART in a recent evaluation study.[11]

Anecdotal evidence suggests that multimonth dispensing of anti-TB drugs was extensively used during the COVID-19 lockdown to ensure continuity in TB treatment. However, evidence of its effectiveness in improving treatment success among people with TB is lacking. Therefore, the multimonth refill of anti-TB drugs (MORAD) study is designed to evaluate the effectiveness of multimonth dispensing of anti-TB drugs (intervention) compared with routine care in improving treatment success among people with drug-susceptible TB aged ≥15 years receiving the standard 6-month anti-TB regimen in rural eastern Uganda. Before the effectiveness study, we will explore stakeholder perceptions on the relevance, appropriateness and delivery of multimonth dispensing of anti-TB drugs. The proposed multimonth dispensing of anti-TB drugs has the potential to reduce direct and indirect costs associated with frequent health facility visits and to ensure person-centred TB care. Evidence from this study will inform policy and guideline changes by the Uganda National TB Control Programme and similar settings in order to improve TB treatment outcomes, including providing preliminary data needed for the design of a large-scale interventional study in Uganda.

Table 1 The MORAD study sites in rural eastern Uganda

Districts	Hospitals (n=4)	Health centre IVs (n=6)
Soroti	Soroti Regional Referral Hospital	Princess Diana and Tiriiri
Kumi	Kumi and Atutur Hospitals	Kumi
Serere		Serere and Apapai
Ngora	Ngora Hospital	Ngora

MORAD, multimonth refill of anti-TB drugs.

MATERIALS AND ANALYSIS

Study setting

The MORAD study will be implemented across 10 TB clinics in 4 districts in rural eastern Uganda (table 1). In this region, the majority of people with TB travel ≥5 km to access TB treatment leading to suboptimal treatment outcomes.[5 6] The study will target health facilities with high patient load (50 or more people with TB registered and treated annually) in order to feasibly reach the desired sample size. The TB clinics are managed by experienced medical, clinical or nursing officers who are the focal persons for TB and all the clinics adhere to the National TB Control Programme guidelines for standardised care.

Trial design

The MORAD study is designed as a two-arm, non-inferiority, open-label, individually randomised trial. Findings will be reported per the Standard Protocol Items: Recommendations for Interventional Trials guideline.[12] The protocol is registered with the Pan African Clinical Trials Registry (PACTR202403586718783). Participants will enrol in the study starting 17 June 2024 and ending 31 October 2024, with the anticipated date of the last follow-up as 31 April 2025.

The participants will include people with drug-susceptible TB aged ≥15 years being initiated on TB treatment. We will include those with clinically diagnosed pulmonary TB (PTB), bacteriologically confirmed PTB and extrapulmonary TB, receiving the standard 6-month regimen at the study sites. We will exclude those with TB meningitis and osteoarticular TB as their treatment lasts longer than 6 months (including potential for

modification depending on the treatment response), those critically ill requiring close clinical and laboratory monitoring including hospitalisation and those likely to migrate during the trial. Participants will be consecutively sampled and distributed proportionately to the size of the TB clinic, guided by existing data on the number of people with TB who are treated annually.

Expert clients (people successfully treated for TB who assist at the TB clinic) will provide non-technical study information during health talks. Research assistants will screen and recruit eligible individuals using standardised screening and enrolment forms. No additional strategies for participation retention will be implemented rather than providing key TB messages under routine care.

Randomisation and blinding

We will perform a stratified block randomisation by study site to ensure balance in important covariates including the number of participants across the trial arms. We will stratify the participants by sex (males vs females) and within each stratum, a block size of 4 will be constructed, and the research assistants will randomise eligible individuals to the intervention or control arm. The randomisation sequence will be a priori-determined, sealed in a well-marked opaque envelope, and only opened whenever eligible individuals consent to participate in the study. Randomised individuals will thereafter be linked to the TB focal person for anti-TB treatment initiation. Blinding of the participants and TB focal persons will be impractical but the data analyst will be blinded to the study arms using unique codes during data analysis.

Intervention versus control group

Table 2 shows the scheduling of anti-TB refills. All participants will receive a standard 6-month anti-TB regimen comprising rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by RH for 4 months (2RHZE/4RH) as a fixed-dose combination, same key TB messages according to national guidelines, and Medication Event Reminder Monitor (MERM) to track TB medication adherence. In the intervention group, the participants will receive multimonth refills of anti-TB drugs, with the treatment schedule as monthly for 2 months followed by a 2-month refill for 4 months (overall, 4 visits). People with bacteriologically confirmed PTB will receive sputum smear follow-up testing at 2 and 6 months, which is sufficient to establish whether the individual is cured or not. The timing and frequency of MORAD will be modified based on the findings from a formative qualitative study. In the control group, participants will receive routine care, with the anti-TB treatment refills scheduled biweekly for 2 months followed by monthly for 4 months (overall, eight visits). People with bacteriologically confirmed PTB receive sputum smear follow-up testing at 2, 5 and 6 months. Individuals who withdraw from the intervention group will automatically fit into the control group.

Study outcomes

TB treatment success will be the primary outcome, measured by treatment completion or cure being recorded as the treatment outcome in the TB treatment register. Individuals with treatment outcomes of failure, death or loss to follow-up will be considered unsuccessfully treated. The secondary outcomes will include monthly adherence to anti-TB treatment and sputum smear conversion at months 2 and 6 among those with bacteriologically confirmed PTB. The monthly anti-TB adherence rate will be calculated as the number of pills taken divided by the number expected to have been taken, expressed as a percentage. Adherence rates <85% will be considered poor, 85%–94% as good and ≥95% as excellent.

Sputum smear conversion will be measured as a change in sputum smear status from positive to negative among patients with bacteriologically confirmed PTB following sputum smear microscopy testing. Non-sputum smear converters will be managed according to the national TB treatment guidelines.

Data collection methods and tools

Data will be collected using a researcher-administered questionnaire and validated tools (table 3). Baseline sociodemographic data will include age, sex, level of education, employment, marital status and the estimated distance to the TB treatment unit in kilometres. Clinical data will include the type of person with TB (new vs previously treated), TB disease classification, HIV status, the form of directly observed therapy short course, treatment supporter availability and type, and pre-existing conditions (eg, diabetes mellitus, hypertension and asthma). Health facility-level data will include the type of ownership, level of care and location (rural vs urban).

Social and lifestyle data will include alcohol consumption and cigarette smoking. Mental health data will include psychological distress and depression. Alcohol consumption will be measured using the Alcohol Use

Table 2 Treatment schedule for the intervention and control participants

Study arm	Intensive phase refills				Continuation phase refills			
Control	2 w	2 w	2 w	2 w	1 m	1 m	1 m	1 m
Intervention	1 m		1 m		2 m		2 m	

2 w denotes a 2-week anti-TB refill, 1 m denotes a 1-month anti-TB refill and 2 m denotes a 2-month anti-TB refill. The dark grey colour denotes routine care and the light grey colour represents the intervention.
TB, tuberculosis.

Table 3 Summary of the data collection schedule

	Baseline	Follow-up and end of the study					
Type of data	0	1	2	3	4	5	6
Sociodemographic data							
Alcohol consumption using AUDIT-C							
Cigarette smoking							
Psychological distress using the Kessler tool							
Depression using PHQ-9							
Treatment adherence							
Sputum smear follow-up testing						X	
End-line data collection							

X denotes no data collection for the intervention group.
AUDIT-C, Alcohol Use Disorders Identification Test Consumption; PHQ-9, Patient Health Questionnaire.

Disorders Identification Test Consumption (AUDIT-C) tool,[13] a 10-item screening tool although the initial measurement will use 3 questions each measured on a 0–4 scale (the overall score will be 12). Individuals with AUDIT-C scores ≥5 will receive a full assessment using a set of 7 extra questions to evaluate for harmful alcohol consumption. The risk of harmful alcohol consumption will be graded based on total scores as 0–7, 8–15, 16–19 and ≥20 to suggest low, increasing, high and possible dependence, respectively. The Kessler Psychological Distress Scale, a 10-item checklist with 5 value responses ranging from 10 to 50, will be used to evaluate psychological distress[14] with total scores of 10–15, 16–21, 22–29 and 30–50 to suggest low, moderate, high and very high psychological distress, respectively.

Depression will be assessed using the Patient Health Questionnaire-9, a 9-item checklist that screens for depression in the past 2 weeks with each question scored on a 0–3 scale,[15] overall 0–27. Individuals with total scores of 0–4, 5–9, 10–14, 15–19 and 20–27 will be considered to have minimal, mild, moderate, moderately severe and severe depression, respectively. All individuals with severe depression will be linked to a mental health unit for further assessment and management.

Adherence will be measured using MERM each month, computed and reported at each clinic visit by the TB focal person. MERM is a digital pillbox that automatically reminds patients to take their medications, enabling real-time monitoring of adherence.[16] For this study, the MERM notifications will be turned off in order to prevent sending automatic messages and impacting adherence and study outcomes. The MERM will have multiple blister packs for anti-TB drugs to support the daily dosing and refills. The MERM will collect data on dosing histories based on pillbox opening, and transmit the data to a central server which will then be downloaded by TB focal persons at refill visits to document the monthly average adherence rates.[16] The treatment outcomes data, categorised into the six WHO standard outcomes, namely cure, completed, failure, loss to follow-up, transfer out and not evaluated will be obtained from the TB register.

Sample size estimation

We hypothesise that the intervention will improve treatment success among people with drug-susceptible TB. The rationale for this hypothesis is focused on the intervention's potential to reduce the need for frequent TB clinic visits thereby enhancing TB treatment adherence as missed TB clinic appointments for medication pick-ups will be minimised. We anticipate a 6% difference in treatment success (effect size) between the intervention and control groups. In our recent study in rural eastern Uganda, we found 81.1% treatment success among people with drug-susceptible TB.[2] Assuming a 6% non-inferiority margin, 80% statistical power, and a 1.11 design effect, the study will need 260 participants (130 intervention vs 130 control) in a 1:1 ratio. This sample size estimation was computed in R V.4.2.1 using the 'SampleSize4ClinicalTrials' package.[17]

Data analysis

We will summarise the baseline data based on the study arms. Numerical data like age will be summarised using the mean and the SD when normally distributed, or the median and the IQR when skewed. Categorical data such as sex will be summarised as frequencies and percentages. We will assess the distribution of baseline categorical data between the study arms using the χ^2 test for larger cell frequencies and Fisher's exact test for smaller cell frequencies. Mean differences in numerical data will be assessed using the Student's t-test if normally distributed or the Wilcoxon-rank sum test if skewed. The level of statistical significance will be set at 5%.

The effectiveness analysis will use the intention-to-treat (ITT) and per-protocol (PP) principles. The ITT analysis will analyse data for all participants randomised to the intervention or control arm, regardless of their adherence while the PP analysis will only analyse data for those who adhered to the randomisation arm. We will use a

multivariable generalised linear mixed-model with identity link and binomial distribution, adjusting for fixed and random effects to estimate the effect of the intervention on the study outcomes and report the adjusted risk differences with a 95% CI. Variables such as age groups, sex, TB disease classification, HIV status, treatment support availability and pre-existing conditions will be considered as fixed effects while random effects will include the district and the health facility ownership type as well as the level and location. To assess if the intervention is non-inferior to routine care, we will consider a 95% CI for the risk difference being less than 6% (the non-inferiority margin). We anticipate that the intervention effect will vary based on factors such as sex, HIV status, TB disease classification and TB type. Therefore, a subgroup analysis using an interaction term between the intervention and these variables will be fitted.

Formative study to inform the intervention before the conduct of a randomised trial

To inform the relevance and appropriateness of the intervention (multimonth dispensing of anti-TB drugs), the randomised trial will be preceded by a formative qualitative study to explore the stakeholder perceptions about the intervention including the needed modifications regarding the frequency and timing.

We will conduct key informant interviews (KIIs) with stakeholders at various levels, and in-depth interviews (IDIs) with people with TB and their treatment supporters (table 4). Eligible stakeholders at the regional and district levels will have ≥3 years of TB work experience. Eligible people with TB will be those on TB treatment for ≥4 months, including their respective treatment supporters. We deem that such individuals and treatment supporters are better placed to share lived experiences while under routine care and to contrast those experiences with the proposed intervention. Eligible TB focal persons will be those involved in TB care for ≥1 year to provide an objective assessment of the potential benefits of the intervention to the healthcare system and people with TB. We will exclude those that we are not able to access during the data collection period. We will conduct 3–4 focus group discussions (FGDs) with 8–10 people with TB aged ≥18 years. Participants from the IDIs will be invited to participate in the FGD. Two individuals will conduct the FGDs, with one as the moderator and the other as a note-taker. The moderator will introduce the discussion topics, set the ground rules and guide the whole discussion. The note-taker will capture the discussions and summarise the key issues. After each FGD, the moderator and note-taker will review and summarise emergent issues. FGDs are expected to take <2 hours. All the participants will be purposively sampled.

Measurements and data collection

The formative qualitative study will use the Consolidated Framework for Implementation Research (CFIR) to thoroughly analyse the implementation contexts and identify both facilitators and barriers to the intervention,[18 19] including exploring the intervention's practicability, relevance and implementation strategy. Table 5 describes the CFIR domains. We will explore treatment adherence challenges among people with TB and their preferences for early follow-up, either at 2 weeks or every 2 months.

We will explore the timing and approach for involving TB treatment supporters, the type of people with TB who might benefit from the intervention, the expected benefits of the intervention for people with TB and the healthcare system and whether the intervention would lead to improvements in TB treatment success. Overall, we will ask whether the stakeholders would recommend the intervention including the reasons. IDIs targeting people with TB and their treatment supporters will be conducted by trained qualitative research assistants in the local language ('Ateso') within the health facility premises. The research assistants will have ≥5 years of qualitative research experience and hold a minimum diploma

Table 4 List and numbers of stakeholders for formative qualitative study

Level	Participant description	Number eligible
National (n=3)	NTLP Program Manager	1
	NTLP Head of Laboratory Services	1
	Director Clinical Services	1
Regional (n=1)	Regional TB Focal Person	1
District (n=12)	District Health Officers	4
	District TB and Leprosy Supervisors	4
	District Laboratory Focal Person	4
Health facility (n=50)	TB Focal Persons	10
	People with TB	2 per health facility (n=20)
	TB treatment supporters	2 per health facility (n=20)
Total		**66**

NTLP, National TB and Leprosy; TB, tuberculosis.

Table 5 The CFIR domains and the descriptions

CFIR domains	Explanation and examples
Intervention characteristics	Features of the intervention that might influence its implementation; for example, whether intervention would be considered a simple or complex approach, whether the frequency of refills is appropriate, the relative advantage of intervention compared with the routine care, and the quality of evidence leading to its trialability
Inner setting	Factors within the healthcare system that might either positively or negatively influence the implementation of multimonth dispensing of anti-TB drugs. Notable factors include leadership or management support for intervention implementation, attitudes of implementers towards multimonth dispensing of anti-TB drugs, newer approaches to the delivery of anti-TB drugs that might compete with multimonth dispensing of anti-TB drugs, education of people with TB and the perception of people with TB and including health workers about multimonth dispensing of anti-TB drugs.
Outer setting	The external or environmental factors that might influence the implementation of multimonth dispensing of anti-TB drugs, either positively or negatively. They will include treatment support availability, the presence of adherence support systems and social factors like alcohol consumption that hinder adherence to treatment among others
Characteristics of the stakeholders involved in implementing the intervention.	For example, people with TB might report symptom resolution leading to compromised treatment adherence. Other considerations include concomitant treatment for other diseases, and personal level factors like sex, age and previous TB treatment among others
Implementation process	Factors that might influence the process of implementation of the intervention such as the timing, initial preparations needed to ensure successful implementation and plans for monitoring and evaluating the implementation among others

CFIR, Consolidated Framework for Implementation Research; TB, tuberculosis.

in health sciences. KIIs will be conducted in person at the workplace in English.

Sample size will depend on the saturation principle, a point at which no new information emerges even when additional data are collected.[20] However, the a priori sample size estimate to reach the saturation point is presented in table 4. We will perform verbatim transcription of qualitative data within 24–48 hours, verify through re-reading and reading, and rectify any discrepancies. The data will be organised and analysed using the CFIR domains through content analysis by two analysts (JI and NW) to prevent subjective biases. JI is a public health specialist with nearly 10 years of experience in mixed-methods research. NW is a sociobehavioural scientist with 12 years of experience in qualitative research. In the analysis, approximately 5–10 transcripts will be first read by the analysts several times to achieve familiarity, enabling them to develop the initial codes that will form the primary codebook attained through discussions and consensus. The analysts will read the remaining transcripts several times and perform both inductive and deductive coding using the existing primary codebook. Newer codes will be allowed to emerge and the analysis might take different and unpredictable directions. Once coding is completed, the codes will be combined to form categories and then basic, organising, central and global themes, all aligned with the CFIR domains and presented with texts. We will adhere to the guidelines set by the Consolidated Criteria for Reporting of Qualitative Research.[21]

Quality control measures and research transparency and reproducibility

We will use pretested and validated tools for data collection. The research assistants and TB focal persons will be trained in responsible research conduct, study protocol, recruitment and data collection procedures. We will replay all audio recordings, summarise the main findings within the first 48 hours and transcribe within 5 days. A team leader will be hired to oversee the research assistants and review completed data collection tools to ensure completeness during data collection. We will input the quantitative data into Epi-Data, along with quality control measures such as skips, alerts, range and legal values. We will create a preanalysis plan and prespecify the regression model to prevent p-hacking, deposit the dataset and statistical analysis codes in Dryad and publish the dataset as Data-in-Brief.

Patient and public involvement

The MORAD study has developed a community engagement plan which has been approved by the IDI-REC and the UNCST. Stakeholders at the local, district, regional and national levels, including people with TB and their treatment supporters will be involved in designing the study. In a formative study, these participants will be asked to provide insights about the relevance and appropriateness of the intervention, and the appropriate implementation strategy, including modifications if needed. This will ensure ownership, compliance and sustainability of

the intervention, including awareness among people with TB.

Trial steering committee

The IDI-REC will assign an independent monitor who will conduct scheduled and unforeseen visits to the study sites to oversee recruitment, randomisation, follow-up, data collection, handling and storage.

A trial steering committee (TSC) comprising a biostatistician or an epidemiologist, bioethicist, participant representative and health workers will be constituted to monitor the study implementation, data quality, outcomes and harm to participants. The TSC will make recommendations to stop the study if interim analysis shows harm or strong benefit, including study design and sample size changes if needed.

Dissemination plan

We will validate the findings through presentations and discussions at each study site and conduct a dissemination workshop to share the findings with stakeholders. We will share study site-specific reports, present the findings at local and international conferences and publish the study findings as manuscripts in peer-reviewed journals.

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Acknowledgements We thank NW for their prospective role in the qualitative data analysis, including the data analysis plan.

Contributors JI is the first and corresponding author; JI and AC conceptualised the study; JI, FB and AC designed the study; JI will acquire the data; JI and FB will analyse the data and JI, FB and AC will interpret the data; JI, FB and AC drafted the initial and final manuscripts; JI, FB and AC performed critical revisions of the manuscript. All authors (JI, FB and AC) approved the final version of the manuscript. JI accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding Funding for this research was provided by the Center for Effective Global Action (CEGA) through funding from the National Institutes of Health (NIH) (award number: N/A).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The MORAD study has received ethical approval from the Infectious Diseases Institute Research Ethics Committee (reference number: IDI-REC-2023-33) and the Uganda National Council for Science and Technology (reference number: HS3863ES). The National TB and Leprosy Control Program at the Uganda Ministry of Health and all District Health Offices have provided administrative clearances. Participants will provide written or thumb-printed informed consent after understanding the study''s social and scientific values, benefits, risks, privacy, confidentiality, scientific validity, and post-enrolment participant protection, including withdrawal (online supplemental material S1 and S2).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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