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Evaluation of alternative bacteriological measures of response to therapy during the initial 16-weeks of MDR-TB (drug resistant tuberculosis) treatment

Submission date
22/04/2021

Recruitment status
No longer recruiting

Registration date
23/04/2021

Overall study status
Completed

Last Edited
04/06/2021

Condition category
Infections and Infestations

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) is a disease caused by bacteria called Mycobacterium tuberculosis. The bacteria usually attack the lungs, but they can also damage other parts of the body. TB spreads through the air when a person with TB of the lungs or throat coughs, sneezes, or talks.
Effective treatment monitoring is vital not only for proper patient management but also for preventing the unnecessary continuation of failing treatment and the emergence of more drug-resistant Mycobacterium tuberculosis (Mtb). Treatment monitoring by sputum culture is the gold standard for TB treatment. However, this method has several problems, including high operational costs and long turnaround times.
The challenge is to develop better alternatives that will protect the currently effective drugs and streamline the development of new drugs for multi-drug resistant tuberculosis (MDR-TB). The aim is to evaluate the effectiveness – compared with culture colony forming units (CFUs) determination – of alternative methods for measuring the response to therapy during the initial 16 weeks of MDR-TB treatment. These methods will be analyzed to determine how well they predict MDR-TB patient treatment outcome.

Who can participate?
Patients with 18 years of age or older and diagnosed with RR/MDR-TB according to local standards methods.

What does the study involve?
Two sputum (spit) samples, a spot and an overnight sample, will be collected from participants at weeks 0, 2, 4, 6, 8 and once during month 3 and 4. Follow-up will be active during the intensive phase and passive during the continuation phase up to 18 months of MDR-TB treatment to document treatment outcomes.
Samples will be pooled and homogenised and divided into three portions. Portion one will be used for respectively, 1) FDA- treated AFB smear microscopy, 2) PMA-Xpert/ULTRA assay, and 3) liquid culture for Mtb-TTP. Portion two will be used for 16s rRNA detection in an MBLA assay and

portion three for CFUs/mL determination. Data will be analysed for correlation of the results of the alternative methods with results based on reducing culture CFUs.

What are the possible benefits and risks of participating?
There will be no direct benefit to the patient from this study. Enrolled patients will benefit from the standard treatment monitoring methods which are not usually readily available in routine. In the long term, the patient will benefit communities if innovative ways of monitoring response to therapy during MDR-TB treatment will be found.
The only potential risk to the patients is a breach of confidentiality. Once a patient has consented to participate in the study, s/he will be assigned a study identification number in order to link obtained results and patient data. Linking of identifying information, such as patient name and date of birth, to the study identification number will appear only on a cover sheet of the patient data form. These data forms will be kept in a locked cabinet only accessible by the investigators. Sputum and urine samples and subsequent isolates will be labeled with the date of sputum collection and the patient's study identification number. After the patient's participation in the study is completed, the cover sheet will be destroyed, unlinking the study identification number and de-identifying the data. Data entry will be performed on-site by the local investigators in a password-protected database. Only the study investigators will have access to these data.

Where is the study run from?
The study is run at Mulago National Referral Hospital TB wards 5 and 6, Kampala, Uganda.

When is the study starting and how long is it expected to run for?
November 2019 to October 2022

Who is funding the study?
This project (MDRTBTx-Monitor) is part of the EDCTP2 programme supported by the European Union (Grant Number – TMA2018CDF-2351)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Alternative measures of response to MDR-TB treatment

Acronym
MDRTBTx-Monitor

Study objectives
There is imperfect correlation of these alternative measures with MGIT-TTP for measuring response to MDR-TB treatment during the initial 16 weeks.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/02/2019, Makerere University, School of Biomedical Sciences Research and Ethics Committee (The Secretariat Makerere University College of Health Sciences, Clinical Research Building, School of Biomedical Sciences IRB Office, P.O Box 7072, Kampala, Uganda; +256 75 2575 050; irbbiomedicalsciences@gmail.com), ref: SBS-651

Study design
Observational cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Alternative measures of response to MDR-TB (drug-resistant tuberculosis) therapy

Interventions

A prospective study of 59 patients' ≥ 18 years of age with MDR-TB diagnosed according to local standards will be enrolled into the study. Two sputum samples, a spot, and an overnight will be taken at weeks 0, 2, 4, 6, 8, 12 and 16 of MDR-TB treatment. Samples will be pooled and homogenized and divided into three portions for:
1) FDA- treated AFB smear microscopy
2) PMA-Xpert/ULTRA assay
3) liquid culture for Mtb-TTP

Sample collection and laboratory procedures
Both overnight and spot samples will be collected and pooled. A urine sample will be collected from consented patients at each interval for future studies. Samples will be taken at weeks 0, 2, 4, 6, 8, 10, 12 and 16 during treatment for clearly stated analysis to establish which of the assays correlate with treatment response. The consented newly diagnosed patients who will be hospitalized for up to the initial two months of MDR-TB treatment, as a routine, will be given instructions on producing an overnight and spot sample. Specimens will be collected in the hospital for the first two months. For month three patients will be given instructions and a sputum container on discharge to collect an overnight sample at night and come with it to the clinic during the monthly follow-up visit and a spot sample will be collected on site.
Samples will be registered at the hospital and then transported to the College of American pathologists (CAP) accredited Mycobacteriology (BSL3) laboratory in the Department of Medical Microbiology, College of Health Sciences, Makerere University for analyses. Samples and their requisition forms will be labelled with participant identification number and not participant's name.
The overnight and spot sputum samples will be pooled, homogenized and divided into three portions. Portion one will be processed with a mixture of sodium hydroxide (NaOH) and sodium citrate (final NaOH concentration 1.5%) for 15 minutes and neutralized with phosphate buffered saline (PBS; pH 6.8). This will be centrifuged for 15 minutes, decanted and a pellet re-suspended in 2 ml of PBS ready for the following procedures. 1) For FDA smear microscopy, approximately 100 µl of the re-suspended pellet will be smeared for FDA- treated AFB smear microscopy following the current standard operating procedures for FDA processing and reporting at the proposed study site laboratory 2) For PMA-Xpert ULTRA assay PMA solution in sterile deionized water will be added to 200µl of liquefied sputum samples to a final concentration of 100µM. After 15minutes light exposure, the specimen will be loaded in Xpert ULTRA cartridge without the Xpert sample reagent and loaded in the Xpert machines with ULTRA software according to manufacturer's instructions and study specific SOPs. Mean Ct values will be obtained from the Xpert machine probes, 3) For MGIT-TTP, samples will be inoculated in MGIT tubes and incubated in MGIT 960 machines for up to six weeks. Any machine positive sample will be cultured on blood agar plate for 24 hours to rule-out contamination and a smear will be made for detection of AFB. All samples with AFB will be subjected to rapid identification assay for the MPT64 antigen which is specific for M. tuberculosis complex (MTBc). Valid machine TTP will be those from samples with no growth on blood agar, AFB positive and MTBc on identification. All results will be interpreted according to site laboratory standards for reporting results and TTP.
The leftover sputum samples and isolates from positive cultures will be stored for future studies. The third portion will be processed for extraction of RNA to be analysed for qPCR to detect M. tuberculosis 16s rRNA using MBLA SOP[17] which will be customized at the study site laboratory. A portion of the extracted RNA will be stored in the H3-Africa biorepository on site for future studies.

All laboratory procedures will be done according to previously developed standard operating procedures (SOPs). No change to the national standards of diagnostic evaluation or treatment

will occur as a result of this study. All proposed laboratory procedures will be done at the College of Health Sciences, Makerere University. All laboratory procedures will be performed by trained personnel following the SOPs and biosafety requirements.

Intervention Type
Other

Primary outcome(s)
Sputum bacterial load burden, measured using Culture colony forming units (CFUs) as a reference standard, with MGIT time to positivity, Xpert PMA, FDA, Smear Microscopy, and TB-MBLA measured at weeks 0, 2, 4, 6, 8, 12 and 16

Key secondary outcome(s))
1. Patient clinical characteristics will be collected using a detailed data collection tool at baseline (week 0)
2. Baseline resistance profiles will be collected from the existing patient records at the clinic and tested using phenotypic drug susceptibility testing (DST) whenever possible
3. Adherence measured using available clinical data and as collected by the study nurse during MDR-TB treatment
4. HIV-status will be collected as documented in the clinic patient records at baseline

Completion date
31/10/2022

Eligibility

Key inclusion criteria
1. Adults >18 years of age
2. Have a productive cough
3. Sputum specimens that are positive for acid fast bacilli by microscopy (1+ to 3+, smear-positive)
4. Have been classified as MDR TB

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

1. Prisoners
2. Subjects <18 years of age
3. Patients who are unable to provide ≥3mL of sputum specimen for testing
4. Patients on anti-TB treatment

Date of first enrolment
12/02/2020

Date of final enrolment
30/09/2022

Locations

Countries of recruitment
Uganda

Study participating centre
Mulago National Referral Hospital, TB ward 5 and 6
Upper Mulago Hill road
Mulago Hospital complex
Kampala
Uganda
7072

Sponsor information

Organisation
Makerere University

ROR
https://ror.org/03dmz0111

Funder(s)

Funder type
Research organisation

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)

Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.
Throughout our study we aim at limiting identifying data collection. This is done through coded data collection, no collection of names, only year of birth, and gender on the case report form (CRF). Only authorized study staff have access to study records and the study database is access controlled according to data management standards. The results from standard diagnostic tests i.e. smear microscopy and culture are made available to participants through their attending clinician. We shall make data available to the public through publications and community engagement as outlined in the dissemination section of this report. Publications will be through open access and data will be made available to the NTP. Records will be retained for audit and inspection purposes after the completion of the study. The essential/source documents will be retained for 2 years after the completion of the study and the investigator will inform EDCTP prior to destroying any study records.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes