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Expanding Xpert MTB/RIF Ultra® and LF-LAM testing for diagnosis of tuberculosis among HIV-positive adults admitted to hospitals in Tanzania and Mozambique: a randomized controlled trial (the EXULTANT trial)

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Abstract

Introduction Tuberculosis (TB) is an important cause of morbidity and mortality among people living with HIV (PLHIV). Current WHO-recommended strategies for diagnosing TB among hospitalized PLHIV rely on symptom screening and disease severity to assess eligibility for urine lipoarabinomannan lateral flow (LF-LAM) and molecular testing. Despite these recommendations, autopsy studies show a large burden of undiagnosed TB among admitted PLHIV. The EXULTANT trial aims to assess the impact of an expanded screening strategy using three specimens (sputum, stool, and urine) for TB diagnosis among PLHIV admitted to hospitals in two high HIV and TB burden African countries.

Methods This is a multicenter, pragmatic, individually randomized controlled trial conducted across eleven hospitals in Tanzania and Mozambique. Participants in the intervention arm will be tested with Xpert MTB/RIF Ultra® from expectorated sputum, stool, and urine samples, with additional urine LF-LAM testing in the first 24 h after hospital admission, irrespective of the presence of the symptoms. The control arm will implement the WHO standard of care recommendations. Hospitalized adults (≥ 18 years) with a confirmed HIV-diagnosis, irrespective of antiretroviral (ART) therapy status or presence of TB symptoms will be assessed for eligibility at admission. Patients with a pre-existing TB diagnosis, those receiving anti-tuberculosis therapy or tuberculosis preventive treatment in the 6 months prior

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to enrolment, and those transferred from other hospitals will not be eligible. Also, participants admitted for traumatic reasons such as acute abdomen, maternal conditions, scheduled surgery, having a positive SARS-CoV2 test will be ineligible. The primary endpoint is the proportion of participants with microbiologically confirmed TB starting treatment within 3 days of enrolment.

Discussion The EXULTANT trial investigates rapid implementation after admission of a new diagnostic algorithm using Xpert MTB/RIF Ultra® in several non-invasive specimens, in addition to LF-LAM, in hospitalized PLHIV regardless of TB symptoms. This enhanced strategy is anticipated to detect frequently missed TB cases in this population and is being evaluated as an implementable and scalable intervention.

Trial registration Trial reference number: NCT04568967 (ClinicalTrials.gov) registered on 2020–09-29.

Keywords Tuberculosis, HIV, TB diagnosis, TB case-finding, Enhanced screening

Introduction

Tuberculosis (TB) remains one of the leading causes of morbidity and mortality worldwide, resulting in 7.5 million newly diagnosed TB cases and 1.3 million deaths in 2022 [1]. Mortality from TB disproportionately affects people living with HIV (PLHIV), with approximately 6.3% of the TB cases occurring among PLHIV and 11.7% of the total deaths [1]. In hospitalized PLHIV, TB is highly prevalent and often fatal [2, 3]. Several autopsy studies, including a meta-analysis of post-mortem studies, have uncovered the large burden of undiagnosed TB among admitted PLHIV (46% of participants undiagnosed at death) [2]. Thus, early diagnosis and rapid initiation of TB treatment are deemed essential strategies to reduce TB related mortality among hospitalized PLHIV [4, 5].

The WHO testing recommendations for PLHIV who have signs and symptoms of TB include testing sputum samples using a molecular WHO-recommended rapid diagnostic test (mWRD) and utilizing urine samples for rapid LF-LAM. The latter is recommended to be performed in seriously ill participants, those with advanced HIV disease, or those with CD4 < 200cells/mm3, regardless of the presence of TB signs and symptoms [6]. However, despite the reasonable sensitivity of mWRDs such as Xpert MTB/RIF Ultra® (hereinafter Xpert Ultra) and urine LF-LAM, microbiological confirmation of TB remains a challenge among hospitalized PLHIV. Approximately 54% of inpatients with TB symptoms are unable to produce a quality sputum specimen [7]. In PLHIV, the nature of the disease is often paucibacillary in respiratory specimens, resulting in low bacillary load in sputum [7–10]. This hinders TB diagnosis based on sputum alone in this population. The use of LF-LAM has been shown to increase TB diagnosis during hospitalization while reducing mortality at day 56 in those with low CD4 counts, the occurrence of severe anaemia, or with clinically diagnosed tuberculosis [11]. However, while many high burden TB countries have developed policies for using LF-LAM, the test is not widely implemented [12]. Utilization is further challenged by inter-reader variability of test interpretation and the need for CD4 count testing.

Bearing the limitations of the current diagnostics, there is a need to develop new testing strategies and diagnostic algorithms for hospitalized PLHIV. Recently, urine and stool samples have shown promise in enhancing bacteriological confirmation for TB among PLHIV who are more likely to test negative through traditional sputum-based diagnostic methods [13–15]. Studies have shown that urine-based Xpert Ultra, alone or in combination with LF-LAM testing, may enhance TB diagnosis in PLHIV admitted to hospital [11, 16, 17]. Detection of *M. tuberculosis* (*M.tb*) DNA in stool can also increase bacteriological confirmation in both children and PLHIV [18–20]. Moreover, multiple-sample approaches using mWRDs and LF-LAM have been shown to improve TB survival while being cost-effective [21].

The EXULTANT trial aims to assess the impact of an expanded TB testing strategy in obtaining bacteriological confirmation among PLHIV within 72 h of hospital admission in Tanzania and Mozambique, two high TB/HIV burden African countries. We hypothesize that combining different biological samples and diagnostic tests (sputum, urine and stool Xpert Ultra in addition to LF-LAM) offered as a screening intervention to hospitalized PLHIV will increase the bacteriological yield compared to the current WHO recommended screening and testing strategies. We expect the enhanced testing strategy will contribute to earlier initiation of TB treatment and, ultimately, to an overall reduction in mortality.

Methods

Study design

This is a multicenter, open-label, pragmatic individually randomized controlled trial to evaluate the impact of an expanded screening strategy using 3 specimens (sputum, stool or rectal swab, and urine) for TB diagnosis among

PLHIV admitted to hospitals in 2 high HIV and TB burden African countries (Tanzania and Mozambique). This trial will allocate hospitalized PLHIV 1:1 to 'intervention' and 'standard-of-care' arms. Participants in the intervention arm will be tested with Xpert Ultra on expectorated sputum, stool or rectal swab, and urine, with additional urine LF-LAM testing performed in the first 24 h after enrollment in the study, irrespective of the presence of TB signs and symptoms, with test results available within the first 72 h. Participants allocated to the 'standard of care' arm will be screened for TB according to the WHO recommendations for TB testing among hospitalized PLHIV.

Study sites and study population

The study will be implemented in eleven hospitals associated with four research centers in Tanzania and Mozambique. In Tanzania, the enrolment of study participants will be taking place at Mbeya Zonal Referral and Mbeya Regional Referral Hospital in collaboration with the National Institute for Medical Research (NIMR), and at St Francis Regional Referral Hospital, Temeke Regional Referral Hospital and the Mwananyamala Regional Referral Hospital all working with Ifakara Health Institute (IHI). In Mozambique, the trial will be implemented at Manhiça District Hospital, Macia District Hospital, and Magude Rural Hospital, and Xinavane Rural Hospital working with Centro de Investigação em Saúde de Manhiça (CISM), and the Mavalane General Hospital and Jose Macamo General Hospital working with Insituto Nacional de Saúde (INS).

The trial will screen for eligibility among consecutive adults who are admitted to the adult hospital ward (18 years old and above) with a confirmed HIV diagnosis (new or existing diagnosis), irrespective of antiretroviral treatment (ART) status, with or without TB symptoms. Participants who are unwilling to provide consent, are currently on anti-TB therapy, have received a TB diagnosis, have taken any anti-TB therapy or TB preventive treatment (TPT) in the 6 months prior to enrolment, have a positive SARS-CoV-2 test (i.e., RT-PCR, antigen-based test), or have been transferred from other non-participating referral hospitals, will not be eligible. Other exclusion criteria include hospital admission for any of the following reasons: trauma, acute abdomen conditions, maternal conditions (delivery or pregnancy), or planned/scheduled surgery. Participants living outside the hospital catchment area or with plans to migrate outside the catchment area within 2 months after recruitment will also be excluded from the study.

Study procedures

Enrollment and randomization

Potential participants will be offered participation in the study within 24 h of admission (as recorded in medical chart). When individuals cannot respond, participation and consent will be obtained from the caregiver or next of kin. After obtaining written informed consent and evaluating all inclusion and exclusion criteria, baseline socio-demographic and relevant clinical characteristics of participants will be collected including history of TB, HIV, and current TB symptoms, among others. This information will be collected from the existing medical records or from the caregiver or next of kin if the participant cannot respond. Additionally, personal contact information (from the participant, caregiver, or next of kin) will be collected to facilitate follow-up. Participants will then be randomized 1:1 to either the control (standard-of-care) or intervention arm. Randomization will be stratified by site using a computer-generated random block size, through a form created in Open Data Kit (ODK) Central, an online system accessible through a user-restricted URL that can be opened in any web browser. Allocation will be pre-defined in an external database and concealed to study staff. Access to the platform is personalized for selected clinicians at each site and password protected. Each participant will be randomized on the date of enrollment (study Day 0).

Study arms

In the 'intervention arm', participants will receive TB testing regardless of the presence of TB symptoms. Diagnostic testing will be performed at the routine or research laboratories using Xpert Ultra on expectorated sputum, stool, and urine, as well as bedside LF-LAM in urine. It is recommended that specimens be collected as soon after enrolment as possible, preferably within the first 24 h. However, specimens may be collected within the first 72 h after enrolment. All Xpert Ultra and LF-LAM results will be sent back to the clinician. Additional samples such pleural, abdominal, and pericardial fluid as well as cerebrospinal fluid will be investigated using Xpert Ultra may be performed at the discretion of the study doctor. Participants with TB will be managed by the routine attending physicians following established national guidelines for hospitalized PLHIV.

Participants randomized to the 'standard of care' arm will be managed as per WHO recommendations [6]. These include testing sputum samples or any relevant extrapulmonary samples using Xpert Ultra as mWRD and urine LF-LAM if TB signs and symptoms (cough, fever, weight loss or night sweats) are reported. Additionally, LF-LAM will be used to test urine of participants who are seriously ill (defined by being unable to walk

unaided, respiratory rate over 30/min, fever of more than 39ºC, and/or a pulse rate of over 120/min), those with advanced HIV disease, or with CD4 < 200cells/mm3. CD4 count and HIV viral load testing will be provided to participants in both arms. The treating physician may order any additional tests to be performed as deemed necessary for patient management. Urine from participants in both study arms, together with two tongue swabs from those in the intervention arm, will be bio-banked for future testing.

Participant follow up

During hospitalization, the study team will record relevant data on the participant's clinical progress, irrespective of study arm, including whether a TB diagnosis is made and/or anti-TB treatment started. Ad-hoc TB investigations (i.e., additional Xpert Ultra tests, LF-LAM testing, X-ray) and the respective results will be captured. Death or diagnoses of comorbidities during hospitalization will also be recorded using the international classification of diseases (9th edition). HIV care management will follow the respective national guidelines.

If discharged, the participant will attend follow-up visits (face-to-face or by phone) at week 4 and week 8 (window -/+3 days for week 4 and -3/+7 days for week 8) for clinical monitoring and confirmation of vital status, whether a new TB diagnosis was made and/or anti-TB treatment started. Study staff will record any new TB investigation performed after discharge and the result (by checking medical records and by asking the participant). Participants will be considered lost to follow-up after three separate phone call attempts (on different days and at different times of the day) and a home visit without success. Deaths happening from discharge to week 8 will also be recorded from hospital records or as reported by the relatives.

Laboratory procedures

Hospitalized participants will be asked to produce sputum, urine, and stool samples and encouraged to drink water to stimulate urine production (unless contraindicated). Rectal swabs will be collected from participants in Mozambique who are unable to spontaneously produce a stool sample within 24 h of enrolment (this procedure is not authorized by the IRB in Tanzania). Tongue swabs will also be collected and stored for later testing. Specimens will be processed at the routine hospital or research laboratories at each site, which have the capacity to perform all necessary laboratory tests and return test results within the rapid timeframe required. Stool or rectal swab Xpert Ultra testing will be done following the KNCV SOS method (https://www.kncvtbc.org/en/sos-stoolbox/). Prior to Xpert Ultra testing, approximately 40–50 mL of urine will be centrifuged at 3000 g for 15 min at 2–8°C, and the urine pellet resuspended in approximately 2 mL of phosphate buffer saline (PBS). Exactly 0.75 mL of the resuspended urine pellet will be mixed with 1.5 mL of Xpert sample reagent (SR), incubated for 15 min, and then added to the Xpert Ultra cartridge for testing. Rapid LF-LAM testing will be done by applying 60 µL of unconcentrated urine to the Alere Determine™ TB LAM Ag assay strip and incubating at room temperature for 25 min (time-set). The strip will then be visually inspected, and the intensity of any visible band on the strip will be graded according to the manufacturer-supplied Reference Scale Card. LF-LAM tests will be interpreted by two independent readers at the hospital, and results will be recorded. In case of discrepancy, a third reader will be used as a tie-breaker. Invalid tests will be repeated on the same urine sample and indeterminate test results rerun on a new urine sample. LF-LAM tests will be read prior to the results of the sputum Xpert Ultra (if performed) and without knowing any clinical details of the participant to reduce bias.

Results will be reported to the attending physicians as soon as they are available. LF-LAM results should be available within two hours from specimen collection, and Xpert Ultra results should be reported within 24 h of sample collection from the participating hospital laboratory.

Study endpoints

The primary trial endpoint is the proportion of participants diagnosed with microbiologically confirmed TB and started on TB treatment within 72 h of enrolment.

Secondary endpoints include: i) Eight-week all-cause mortality among all participants enrolled; ii) Proportion of participants who are diagnosed with microbiologically confirmed TB and are started on treatment at 7 days, 14 days, 4 weeks and 8 weeks of enrolment; iii) Proportion of participants who are diagnosed with TB (irrespective of bacteriological confirmation) and are started on TB treatment within 3 days of enrolment; iv) Time to TB diagnosis among microbiologically-confirmed TB cases v) Time to TB treatment initiation among microbiologically confirmed and all TB casest; vi) Proportion of study participants who are able to provide the different specimens (sputum, stool and urine samples) within 24, 48 and 72 h of enrolment and vii) in-hospital and 4-week all-cause mortality among all participants enrolled (assessed as the eight-week all-cause mortality). Another endpoint of interest is the proportion of participants with rifampicin resistance who are started on treatment.

Endpoints will be captured during hospitalization through face-to-face interviews, review of medical records, and during the week 4 and week 8 follow-up

visits. In order to ascertain TB treatment initiation and vital status, study staff will also extract information from the national TB registers and will conduct a household visit in events where participants do not answer the phone. In this study, microbiologically-confirmed TB will be defined as any positive test result including Xpert Ultra tests performed on urine, sputum, stool or extrapulmonary samples, and LF-LAM urine test.

Sample size

The sample size of the trial was calculated based on a series of key assumptions about the proportion of admitted PLHIV diagnosed with TB in hospitals in Sub-Saharan Africa and the potential contribution of the different tests proposed in this study [11, 17, 22]. Based on the yield of Xpert in previous studies, the added sensitivity of Xpert Ultra and the expected proportion of participants with criteria for LAM testing, we assumed that the current WHO recommended algorithm will diagnose 19% of participants with bacteriologically confirmed TB.

We have estimated that the universal screening in our intervention arm with urine, sputum, stool Xpert Ultra and LF-LAM would lead to an absolute 7% increase in bacteriological confirmation. This is based on various assumptions. First, an added 1% from the control arm given that TB LAM and sputum testing will be performed universally. Second, previous studies using Xpert in urine have shown that urine could contribute to around 4% additional bacteriological confirmation [11, 23]. This estimation is based on the calculation of an increase of positivity of 4% given by the addition of Xpert Urine [23] (1) in bacteriologically confirmed cases and the added Yield of Xpert Ultra (4–6) in comparison to Xpert [10, 24, 25].

Although limited evidence of the contribution of Xpert on stool has been reported in this particular population, we have conservatively estimated that it could add a 1% absolute increase in bacteriological confirmation. An additional 1% comes from the increased yield of Xpert Ultra (instead of Xpert) in urine and stool [26].

Assuming that we will find 19% of bacteriologically confirmed cases in the control arm following the WHO indications for sputum Xpert Ultra and LF-LAM in HIV hospitalized participants, a two-sided type I error of 5% and a pretreatment loss to follow up of 5%, the inclusion of 586 participants per arm would provide an 80% power to detect a 7% increase in the percentage of bacteriologically confirmed TB diagnosis in the intervention arm.

Statistical analysis

The trial will be analysed according to a pre-specified statistical analysis plan, agreed to by statisticians that will not be involved in study implementation. We will analyse the data using an intention to treat (ITT) approach as the primary analysis, but we will also perform a per protocol (PP) analysis with those meeting protocol procedures. Thus, in the primary analysis, we will include all randomized participants and no participant will be excluded in the statistical analysis based on incomplete sample collection or schedule of study visits (Table 1).

We will compare the primary endpoint between study arms, from which time-to-endpoint will be calculated as the difference in days between the enrolment date and date of death, treatment initiation, or TB diagnosis for endpoints of all-cause mortality, for TB treatment initiation, and TB diagnosis, respectively. We will test this relationship using a Chi-square test and will accept differences if the test p-value is lower than critical value (0.05). If data do not meet application conditions, we will use the Fisher Exact test. We will calculate logit-transformed 95% confident intervals. We will compare the proportions as a prevalence difference and we will stratify by study countries and baseline CD4 counts. For secondary endpoints related to the proportion of participants with TB or bacteriological TB starting treatment by a specific time point, we will compare study arms similarly to the primary endpoint. We will also estimate Kaplan Meier curves to assess the proportion of participants initiating TB treatment over time, with comparisons using the log-rank test. Comparisons of mortality by study groups will be done as a risk difference with 95% CI, and subgroup analysis made by country, site, CD4 count and viral load.

A per protocol analysis of main study endpoints will be conducted using a per protocol population, including those in whom the protocol-recommended tests were done and results were available within 3 days from enrolment. Reporting of study results will follow CONSORT guidelines. Statistical analysis will be performed using R version 4.3.2 or higher.

Ethical considerations

All sites have obtained local and national level ethical and regulatory approvals according to the respective requirements at each site (Ref: 27/CNBS/22 in Mozambique, SZEC-2439/R.A/V.1/135a and TMDA/WEB0022/CTR/0002 in Tanzania). Hospitalized participants will provide written informed consent in their respective languages prior to enrolment. When participants cannot respond, participation and consent will be offered to the caregiver or next of kin. The trial has been registered under the Clinical Trials Registry maintained by the National Library of Medicine at the National Institutes of Health, ClinicalTrials.gov Identifier: NCT04568967.

Table 1 Schedule of events in EXULTANT clinical trial

	Day 0 (Enrolment) Control Arm	Day 0 (Enrolment) Intervention arm	Day 0–3 (< 72 h)	Daily (Inpatient)	At discharge	Week 4 (± 3 days)	Week 8 (-3/ + 7 days)
Baseline evaluation							
Informed consent	X	X					
Inclusion criteria verified	X	X					
Locator information	X	X					
Brief medical history	X	X					
Proof of HIV Status	X	X					
WHO symptom screening	X	X		X			
TB and other lab investigations	Urine LF -LAM[b]	Urine LF-LAM					
Samples collected and tests	Sputum Ultra[a]	Sputum Ultra					
	Blood CD4 count / viral load[c]	Stool Ultra					
		Urine Ultra					
		Urine LF-LAM					
		2 × Oral Swabs					
		Blood CD4 count / viral load					
Results issued			X				
Further contacts							
Verification of TB diagnosis / ad hoc investigations			X	X	X	X	X
Verification of TB treatment initiation			X	X	X	X	X
Verification of vital status			X	X	X	X	X
HIV care/ART status			X	X	X	X	X

[a] Sputum Xpert Ultra whenever the participant has cough, fever, weight loss or night sweats and/or Ultra on any tissue (including lymph nodes) from participants with suspected extra pulmonary TB

[b] Urine LAM if participants have signs and symptoms of TB (pulmonary and/or extra pulmonary), or with advanced HIV disease (1) or who are seriously ill (2) or else irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm3

[c] CD4 count testing will be done if not available within the last 3 months. Most recent viral load will be captured (if available)

Discussion

The EXULTANT trial aims to provide evidence of the effect of testing multiple non-sputum based specimens to increase bacteriological confirmation and prompt TB treatment initiation among hospitalized PLHIV under programmatic conditions. The intervention advocates for a universal screening strategy among admitted PLHIV, given the consistently high burden of TB observed in numerous studies among this vulnerable population. Relying solely on symptoms as an initial step for further molecular testing has proven to be inadequate, due to the scarcity of sputum availability and the low sensitivity of this screening method in admitted PLHIV, leading to many TB episodes being missed [7, 27, 28]. Furthermore, the intervention introduces a time-sensitive dimension, aiming to conduct tests and return results to clinicians within 3 days from enrolment. The rationale for this approach is that an early and diligent TB diagnostic workup will minimize undiagnosed TB during hospitalization, consequently increasing the number of individuals correctly initiated on treatment. This approach could ultimately reduce mortality and morbidity.

The proposed strategy leverages already validated and widely available diagnostic tests such as Xpert Ultra in sputum and urine LF-LAM, both of which are endorsed by WHO and part of many National guidelines in high-burden TB and HIV countries. Additionally, it introduces an innovative sample collection strategy that utilizes easily accessible non-invasive and non-sputum-based specimens. The feasibility of this intervention, if proven beneficial, could be easily translated and scaled up programmatically, thereby increasing TB case detection and treatment initiation among admitted PLHIV on a broader scale. The EXULTANT trial design has additional strengths. The study encompasses a diverse profile of HIV-positive participants receiving care from a range of different hospital facilities, various levels of care, and diverse geographical locations, spanning two different countries (Mozambique and Tanzania), as well as rural and urban settings, which will improve

the generalizability of our findings. Furthermore, the EXULTANT trial is a pragmatic trial, embedded within the public health system and aligned with routine programmatic structures. Decisions related to admission, clinical management, treatment initiation, and follow-up visits will follow routine patient care standards. This pragmatic approach ensures that the study findings are rooted in real-world scenarios, contributing to the relevance and applicability of the results in routine clinical practice.

The EXULTANT trial also anticipates certain limitations and circumstances that warrant consideration. First, we expect challenges in obtaining all study samples for each participant. Previous studies have illustrated the complexities in obtaining sputum samples [27]. Studies in children and adults also show that stool collection, despite being acceptable, might not always be possible [29–31]. It is possible that the proposed intervention will be compromised by the capacity of the participants and clinicians to collect the indicated specimen types. Second, although it is an individually randomized clinical trial, given the nature of the intervention, the trial is not blinded for participants and clinicians, introducing the possibility of performance bias in either the control, the intervention arm or both. Attending physicians might lean towards initiating TB treatment more frequently on clinical grounds in the control arm, due to less intensive testing. Conversely, in the intervention arm, increased testing might bias clinicians towards confirming LF-LAM, when bands show low intensity. This limitation has been minimized by including microbiologically-confirmed TB as the primary endpoint, but also through comprehensive training on LF-LAM interpretation for all study staff in both arms. Third, the use of stool Xpert Ultra, though a recommended test for pediatric TB diagnosis, lacks official WHO endorsement for adults living with HIV [32]. Similarly, Xpert Ultra urine is not currently recommended in any population despite some promising evidence from observational studies [33]. Some clinicians, depending on the clinical presentation of the participant, might be reluctant to start treatment despite a positive Xpert Ultra stool or urine test, also introducing bias towards the null effect of the intervention. Fourth, while the selected sites have been carefully chosen due to their availability of GeneXpert platforms at the hospital facilities and experience in TB research, delays in the sample collection or result turnaround-time (TAT) can still occur. Fifth, in Mozambique, rectal swabs will be performed, but not in Tanzania (procedure not approved by IRB). This circumstance might overrepresent the impact of the intervention at Mozambican sites, but could underestimate the impact of stool testing due to lack of specimens in Tanzania. We believe the proportion of patients not able to provide spontaneous stool will be low, although we will still consider the potential reduced effect in Tanzania (due to absence of rectal swab collection in some patients) in the analysis. Lastly, increased uptake of TPT among PLHIV, a criterium for exclusion in the study, may result in lower microbiologically confirmed TB among enrolled participants in the study settings.

In conclusion, The EXULTANT trial investigates a new diagnostic algorithm using existing tools with the aim to improve the number of laboratory-confirmed TB diagnosis among PLHIV admitted to the hospital. Expedited diagnosis by means of easy-to-collect specimens tested using the widely available Xpert Ultra, in addition to LF LAM, applied universally soon after admission is anticipated to be an implementable and scalable intervention. To further assess the viability of this approach, a cost-effectiveness analysis is being considered, in order to evaluate how the additional costs associated with the proposed intervention would compare to the potential gains in TB diagnoses being missed, as compared to the WHO recommended standard of care.

Abbreviations

ART	Antiretroviral treatment
HIV	Human immunodeficiency virus
ITT	Intention to treat
mRDT	WHO-recommended molecular rapid diagnostic test
ODK	Open data kit
PBS	Phosphate buffer saline
PLHIV	People living with HIV
SOS	Simple-one-step method
SR	Sample reagent
TAT	Turn around time
TB	Tuberculosis
TPT	TB preventive treatment
WHO	World Health Organization

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CM, MC, RN, and CK wrote the first draft of the manuscript and prepared the figures. VL, LTP, JE, ALGB, and APN provided critical input and edits to the manuscript. All authors reviewed the manuscript and provided comments.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The protocol has been approved by Mozambique's National Bioethics for Health Committee (27/CNBS/22) and the Tanzania National Institute for Medical Research (SZEC-2439/R.A/V.1/135a and TMDA/WEB0022/CTR/0002). Written informed consent will be obtained from all participants prior to enrolment.

Consent for publication
This section is not applicable, as the manuscript represents a study protocol.

Competing interests
The authors declare no competing interests.

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