The use of a urine lipoarabinomannan test in clinical decision-making regarding empiric tuberculosis treatment among HIV-positive patients suspected to have tuberculosis

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Background. Tuberculosis (TB) is a major contributor to mortality among patients affected by HIV. TB diagnosis can be challenging, especially in those who are severely ill and unable to produce sputum. Urine lipoarabinomannan (LAM) is a rapid point-of-care diagnostic tool that is used on urine. The dilemma arises if a urine LAM test yields a negative result when the clinical presentation is strongly suggestive of TB.

Objective. To investigate how a urine LAM test result changes the physician's decision to start TB treatment in people living with HIV in Kalafong Provincial Tertiary Hospital (KPTH).

Method. A cross-sectional study was done at KPTH in the internal medicine wards, family medicine and HIV outpatient departments. Patients who were HIV positive with a strong TB diagnosis suspicion, had a CD4 count <200 cells/mm^3, were aged >13 years and had a urine LAM done to investigate TB were included. Outcomes investigated were: presenting symptoms, clinical signs, radiological and haematological investigations, including CD4 count and HIV viral load, urine LAM results and whether TB treatment was initiated or not. At KPTH, a register of all patients who have been given a urine LAM test is held at the TB notification centre, which was where the information regarding urine LAM results was retrieved from, as well as whether treatment was initiated or not. The patients' clinical hospital records and National Health Laboratory Service lab results were retrieved for necessary information.

Results. There were 430 patient records and urine LAM results retrieved: 307 (71.4%) had negative results and 123 (28.6%) had positive results. Of the 307 (71.4%) with a negative result, 120 (39.1%) were initiated on treatment, and only 3 of those who had positive results (1.6%) did not receive treatment. The urine LAM test results appeared to influence clinicians' decisions to treat when the result was positive. If the urine LAM was negative, clinicians still initiated treatment based on adequate clinical suspicion and other investigations. There was significant incongruency between patients with a negative urine LAM test who received TB treatment (p<0.001).

Conclusion. The use of the urine LAM did not change the physician's decision to start TB treatment where the was a high suspicion of TB based on clinical presentation and other investigations. Physicians depended more on their clinical intuition where the urine LAM was negative.

Keywords: tuberculosis, TB, HIV, urine lipoarabinomannan, urine LAM

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HIV is a global pandemic, with ~39 million people infected by the end of 2022.[1] Africa is the most affected continent, accounting for 25.6 million of these cases.[2] In 2022, there were ~630 000 AIDS-related deaths worldwide.[1] Tuberculosis (TB) remains one of the leading causes of death among people living with HIV (PLHIV).[2] Globally, ~10.6 million people were affected by TB at the end of 2022,[3] with one-quarter of the world's population infected, making TB the leading communicable disease cause of death worldwide.[4] The World Health Organization (WHO) reported 167 000 deaths among PLHIV due to TB in 2022,[3] underscoring TB as a significant public health concern.

Africa leads in TB/HIV co-infection rates, and is the second most affected continent by TB after Asia, contributing 23% of the global burden in 2021, with 2.4 million cases.[5] In 2021, of the 1.6 million TB-related deaths worldwide, 136 000 PLHIV were from Africa, making TB the dominant cause of death among PLHIV on the continent. More than 50% of TB patients in sub-Saharan Africa are co-infected with HIV.[4] In South Africa (SA), TB is the leading cause of death, driven by the HIV epidemic, with an estimated 270 000 PLHIV developing TB annually, and 89 000 dying from it.[6]

The TB bacterium is inhaled into the lungs, where macrophages kill or contain it, termed latent TB.[4,6,7] As the mycobacteria continue to replicate inside the macrophages, the bacterial load increases. It eventually escapes the macrophages and disseminates to the rest of the lungs. Here the transmission of TB bacilli is facilitated during expectoration of sputum.[4] However, the more advanced HIV disease is in a person, the more disseminated the mycobacterial infection becomes, with less sputum production. Means other than sputum microscopy are therefore necessary to diagnose TB. The risk of infection also depends on the infectiousness of the source, proximity to the source, bacillary load and the host's immune status.[8]

Lawn *et al.*[9] reported that ~45.8% of HIV patients in sub-Saharan Africa die of undiagnosed TB. High mortality and morbidity among severely ill patients are due to challenges in traditional diagnostic tools, making it difficult to obtain sputum, resulting in ~36% of TB cases being undiagnosed or reported late.[4,10]

The WHO recommends the GeneXpert test for diagnosing both pulmonary and extrapulmonary TB.[11] This test detects *Mycobacterium tuberculosis* in specimens, with a sensitivity of 85% and specificity of 98%, and it also provides information regarding

rifampicin sensitivity.[12,13] It is an automated polymerase chain reaction test, and results are obtained within 2 hours after initiating the test.[13]

Sputum microscopy, using Ziel-Nielsen or auramine stains, detects mycobacteria, but has a high false negative rate in advanced HIV-infected patients.[11] The advantage is that it is simple to use, inexpensive and faster. However, it has a low sensitivity and specificity of 50% and 60%, respectively, and cannot detect drug sensitivity.[13]

Culture, the definitive diagnostic method for TB, involves growing TB bacteria from specimens, but is more expensive and time-consuming, taking several weeks to get results.[12,14] It can, however, also assist in drug sensitivity testing.[13]

A randomised controlled trial by Peter *et al.*[10] found that the urine lipoarabinomannan (LAM) test is accurate for early TB detection, contributing to a mortality reduction of ~17%. According to Lawn *et al.*,[15] the specificity of urine LAM is 98% in severely ill PLHIV. LAM is a lipopolysaccharide on the outer cell wall of *M. tuberculosis*, and acts as an antigen. During immune activation and subsequent destruction of *M. tuberculosis*, LAM is released and filtered through the kidneys, where it becomes detectable in urine.[14]

The Alere Determine TB LAM Ag test strip is the only commercially available urinary LAM test kit.[16] The WHO recommends its use for inpatients with symptomatic TB, or CD4 counts <200 cells/μL regardless of TB symptoms. For outpatients, it is recommended for those with TB signs and symptoms and CD4 counts <100 cells/μL.[16] The SA National Department of Health[17] differs slightly, recommending the urine LAM test for inpatients regardless of symptoms and CD4 count, and for outpatients with symptoms and CD4 counts <200 cells/μL. The test involves applying 60 μL of urine to the strip and reading the results after 25 minutes,[16] making it a suitable test for outpatient use.

Empirical TB treatment involves initiating treatment in patients suspected of having TB without positive bacteriological results, but with clinical features and compatible chest X-ray findings.[18,19] McCarthy *et al.*[18] reported that empirical TB treatment is common practice in SA hospitals, associated with improved mortality in areas with limited diagnostic tests. However, Kebede *et al.*[19] reported that empirical treatment did not affect mortality or survival rates, and led to overtreatment. Hermans *et al.*[20] found that routine use of GeneXpert reduced empirical treatment rates owing to decreased TB notifications. Peter *et al.*[21] observed that urine LAM detected patients with advanced HIV and TB disease who had not yet been initiated on TB treatment. Urine LAM testing therefore assists with identifying patients with disseminated TB, who would otherwise not have been provided with treatment, owing to undiagnosed disease. Urine LAM has subsequently been associated with early treatment initiation in patients with CD4 counts <100 cells/μL.

At Kalafong Tertiary Provincial Hospital (KPTH), the high mortality rate among HIV/TB co-infected patients highlights the limitations of existing diagnostic tools, including delayed results and inability to obtain sputum from patients who are unable to expectorate. This leads to prolonged hospital stays and increased transmission risk. Urine LAM offers a quicker, cheaper point-of-care diagnostic alternative. However, a dilemma arises when the test yields negative results despite strong clinical suspicion of TB in the absence of other diagnostic tools.

Methods

A descriptive cross-sectional study was conducted at KPTH in the internal medicine wards and the family medicine and immunology outpatient departments. The hospital is situated in Atteridgeville, and serves the uninsured population of the western and southern districts of Tshwane. A convenience sampling strategy was followed, involving consecutive patients who underwent urine LAM testing. According to KPTH's standard operating procedures (SOPs), urine LAM testing should be performed on PLHIV with a CD4 count <200 cells/μL suspected of having TB. However, patients confirmed to have TB by other means should not receive urine LAM testing, as it adds no diagnostic value.

Exclusion criteria were PLHIV investigated for TB in other wards than the internal medicine wards, or seen in outpatient clinics other than the family medicine and immunology clinics. Additionally, people without HIV, and PLHIV with CD4 counts >200 cells/μL, and patients <13 years old were excluded from the study.

Data collected included demographic information (age, sex, race, comorbidities and location). Clinical variables measured included symptoms such as cough, night sweats, weight loss and diarrhoea, as well as physical examination findings such as emaciation, fever, lymphadenopathy, hepatomegaly and splenomegaly. Laboratory variables included haemoglobin, white cell count, mean corpuscular volume, mean corpuscular haemoglobin, platelets, neutrophils, lymphocytes, C-reactive protein, erythrocyte sedimentation rate, CD4 count, HIV viral load, renal function, electrolytes and liver function tests. Imaging variables included chest X-ray and abdominal ultrasound findings. Histology, cytology and culture results were recorded if available. The initiation of TB treatment was also recorded.

A register of patients who underwent urine LAM testing in the medical wards and outpatient departments was maintained, with results stored at the hospital TB notification centre (focal point). Patient identifiers were extracted from this register, and clinical records were retrieved from the hospital records department. Relevant clinical data were extracted and recorded on clinical record forms. TB treatment data were verified using records from the hospital TB notification centre, and TB notification forms in the patients' clinical records. Laboratory results were obtained from clinical records, or from the National Health Laboratory Service LabTrack system if not found in hospital records.

Data were initially captured on paper-based forms, then electronically using Google Forms, and stored on Google Sheets in password-protected cloud-based storage. The patient's hospital number was the only identifier recorded, to ensure anonymity. Data cleaning was performed in Excel (Microsoft, USA) before analysis.

The sample size was calculated with an α threshold of 0.05 and a power ≥80%. Assuming that 50% of patients undergoing urine LAM testing would have a negative result, and that 40% of those with a negative result would be empirically started on TB treatment, the minimum sample size was determined to be 196 patients with a negative urine LAM test. Assuming a 50% urine LAM negative rate, an overall sample size of 392 urine LAM tests was required. To account for potential missing data, the final sample size was inflated to ≥420 patients.

All variables were described according to the type and distribution of data. The primary aim was to assess the proportion of patients with a negative urine LAM test who received TB treatment. A comparison was made between the proportion of patients started on TB treatment with positive v. negative urine LAM tests. The proportion of patients undergoing urine LAM testing out of all patients investigated for TB was calculated. A test for congruence between TB treatment initiation and urine LAM test results (positive or negative) was performed using McNemar's test.

Ethical considerations

The research commenced following approval from the Ethics Committee of the Faculty of Health Sciences of the University of Pretoria (ref. no. 291/2022). Permission to access hospital data was

obtained from the chief executive officer of KPTH, who is the custodian of the data. The researcher used hospital numbers instead of patient names and surnames to ensure patient anonymity.

Results

Demographics and descriptives

A total of 500 patients were screened, of whom 430 were included in the study. Seventy patients did not comply with the hospital's standard operating procedures for testing (Fig. 1). Of the 403 patients, 205 (47.7%) were female and 225 (52.3%) were male. The mean age of participants was 39.4 years, median 39 years and range 13 - 73 years. Most patients (357, 83%) had no comorbidities other than HIV. However, 18 (17.9%) had additional comorbidities: 4 (0.9%) had chronic renal disease, 9 (2.1%) had diabetes mellitus, 4 (0.9%) had destructive lung disease and 1 (0.2%) had asthma. It is important to note that inclusion criteria required PLHIV with a CD4 count <200 cells/μL, with the mean CD4 count being 54.69 cells/μL.

Chest X-ray and sonography were used to assess TB, with 124 patients (29.1%) showing chest X-ray features suggestive of TB, and 61 patients (14.2%) showing sonographic features suggestive of TB (splenic micro-abscesses, abdominal lymphadenopathy or pericardial effusions with fimbriae).

Out of the 430 patients, 123 (28.6%) had a positive urine LAM test. Positive culture results were reported for only 32 patients (7.4%), while 135 (31.3%) had negative culture results. For 263 patients (61.2%), no culture results were available owing to specimen rejection, or the cultures never being requested (Table 1).

Symptoms and signs

Most patients presented with respiratory and general symptoms. The most frequently encountered respiratory symptoms were cough (237 patients, 55.1%), dyspnoea (83 patients, 19.3%) and pleuritic chest pain (60 patients, 14%). Among general symptoms, weight loss was most common (222 patients, 51.5%), followed by night sweats (138 patients, 32.1%) and malaise (73 patients, 17%).

The most frequent respiratory clinical signs observed were crackles (114 patients, 26.5%), hypoxia (42 patients, 9.8% with saturation <90%), bronchial breathing (12 patients, 2.8%) and pleural effusions (9 patients, 2.1%).

Of the 430 patients included in the study, 183 (42%) were subjectively described as emaciated, 55 (12.8%) had fever, 34 (7.9%) had lymphadenopathy and 25 (5.8%) were reported to be delirious (Table 2).

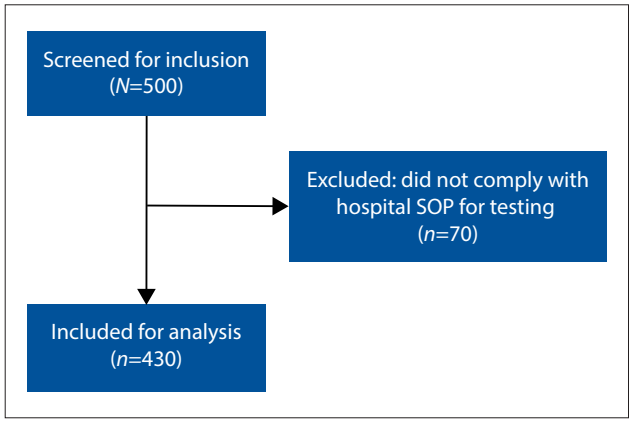

Fig. 1. Study enrolment: 500 records were screened for inclusion, and 70 excluded owing to absence of variables required for the study, and CD4 count >200 cells/μL. (SOP = standard operating procedure.)

Outcome

A urine LAM test was performed on 430 patients. Of these, 307 (71.4%) had a negative urine LAM test, and 120 (39.1%) of these received TB treatment. Among the 123 patients (28.6%) with a positive urine LAM test, only 3 (2.4%) did not receive treatment; 1 patient died before treatment could be initiated, and the reasons for the other 2 were unclear (Table 3).

The incongruence between negative urine LAM test results and the initiation of TB treatment was statistically significant, with $p<0.001$ using McNemar's test.

The urine LAM test results appeared to influence clinicians' decisions to treat when the result was positive. If the urine LAM test was negative, clinicians still initiated treatment based on adequate clinical suspicion and considering other investigations.

Discussion

All patients in the study were living with HIV and had a CD4 count <200 cells/μL. For patients with a high clinical suspicion of TB, urine LAM results did not alter physicians' decision to initiate TB treatment. The study indicates that physicians relied more on clinical findings and circumstantial evidence from investigations when deciding on initiating TB treatment, in the event of a negative urine LAM test.

Most patients in the study presented with cough and constitutional symptoms, including night sweats and weight loss, which likely prompted physicians to initiate TB treatment. In the absence of GeneXpert and culture results, resulting from patients' inability to produce sputum and the time to generate culture results, empirical TB treatment was initiated when the urine LAM test was negative.

Previous studies have focused on the diagnostic yield of urine LAM, using it in conjunction with other diagnostic tools.[9,11,14] For instance, Lawn *et al.*[15] included patients who were unable to produce sputum, those who were severely ill and those requiring hospitalisation. These patients had sputum induction performed by

Table 1. Demographics and descriptives

Variable	*n* (%)*
Sex	
Male	205 (47.7)
Female	225 (52.3)
Age, years, mean (SD), median (IQR)	39.4 (11.1), 39 (13 - 73)
Comorbidity	
Asthma	1 (0.2)
Diabetes mellitus	9 (2.1)
Chronic renal failure	4 (0.9)
Destructive lung disease	4 (0.9)
None	357 (83)
Radiographic suggestive	
Chest X-ray	125 (29.1)
Sonography	61 (4.2)
Urine LAM	
Positive	123 (28.6)
Culture	
Positive	32 (7.4)
Negative	135 (31.4)
Not done	263 (28.6)
CD4 count, mean (SD)	54.69 (48.06)

SD = standard deviation; IQR - interquartile range, LAM = lipoarabinomannan.
*Unless otherwise indicated.

experienced personnel. In that study, urine LAM was used alongside other diagnostic tools (GeneXpert, sputum microscopy and culture), with a sensitivity of 39% and specificity of 98.9%. This was higher than previous studies, which found the specificity to be lower, at 90% in a pragmatic randomised trial by Peter *et al*.,[10] and 85% in a prospective cohort study in Thailand.[11]

Table 2. Symptoms and signs

Symptom	*n* (%)
Respiratory	
Cough	237 (55.1)
Dyspnoea	83 (19.3)
Chest pain	60 (19.3)
Haemoptysis	4 (0.9)
Gastrointestinal	
Diarrhoea	97 (22.6)
Jaundice	5 (1.2)
Vomiting	6 (1.4)
Central nervous system	
Collapse	1 (0.2)
Seizures	7 (1.5)
Headache	24 (5.6)
Photophobia	2 (0.5)
General	
Malaise	73 (17)
Loss of weight	222 (51.6)
Night sweats	138 (32.1)
Musculoskeletal	
Joint pains	2 (0.5)
Sign	
Respiratory	
Hypoxia	42 (9.8)
Crackles	114 (26.5)
Bronchial breathing	12 (2.8)
Pleural effusion	9 (2.1)
Gastrointestinal	
Hepatomegaly	22 (5.1)
Splenomegaly	1 (0.2)
Jaundice	5 (1.2)
Central nervous system	
Neck stiffness	16 (3.7
Delirium	25 (5.8)
General	
Emaciated	183 (42)
Fever	55 (12.8)
Lymphadenopathy	34 (7.9)
Clubbing	3 (0.7)
Other	
Kaposi sarcoma	3 (0.7)
Oral candidiasis	35 (8.1)
Pale	37 (8.6)
Tachycardia	32 (7.4)

Urine LAM positivity is associated with a high diagnostic yield in severely ill patients with a CD4 count <50 cells/μL.[7,11,14] Therefore, it is reasonable to use urine LAM in severely ill patients requiring hospitalisation, as those with TB might be missed otherwise.[9] No reviewed study based the decision to start TB treatment solely on urine LAM results; other tests had to confirm TB before treatment initiation.[9,11,14] In a study by Ahsberg *et al*.,[23] where urine LAM was added to routine testing, <50% of patients with a positive urine LAM were started on TB treatment. In contrast, in our study, clinical suspicion took precedence over any diagnostic test, including urine LAM, in deciding whether to initiate treatment.

Urine LAM has shown a mortality benefit in patients with advanced disease, and the WHO now recommends its use in patients with a CD4 count <200 cells/μL who require hospitalisation.[9,16] Lawn *et al*.[15] demonstrated a strong association between advanced HIV/TB co-infection and 90-day mortality.[14] In clinical practice, obtaining a sputum sample in severely ill patients is often challenging, delaying the initiation of life-saving treatment.[11] Therefore, the threshold for initiating TB treatment should be low among PLWHIV with a low CD4 count who are severely ill, owing to the high disease burden. The urine LAM test, as a rapid point-of-care test, has been shown to reduce diagnostic and treatment delays, as well as mortality,[9] making it a valuable diagnostic tool for patients unable to expectorate and those with extrapulmonary TB. However, in patients with a significant clinical suspicion of TB and a negative urine LAM test result, deciding on treatment initiation can be challenging. At KPTH, where there is high mortality among patients with advanced HIV disease, urine LAM does not seem to influence the decision to initiate treatment if the test result is negative. Its value could be assessed prospectively by evaluating the response to TB treatment, which was not assessed in this study.

Study limitations

The study had several limitations. The definitive modality for TB diagnosis is culture; however, most culture specimens in this study were either rejected (being either insufficient or unsuitable) or not requested, making it challenging to determine the diagnostic yield of the urine LAM test compared with other diagnostic modalities. Another limitation was the lack of follow-up on patients initiated on treatment to determine clinical improvement, adherence to treatment and mortality. Patients were discharged to local clinics nearest to their homes, and those from outside Gauteng Province were transferred back to their home province, posing a further challenge in follow-up. Follow-up could have assisted with determining the morbidity and mortality rate of patients initiated on treatment regardless of the urine LAM results. The study did not investigate in-hospital mortality after initiation of TB treatment, or the re-admission rate following discharge. Other studies have found a high mortality rate among patients with a positive urine LAM when followed up retrospectively,[9,14] which was not the aim of this study.

Table 3. Total patients (*n*) who tested negative and positive on urine LAM and treatment outcomes (98% specificity of urine LAM)

	Treatment category, *n* (%)		
Urine LAM test result	Not treated	Treated	Total tested, *n* (%)
Negative	187 (60.9)	120 (39.1)	307 (71.4)
Positive	3 (2.4)	120 (97.6)	123 (28.6)
Total tested	190 (44.2)	240 (55.8)	430 (100)

LAM = lipoarabinomannan.

A future cohort study is required to follow up on patients where a negative urine LAM test is used to decide on treatment initiation v. empirical treatment based solely on clinical suspicion. The aim will be to determine whether there is a benefit regarding reduction in mortality rate. This highlights the problem of a reference standard for TB diagnosis, and the ultimate response to treatment as a reference standard. Clinical improvement is often subjective, and dependent on treatment adherence. The influence of socioeconomic circumstances and social support could also be investigated. In a setting with a high prevalence of HIV/TB co-infection, it is vital to establish whether patients with a positive urine LAM test result had previously been initiated on antiretrovirals or were newly diagnosed with HIV.

Conclusion

A positive urine LAM test result provides sufficient diagnostic certainty to clinicians to initiate TB treatment. However, negative urine LAM test results frequently prove to be inadequate for clinicians to withhold TB treatment in patients with clinical suspicion of TB.

Data availability. Data are available upon request from DGvZ.

Declaration. This study was done and submitted in partial fulfilment of the requirement in respect of TRM's MMed in Internal Medicine in the Department of Internal Medicine in the Faculty of Health Sciences at the University of Pretoria.

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