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Should urine-LAM tests be used in TB symptomatic HIV-positive patients when no CD4 count is available? A prospective observational cohort study from Malawi

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ABSTRACT

BACKGROUND

Current eligibility criteria for urine lateral-flow-lipoarabinomannan assay (LF-LAM) in ambulatory, HIV-positive patients rely on the CD4 count. We investigated the diagnostic yield of LF-LAM and the 6-month mortality in ambulatory, TB symptomatic, HIV-positive patients regardless of their CD4 count.

METHODS

We conducted a prospective, observational study that included all ambulatory, ≥15-year-old, TB symptomatic (cough, weight loss, fever, or night sweats) HIV-positive patients presenting at 4 health facilities in Malawi. Patients received a clinical examination and were requested urine LF-LAM, sputum microscopy and Xpert MTB/RIF. TB was defined as bacteriologically confirmed if Xpert was positive.

RESULTS

Of 485 patients included, 171 (35.3%) had a CD4<200 and 32 (7.2%) were seriously ill. Median CD4 count was 341 cells/μL (IQR: 129-256). LAM was positive in 24.9% patients with CD4<200 (50% LAM Grades 2-4) and 12.5% with CD4≥200 (12.8% LAM Grades 2-4). Xpert was positive in 14.1% (44/312). Among Xpert-positive patients, LAM-positivity was: 56.7% (CD4<200) and 42.9% (CD4≥200), p=0.393. Of the patients without an Xpert result, 13.4% (23/172) were LAM-positive (i.e. potentially missed patients). Overall mortality was 9.2% (44/478). More pronounced LAM-positive patients had higher mortality than LAM-negative (Grades 2-4: 36.0%; Grade 1: 9.1%; Negative: 7.4%; p<0.001). LAM-positive patients with CD4<200 cells/μL had higher risk of mortality than LAM-negatives (aHR:3.2, 95CI:1.4-7.2, p=0.006), particularly those with LAM Grades 2-4 (aHR:4.9, 95CI:1.8-13.3, p=0.002).

CONCLUSIONS

Urine-LAM testing can be useful for TB diagnosis in HIV-positive TB-symptomatic patients with no CD4 cell count. LAM grade can identify patients at higher risk of death in this situation.

Keywords: Diagnosis, Immunodeficiency, Screening, Point-of-Care, Malawi

INTRODUCTION

Mortality from tuberculosis (TB) remains high among people living with HIV (PLHIV), accounting for nearly half a million cases and 32% of AIDS-related deaths in 2017 [1]. Underdiagnosis of TB, especially in places without widespread health care access, is a principal barrier to combatting the disease. In resource-limited settings, microscopy often

remains a primary diagnostic method despite its poor sensitivity. Improved molecular diagnoses such as Xpert MTB/RIF have good sensitivity and excellent specificity but are still not widely available. An additional challenge is that these techniques rely on sputum samples that can be difficult to produce, especially for very ill HIV-positive patients. Transferring sputum samples from peripheral health facilities to laboratories for testing can additionally cause delays or losses. As a result, clinicians in low-resource, peripheral facilities often rely on their clinical judgement to diagnose TB.

Consequently, the emergence of easier to use, point-of-care (POC) tests using urine to identify TB (detecting the mycobacterial lipoarabinomannan [LAM] antigen), have been a welcome addition to the TB diagnostics environment[2,3]. The lateral-flow TB LAM Ag (LF-LAM) assay has shown encouraging sensitivity and specificity (45% and 92%)[4], and two large trials have shown a substantial reduction in mortality among hospitalized patients who immediately initiated treatment after a positive result [5,6]. International guidance currently recommends that LAM may be used to assist TB diagnosis in HIV-positive ambulatory outpatients with signs and symptoms of TB who are severely immunocompromised (CD4 count ≤100 cells/μL) as well as those who are seriously ill [7]. Yet, for the majority of outpatients (who are not seriously ill) these recommendations are based on the assumption that a patient's CD4 cell count is readily available, when in fact this is often far from certain. Many resource-limited contexts still struggle with limited and inconsistent access to CD4 testing, an issue which may be compounded as viral load is the preferred technology to monitor ART efficacy in HIV patients.

Thus, we investigated the diagnostic yield of urine LF-LAM in HIV-positive, outpatients with symptoms of TB regardless of whether patients had a CD4 cell count immediately available. We assessed these test results by level of immunosuppression and the risk of mortality at 6

months. We also explored whether clinical signs could be used as a proxy for CD4 count to determine LAM testing eligibility.

METHODS

Design and population

This prospective, observational study, conducted between September 2015 and April 2017, consecutively included all ambulatory, ≥15-year-old, TB symptomatic (self-reported cough, weight loss, fever, or night sweats), HIV-positive patients presenting to the Out-Patient Department (OPD) of Chiradzulu District Hospital or to any of three health centers in the district (Namitambo, Milepa, Mauwa) in southern Malawi. The four facilities were active clinical sites run by the Malawi Ministry of Health with free TB and HIV care supported by Médecins Sans Frontières (MSF). Those who had taken fluoroquinolones or anti-TB drugs the month prior to their first consultation were excluded. Non-availability of an immediate CD4 count result or the lack of a urine or sputum sample were not grounds for exclusion from the study. This study is part of a multi-country study conducted in 6 health facilities of Malawi and Mozambique and designed to assess the usefulness and feasibility of the LF-LAM in programmatic conditions. The results on the diagnostic value of including LF-LAM in TB diagnostic algorithms in HIV-positive patients severely immunocompromised have been previously reported [8].

Diagnostic Procedures

Participants' initial evaluation included an examination conducted by a clinical officer and the request of a urine sample, two spontaneously expectorated sputum samples (on spot and early morning) and a chest X-ray. Fresh urine was tested for LF-LAM (Determine TB-LAM Ag

test, Abbott, Waltham, MA, USA [formerly Alere]) on the same day with results interpreted using a 4-grade scale, with grade 1 or above constituting a positive result (according to the manufacturer's instructions). Per the Malawi National TB Program's request at the time of the study implementation, LAM test results did not inform patient management or treatment initiation during the first 10 (of 14) months of the study recruitment period. Thus, tests were conducted at Chiradzulu District Hospital during the first 10 months of the study recruitment period (from September 2015 to June 2016), and at the point-of-care during the latter period (July to October 2016). Smear microscopy on sputum used auramine staining and Light Emitting Diode Fluorescence, and the presence of at least one acid fast bacilli (AFB) per 100 high power fields (HPF) on one slide was considered smear positive. All facilities could perform microscopy on-site except Mauwa. Xpert MTB/RIF technology (Cepheid, Sunnyvale, CA, USA) was only available at Chiradzulu District Hospital, and sputum samples from the peripheral centers were transferred there. Chest X-ray was performed only at Chiradzulu District Hospital and only on selected days each week. In the absence of clinical or radiological findings suggestive of TB, patients were prescribed a broad-spectrum antibiotic (e.g. amoxicillin 3 grams/day) for 1 week and were reassessed 5 days after the first consultation. The treating clinicians decided whether or not to start TB treatment at any time during the diagnostic process based on their clinical assessment, the biological test results, and the chest X-ray findings, according to the national guidelines for TB diagnosis and treatment. TB was defined as bacteriologically confirmed if Xpert was positive.

Statistical analyses

Descriptive analyses explored demographic and clinical characteristics recorded during a patient's initial consultation as well as testing and treatment results. Continuous variables were summarized as median and inter-quartile ranges (IQR) and compared with Wilcoxon

rank-sum testing. Categorical variables were expressed as counts and percentages and compared with Chi-Square tests. We calculated and reported 'time-to-result' (days from initial consult to the clinician receiving the result) and 'time-to-treatment' (initial consultation to TB treatment initiation). To explore whether clinical signs could be used to determine LAM testing eligibility, we compared LAM-positivity in patients presenting a clinical sign and in those not presenting it. We used Chi-square tests to compare the proportions.

Cox proportional-hazards regression was used to assess the association between LAM results by grade (negative, positive Grade 1, positive Grade 2-4) and mortality in the 6 months following a patient's initial consultation. As no death occurred in LAM-positive patients with CD4 ≥200 cells/µL, these analyses were restricted to patients with CD4<200 cells/µL. Univariate models included age (≥30 years, <30 years), sex (women, men), antiretroviral treatment (on ART, not on ART), Body Mass Index (BMI≥18 Kg/m^2, <18 Keg/m^2), CD4 count (<100 cells/µL, 100-199 cells/µL), health care setting at first consultation (hospital OPD, peripheral health centre), whether a patient was treated for TB (yes, no), or whether a patient was seriously ill (defined as temperature >39°C, respiratory rate >30 respirations/minute, cardiac rate >120 beats/minute, or an inability to walk without help). We built the multivariate model including clinically relevant variables and variables with p-value <0.2 in univariate analyses. We used a backward elimination stepwise approach to select the variables included in the final model while maintaining variables that had an effect in the association between LAM and mortality. We checked for confounders and effect modifiers to ensure that the results were robust. Hazard ratios (HR) were estimated along with their 95% confidence intervals (CI) using an alpha level of 5%.

Data were analyzed using Stata 13 (College Station, Texas, USA).

Ethical Considerations

The study was approved by the Médecins Sans Frontières Ethical Review Board and the National Ethical Review Committee in Malawi. Eligible participants provided written informed consent and, for those aged 15-17 years, a legal guardian's consent was provided in addition to the assent of the participant.

RESULTS

Study population and TB diagnosis

A total of 485 ambulatory patients were included, 55.3% (268) in the peripheral health centers and 44.7% (217) in the hospital OPD. Median CD4 count was 341 cells/μL (IQR: 129-546), 171 (35.3%) had a CD4<200 cells/μL and 32 (7.2%) were seriously ill. The study cohort's demographic and clinical characteristics are detailed in Table 1.

Overall, 99.0% (480) received a urine-LAM test result, 87.6% (425) a microscopy result, 64.3%% (312) an Xpert result, and 14.2% (69) a chest X-ray result. The median time to receive a LAM, Xpert, or X-ray result was 0 days (IQR 0-0), 2 days (IQR 1-5), and 6 days (IQR 1-14), respectively. The median time to TB treatment was 4 (IQR 2-7) days. More than half, 57.8% (155) of the patients followed in the peripheral health centers did not have an Xpert result compared to 9.3% (18) of those seen at the hospital OPD. Conversely, patients followed in the health centers, were less frequently LAM-positive, 11.7% (31) compared to 23.4% (50) of those attending the hospital OPD, probably as a result of higher CD4 counts: 21.3% (57) with CD4<200 cells/μL in the health centers compared to 52.5% (114) among those in the hospital OPD.

Among patients with a result, 16.9% (81) had a positive LAM, 14.1% (44) a positive Xpert and 10.6% (45) a positive microscopy. Of the 173 patients without an Xpert result, almost all (172) had a LAM result and 13.3% (23) were LAM-positive (i.e. potentially missed patients) (Figure 1). Using the two methods together (LAM and Xpert) identified 102 (21.0%) positive participants, a 2.3-fold increase over what identified Xpert alone.

During the study period, 65 (13.4%) participants initiated anti-TB therapy. Yet, if LAM-positive results had been used to initiate patients' treatment for the entire duration of the research period, an additional 51 LAM-positive patients (who were not identified by other tests and were therefore not treated for TB) could have initiated anti-TB therapy, a 1.8-fold increase over what was actually achieved.

LAM results by immunosuppression level

LAM-positivity was 24.9% in patients with CD4<200 cells/μL and 12.5% in patients with CD4≥200 cells/μL. More pronounced LAM-positivity (Grades 2-4) was more frequently found among the more immunocompromised: 50.0% (<200 cells/μL) vs. 12.8% (≥200 cells/μL; p<0.001) (Table 2). And, patients with higher degrees of positivity (LAM Grades 2-4) were also more frequently Xpert-positive (58.8%) than those with Grade 1 (31.7%), (p=0.055). However, LAM-positivity among Xpert-positive patients was not statistically different across immunosuppression levels: 56.7% (CD4<200) vs 42.9% (CD4≥200) (p=0.393).

Clinical Signs Associated with LAM-Positive Results

Though patients with some clinical symptoms at presentation (reported weight loss and ≥38°C measured temperature) were more frequently LAM-positive (Supplement Table S1, http://links.lww.com/QAI/B387), these clinical signs (separately or together) were not instructive for determining LAM-testing eligibility in the absence of CD4. This is because

weight loss was reported by 81.2% of all patients, and a ≥38°C temperature occurred in only 11.1% of those with LAM-positive results. LAM-positivity was higher in 'Seriously ill' patients compared to those not seriously ill but the difference was not statistically significant.

LAM-Positivity and Mortality

Of all patients, 478 (98.6%) had their vital status assessed 6 months after their initial consultation, among whom 44 (9.2%) died. The cause of death of the patients was not ascertained. LAM-positive patients had higher mortality than LAM-negative participants (17.5% vs 7.4%; p=0.004), as did those with more pronounced LAM-positive results (Grades 2-4: 36.0%; Grade 1: 9.1%; Negative: 7.4%; p<0.001). However, no death occurred in LAM-positive patients with CD4≥200 cells/µL. In patients with CD4<200 cells/µL, mortality was 18.6% (31/136) and the adjusted model showed that LAM-positive patients had a higher risk of mortality than LAM-negatives (aHR: 3.2, 95CI: 1.4-7.2, p=0.006), particularly those with LAM Grades 2-4 patients (aHR: 4.9, 95CI: 1.8-13.3, p=0.002; Table 3, Figure 2). In addition, during the period when LAM was not used for patients' management, the mortality among untreated LAM-positive patients with CD4<200 cells/µL (i.e. missed TB patients) was 41.2% (7/17) compared to 25.0% (4/16) among those treated, though this difference was not statistically significant, p=0.325. Mortality was the greatest among untreated LAM-positive Grades 2-4 patients: 66.7% (4/6).

DISCUSSION

This was an investigation of TB symptomatic, outpatients, HIV-positive, tested with LAM regardless of whether they had a CD4 cell count available. Though LAM and Xpert-positivity were predictably higher among the most immunocompromised, a considerable proportion of those less immunocompromised were also LAM-positive, indicating that excluding this group

from routine LAM testing may be missing opportunities to identify TB. We show that integrating urine-LAM into standard care could have doubled the number of TB-positive patients identified in the cohort. In this cohort, clinical signs did not serve as a proxy for CD4 to determinate eligibility for LAM-testing. However, LAM grade can identify patients at higher risk of death.

Previous research has found LAM-positivity in 9-35% of outpatients regardless of CD4 levels [9–13]. In primary care settings without same-day X-ray facilities, POC-LAM has been shown to significantly increase same-day treatment initiation [10]. Our findings add to this chorus of research suggesting that current international recommendations may not go far enough, and that the criteria recommending LAM use in only the severely immunocompromised (CD4<100) may need to be expanded (WHO guidelines on the use of LAM are currently under review). The recommendation is largely based on previous studies showing low test sensitivity in patients with higher CD4 counts [4]. In our study, LAM-positivity among Xpert-positive patients with CD4>200 cells/µL was relatively high, around 43%. However, we should also consider that despite the high specificity of LAM in patients less immunocompromised reported in other studies [4], the lower TB prevalence in this group may lead to low positive predictive values and some LAM-positive patients may not have TB. Using a greater LAM Grade for a positive test threshold could improve further the specificity but would also reduce the diagnostic sensitivity[14]. Yet, a test's value should not only depend on whether it has the highest accuracy, but also on whether other diagnostic tools are available in a facility and whether a patient actually receives the test result. The third of patients in our cohort (and more than half of those attending the peripheral health centers) did not have an Xpert result, largely because of difficulties producing a sputum sample, issues related to the availability of staff to collect samples and challenging sample transport (common in resource-limited settings). These patients could have avoided having their TB diagnosis based entirely

on clinical judgement had TB-LAM been used for clinical decision making. Systematic Xpert testing remains important for diagnosing TB and for testing rifampicin resistance. However, in settings where Xpert results are not available or are frequently delayed, POC-LAM in all TB-symptomatic patients regardless of CD4 count can be a useful parallel testing option to Xpert.

Though some clinical signs (higher WHO clinical stage, low BMI, tachycardia, lower blood pressure) have previously been reported to be associated with higher LAM yields [11,12,15,16], in this study 'seriously ill' patients and those with low BMI did not have higher LAM-positivity. Moreover, despite the fact that patients with reported weight loss and >38°C temperature were more frequently LAM-positive, weight loss was so common in the cohort that this finding would be less meaningful, and testing only patients with >38°C temperature would miss a high proportion of those who could benefit from LAM.

Our findings also indicate that it is important to take the degree of LAM-positivity (grade) into consideration when managing patients, as patients with stronger positivity (higher LAM grades) had substantially higher mortality than those with lower LAM grade or LAM-negative, perhaps explained by a higher bacillary load. Others studies in South Africa have also found a higher risk of mortality associated to higher LAM grades in patients newly diagnosed with HIV[11,17,18]. Although no death occurred in LAM-positive patients less immunocompromised (CD4>200), LAM grade may be important when CD4 count is unknown, as patients with higher grade were also more immunocompromised, making them a population where LAM grade would be useful to identify their increased risk of death. Additionally, in patients with CD4 <200 cells/µL, higher grades were also associated with a higher risk of mortality and LAM testing may potentially decrease mortality if patients are treated rapidly.

This study has some limitations: bacteriologically confirmed TB was defined using only Xpert in sputum due to the limitations of the study context, creating an imperfect reference standard for LAM since other specimens (blood, urine, tissue) increase TB detection [19]. Yet, the real-world conditions (despite MSF support) in which the study was conducted should also be considered a strength, producing results that reflect on-the-ground realities and the value of LAM.

In Malawi and similar contexts where TB diagnostics tools are limited, urine-LAM can be useful to diagnose TB regardless of whether CD4 counts are available. Incorporating LAM into the standard care could diagnose more patients with signs and symptoms of TB. In addition, LAM grade is useful to identify patients at higher risk of death when CD4 count is unknown. Our findings do not support using specific clinical signs as a proxy for CD4 when prioritizing urine-LAM eligibility.

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FIGURE CAPTIONS

Figure 1: TB diagnosis, TB treatment and 6-months mortality

(Note: LAM result was not used for the patients' management during the first months of recruitment, vital status was not available for 4 patients with an Xpert negative result and 3 patients with no Xpert result)

Figure 2: Mortality over time by LAM result and grade in patients with CD<200 cells/µL

Table 1 – Patients' demographic and clinical characteristics at first consultation.

VARIABLE	PATIENTS N=485
Female	282 (58.1)
Age, median [IQR]	41 [34 – 49]
BMI, median [IQR]	18.8 [16.9-21.0]
<16	68 (14.1)
16-16.9	56 (11.6)
17-18.4	92 (19.1)
>=18.5	266 (55.2)
CD4 cells/µL, median [IQR]	341 [129 – 546]
<100 100-199 ≥200	96 (19.8) 75 (15.5) 314 (64.7)
Patient on ART at first consultation	428 (88.3)
TB-related symptoms	
Cough	477 (98.4)
Fever	401 (82.7)
Weight loss	394 (81.2)
Night sweats	359 (74.0)
Chest pain	412 (85.0)
Difficulty to breath	347 (71.6)
Hemoptysis	41 (8.5)
Clinical exam findings	
Temperature ≥38°C	30 (6.2)
Respiratory rate >20/min	43 (8.9)
Cardiac frequency >100/min	17 (3.5)
Seriously ill*	
Declared by clinician	17 (3.5)
Recalculated using information from the clinical exam	35 (7.2)
Anemia	
Severe (Hb<8 g/l))	48 (10.0)
Mild/moderate (Hb 8-11.9 g/l))	204 (42.3)
No anemia (Hb>=12 g/l)	230 (47.7)
Unable to produce sputum	40 (8.3)
Health care setting	
Out-patient-Department (OPD) of the Hospital	268 (55.3)
Health Centre in the District	217 (44.7)

Data given as n (percent) or median (IQR).
ART, antiretroviral therapy; BMI, body mass index; Hb, hemoglobin concentration; TB, tuberculosis.
**Seriously ill patients were categorized based on four danger-signs: temperature >39°C, respiratory rate >30 respirations/minute, cardiac rate >120 beats/minute, or inability to walk without help*

Table 2: LAM and Xpert results by CD4 count

	All (N=485)	CD4 <100 cells/µL (N=96)	100-199 cells/µL (N=75)	≥200 cells/µL (N=314)
LAM				
Positive	81 (16.9)	30 (31.6)	12 (16.2)	39 (12.5)
Negative	399 (83.1)	65 (68.4)	62 (83.8)	272 (87.5)
Missing	*5*	*1*	*1*	*3*
LAM grade				
Grade 1	55 (67.9)	14 (46.7)	7 (58.3)	34 (87.2)
Grades 2-4	26 (32.1)	16 (53.3)	5 (41.7)	5 (12.8)
Xpert				
Positive	44 (14.1)	16 (22.2)	14 (26.4)	14 (7.5)
Negative	268 (85.9)	56 (77.8)	39 (73.6)	173 (92.5)
Missing	*173*	*24*	*22*	*127*
LAM or Xpert positive	102 (21.0)	32 (33.3)	23 (30.7)	47 (15.0)

Table 3: LAM grade and mortality in the first 6 months after the initial consultation in patients with CD4<200 cells/µL (Cox Proportional Hazard regression)

	death/patients (%)	HR	95%CI	p	aHR	95%CI	p
Overall	31/136 (18.6)						
Age (years)							
≥30	20/140 (14.3)	1			1		
<30	11/27 (40.7)	3.35	1.60-7.00	0.001	1.83	0.81-4.10	0.144
Sex							
Women	15/73 (20.6)	1					
Men	16/94 (17.0)	0.83	0.44-1.68	0.608	-		
ART							
On ART	26/131 (19.9)	1					
Not on ART	4/31 (12.9)	0.63	0.22-1.82	0.397	-		
BMI (Kg/m^2)							
≥18.5	14/85 (16.5)	1					
<18.5	16/79 (20.3)	1.28	0.63-2.63	0.494	-		
CD4 count (cells/µL)							
100-199	6/73 (8.2)	1			1		
<100	25/94 (26.6)	3.59	1.47-8.76	0.005	2.23	0.87-5.74	0.096
Seriously ill							
No	25/148 (16.9)	1			1		
Yes	6/19 (31.6)	2.15	0.88-5.25	0.092	2.17	0.83-5.67	0.113
TB treatment							
No	22/124 (17.7)	1			1		
Yes	9/43 (20.9)	1.19	0.55-2.58	0.662	0.45	0.17-1.18	0.106
Health care facility							
Peripheral health centers	8/57 (14.0)	1					
Hospital Out-patients Department	23/110 (20.9)	1.59	0.71-3.55	0.259	-		
LAM result							
Negative	16/124 (12.9)	1			1		
Positive Grade 1	5/21 (23.8)	2.10	0.77-5.74	0.147	2.14	0.74-6.20	0.159
Positive Grade 2-4	9/20 (45.0)	4.37	1.93-9.89	<0.001	4.91	1.81-13.28	0.002

ART: antiretroviral therapy; BMI: Body Mass Index; HR: hazard ratio; aHR: adjusted hazard ratio