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MAJOR ARTICLE

Urine Lipoarabinomannan Testing for All HIV Patients Hospitalized in Medical Wards Identifies a Large Proportion of Patients With Tuberculosis at Risk of Death

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Background. Diagnosing tuberculosis (TB), the leading cause of death in people with HIV, remains a challenge in resource-limited countries. We assessed TB diagnosis using a strategy that included systematic urine lipoarabinomannan (LAM) testing for all HIV patients hospitalized in medical wards and 6-month mortality according to LAM results.

Methods. This prospective, observational study included adult HIV patients hospitalized in the medical wards of a public district hospital in Malawi regardless of their TB symptoms or CD4 count. Each patient had a clinical examination, and Alere Determine TB-LAM, sputum microscopy, sputum GeneXpert MTB/RIF (Xpert), chest x-ray, and CD4 count were systematically requested.

Results. Among 387 inpatients, 54% had a CD4 <200 cells/μL, 64% had presumptive TB, and 90% had ≥1 TB symptom recorded in their medical file. LAM results were available for 99.0% of patients, microscopy for 62.8%, and Xpert for 60.7%. In total, 26.1% (100/383) had LAM-positive results, 48% (48/100) of which were grades 2–4. Any TB laboratory test result was positive in 30.8% (119/387). Among patients with no Xpert result, 28.5% (43/151) were LAM-positive. Cumulative 6-month mortality was 40.1% (151/377): 50.5% (49/97) in LAM-positives and 36.2% (100/276) in LAM-negatives ($P = .013$). In multivariable regression analyses, LAM-positive patients had a higher risk of mortality than LAM-negatives (adjusted odds ratio, 2.5; 95% CI, 1.1–5.8; $P = .037$).

Conclusions. In resource-limited hospital medical wards with high TB prevalence, a diagnostic strategy including systematic urine LAM testing for all HIV patients is an easily implementable strategy that identifies a large proportion of patients with TB at risk of death.

Keywords. CD4 lymphocyte count; death; in-patients; low-income countries; point-of-care testing.

Diagnosing tuberculosis (TB), the leading cause of death in people with HIV, remains a challenge in resource-limited countries [1]. Molecular technologies like the Xpert MTB/RIF assay demand laboratory infrastructure that is often unavailable in resource-constrained [2], peripheral health facilities and require sputum samples that can be difficult to produce for very sick patients [3, 4].

The Determine TB-LAM Ag assay (LAM), testing urine for the presence of lipoarabinomannan, a *Mycobacterium* cell wall antigen, has been a welcome addition to the TB diagnostics landscape for patients with HIV [5]. The LAM test can be performed at the point of care (POC), with little training and with results available in 25 minutes. Urine sampling is advantageous for very ill patients who are unable to produce sputum, like many of those hospitalized with HIV. And although the assay's sensitivity is dependent on a patient's immunosuppression level (reflected by their CD4 count), the use of LAM has been shown to decrease mortality in hospitalized patients with TB symptoms [6, 7].

Despite these advantages and evidence, urine LAM testing is currently limited in most Sub-Saharan African countries [8], a region where resource constraints make rapid testing especially valuable.

Initial 2015 guidance on LAM testing was reviewed and strengthened in 2019 [9, 10]. Currently, the World Health Organization (WHO) recommends LAM use in in-patient settings for HIV-positive patients with (1) signs and symptoms of TB, or with (2) advanced HIV disease or who are seriously ill, or (3) irrespective of signs and symptoms of TB if CD4 count is <200 cells/μL [10]. We assessed TB diagnosis using a diagnostic strategy that included LAM testing for all HIV patients hospitalized in medical wards, regardless of their symptoms of TB and CD4 counts. We also assessed mortality 6 months after admission according to LAM results.

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METHODS

Design, Setting, and Population

This prospective, observational study recruited and followed adult (≥15-year-old) patients with HIV hospitalized in the medical wards of Chiradzulu District Hospital (CDH), a public hospital supported by the Ministry of Health in Southwestern Malawi, from August 2015 to September 2017. Since 2001, Médecins Sans Frontières (MSF) has supported the hospital HIV out-patient clinic and 10 HIV out-patient clinics in the district. The hospital medical wards were not supported by MSF. All patients were included consecutively regardless of their presenting symptoms or CD4 count. Patients who had taken fluoroquinolones or antituberculosis drugs in the month prior were excluded.

Study Procedures

Upon admission, each patient received a clinical examination including TB symptom assessment. Clinicians recorded the findings of the clinical examination and whether they considered the patient to have presumptive TB. Urine LAM test, sputum microscopy, sputum GeneXpert MTB/RIF test (classic cartridges), and chest x-ray were requested systematically and in parallel for all patients at admission, as per the study procedures. There was no time limit for sputum or urine collection during hospitalization if a patient was not able to produce a sample at admission. The clinician in charge of treatment decided whether and when to start TB treatment according to national guidelines. During the initial period of study until July 2016, national guidelines did not endorse the use of LAM to diagnose TB; subsequently, the LAM tests done through the study were not used for clinical management, and clinicians were blinded to the LAM results during this period. Clinicians could use the LAM results for patient management during the second period of the study, after July 2016. Urine LAM testing was conducted using the Determine TB-LAM Ag assay (Abbott, Waltham, MA, USA [formerly Alere]) and interpreted using the 4-grade scale provided by the manufacturer (LAM positivity was defined as grade ≥1). LAM readers did not have access to other TB test results when interpreting the LAM test. Patients provided 2 sputum samples (1 "on-the-spot" and 1 in the early morning) on which microscopy using auramine staining, light-emitting diode fluorescence microscopy, and GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) were performed. Sputum induction was not conducted. Patients were followed for 6 months regardless of their TB treatment status and were re-assessed at 6 months. A tracing system was in place for patients not attending follow-up study consultations. Tracing was done through phone or physically with full respect for the patient's privacy and maintaining confidentiality. Study staff and community health workers affiliated with the primary health care clinics in the area supported tracing activities.

Definitions

Patients with presumptive TB were those the clinician evaluated as requiring investigation for TB. This question was specifically asked of the clinician, and the information was prospectively collected.

Patients were retrospectively classified as presenting with TB screen symptoms [11] when the clinician had recorded at least 1 symptom among cough, fever, night sweats, and weight loss in the medical file. The clinician recorded the presence of prespecified TB-related symptoms (including these 4) as per the study procedures.

Seriously ill patients were those with temperatures >39°C, respiratory rates >30/min, heart rates >120/min, or who were unable to walk without help [10].

Patients eligible for LAM testing according to the latest WHO guidance (December 2019) [10] were those with 1 of the following criteria: at least 1 TB screen symptom recorded in the medical file (even if considered to not have presumptive TB by the clinician), advanced HIV disease, seriously ill, or CD4 count <200 cells/μL. To note, this classification was made "a posteriori," as this guidance was made after the study's implementation.

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), categorical variables as counts and percentages. A 95% confidence interval was used throughout. We assessed LAM positivity and grade in several patient subgroups, and we used the chi-square test to compare LAM positivity between patients with CD4 count <200 cells/μL vs ≥200 cells/μL, seriously ill vs not, presumptive TB vs not, eligible for LAM testing as per the 2019 WHO guidance vs not. We assessed mortality stratified by LAM result and grade during hospitalization and cumulative mortality at 6 months after admission in the several patient groups: CD4 count <200 cells/μL, ≥200 cells/μL, seriously ill, not seriously ill, presumptive TB, no presumptive TB. We used the chi-square test to compare mortality between LAM-positive and LAM-negative patients in each of these groups. Finally, we conducted multivariable analyses to investigate factors associated with mortality at 6 months after admission. We adjusted this model for patient demographics and clinical characteristics chosen a priori: age (per 1-year increase), gender (women vs men), body mass index (BMI; <17 kg/m^2 vs ≥17 kg/m^2), seriously ill (yes vs no), hemoglobin level (<12 g/dL vs ≥12 g/dL), CD4 count (<200 cells/μL vs ≥200 cells/μL), LAM result (positive vs negative), and study period (second period when LAM was used for patient management vs first period). All variables were included in the final multivariate model, and an interaction term between LAM result and CD4 cell count was also included in the model to account for effect modification. Adjusted risk ratios with 95% CIs were assessed, and an alpha level of 5% was used for all statistical

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tests. In addition, we computed the marginal predicted probability of death using parameter estimates from the final model both for LAM-positive and LAM-negative patients stratified by CD4 count and period of inclusion in the study. Kaplan-Meier estimates and log-rank tests were used to estimate mortality differences by LAM result and grade over time. For this analysis, patients who were lost to follow-up were censored at their last visit date. Data were analyzed using Stata, version 13 (College Station, TX, USA).

Patient Consent Statement

This study was approved by the MSF Ethical Review Board (Protocol #1422) and the National Ethical Review Committee of Malawi (Protocol #850). Written informed consent was obtained from all participants aged ≥18 years and from parents or legal guardians of 15–17-year-olds. Assent was obtained from minor participants. Consent was provided via a relative or next-of-kin for patients who were confused or otherwise unable to provide consent.

RESULTS

Demographic and Clinical Characteristics

A total of 387 patients with HIV hospitalized in the medical wards were consecutively included regardless of clinical presentation or CD4 count among 580 patients screened. The reasons for noninclusion among hospitalized patients were that 130 patients had taken fluoroquinolones in the month before enrollment and that for 63 informed consent was not obtained. In total, 216/387 (55.8%) were included during the first period of the test when LAM results were not used for patient management, and the remaining 171/387 (44.2%) were included during the second period.

At admission, 53.7% of the patients had a CD4 <200 cells/μL, and 32.6% were seriously ill. The median CD4 count (IQR) was 173 (51–370) cells/μL. A large majority of patients (81.9%) were on antiretroviral therapy (ART). Clinicians found that 64% of patients had presumptive TB. Using clinician assessment and patient CD4 count, 85% of the patients would have been tested with LAM according to the 2019 WHO LAM testing criteria. According to the symptoms recorded in the medical file, 90% of patients presented at least 1 TB screen symptom. Considering the symptoms recorded and patient CD4 count, 95% of the patients met 2019 WHO LAM testing criteria. Patient clinical and demographic characteristics can be found in Table 1.

TB Diagnosis and Treatment

Nearly all patients (383/387, 99.0%) had an LAM result, 62.8% (243/387) had sputum smear microscopy results, 60.7% (236/387) had Xpert results, and 35.9% (165/387) had a chest x-ray. Among patients with a test result, 26.1% (100/383) were urine LAM positive, 13.2% (32/243) were sputum microscopy positive, and 14.0% (33/236) were sputum Xpert positive.

Table 1. Demographic and Clinical Characteristics at Admission of 387 Hospitalized HIV Patients, Malawi, 2017

	Patients, No. (%)
Female	216 (55.8)
Age, median [IQR], y	38 [32–45]
BMI, median [IQR], kg/m^2	18.4 [16.6–20.7]
CD4, median [IQR], cells/μL	173 [51–370]
CD4	
<100 cells/μL	141 (37.1)
100–199 cells/μL	63 (16.6)
200–349 cells/μL	74 (19.5)
≥350 cells/μL	102 (26.8)
Missing	7
On ART at admission	305 (81.1)
Seriously ill[a]	126 (32.6)
Reported symptoms	
Cough	230 (59.4)
Fever	228 (58.9)
Night sweats	154 (39.8)
Weight loss	277 (71.6)
Chest pain	201 (51.9)
Hemoptysis	19 (4.9)
Difficulty breathing	170 (43.9)
Presumptive TB (according to clinician assessment)	247 (64.2)
≥1 TB screen symptom (recorded in medical file)[b]	349 (90.2)
Eligible for LAM test as per 2019 WHO guidelines[c]	368 (95.1)
Sputum sample production	
Spontaneous sputum	249 (64.3)
Unable to produce sputum	133 (34.4)
Missing information	5
Haemoglobin	
<8 g/L	122 (31.7)
8–11.9 g/L	185 (48.1)
≥12 g/L	78 (20.3)
LAM in urine	
Positive	100 (26.1)
Negative	283 (73.9)
Not done	4
Sputum smear microscopy	
Positive	32 (13.2)
Negative	211 (86.8)
Not done	144
Xpert MTB/RIF in sputum	
MTB detected	33 (14.0)
Not detected	202 (86.0)
Error	1 (0.4)
Not done	152
Xpert MTB/RIF rifampicin resistance	
Yes	2 (7.1)
No	26 (92.9)
Missing	5
TB laboratory test positive[d]	119 (30.8)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; LAM, lipoarabinomannan; TB, tuberculosis; WHO, World Health Organization.

[a]Seriously ill: temperature >39°C, respiratory rate >30/min, heart rate >120/min, or unable to walk without help.

[b]TB screen symptoms: cough, fever, weight loss, night sweats.

[c]Eligible for LAM as per 2019 WHO guidelines: ≥1 TB symptom recorded in the medical file (regardless of whether the clinician found the patient to have presumptive TB), serious illness, or CD4 <200 cells/μL.

[d]TB laboratory test positive: any positive result from LAM, smear microscopy, or Xpert MTB/RIF.

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In total, 30.8% (119/387) of the patients had a positive TB laboratory test result (LAM, microscopy, or Xpert). LAM was positive in 84% (100/119), Xpert in 28% (33/119), and sputum microscopy in 27% (32/119). Of the 119 patients with a positive TB test result, LAM was the only positive test in 80/119 (67.2%) patients. Half of these (40/80) did not have any other laboratory result available. LAM was positive in 59.4% (19/32) of the patients with a positive Xpert result (for whom an LAM result was available).

A third of the patients (133/387, 34.4%) were unable to produce sputum. Of the 152 patients with no Xpert result, 151 had an LAM result and 43/151 (28.5%) were LAM positive. Among 137 patients with no other TB diagnostic results available besides LAM, 40/137 (29.2%) were LAM positive.

Overall, 90/387 (23.3%) patients started TB treatment. The proportion of patients starting TB treatment was 16.2% (35/216) during the first period of the study and 32.2% (55/171) during the second period ($P < .001$). During the first period of the study, while LAM test results were used for study purposes only and not for patient management, 68.8% (44/64) of the LAM-positive patients and 62.5% (45/72) of the patients with a positive TB test did not initiate TB treatment, compared with 2.8% (1/36) and 10.6% (5/47), respectively, during the second period ($P < .001$ for each comparison). During the second period of the study, while LAM results were used for patient management, 95% of the patients with a positive TB test initiated TB treatment the day of admission or the next day.

LAM Results by Patient Group

Almost half of 100 LAM-positive patients (48/100, 48%) had LAM positivity grade 2–4. Patients with CD4 <200 cells/μL and those with presumptive TB had higher LAM-positive rates and grades (Table 2).

LAM was positive in 18.7% (25/134) of the patients with no presumptive TB, in 23.7% (9/38) with no TB screen symptoms, and in 5.3% (1/19) who were not eligible for LAM as per the 2019 guidelines.

Mortality During Hospitalization and Cumulative Mortality at 6 Months

Outcomes were available for 381 patients at the end of hospitalization and for 377 at 6 months after admission. Mortality during hospitalization was 12.6% (48/381) and was higher among patients with LAM-positive results than those with LAM-negative results (19.8% vs 9.6%; $P = .008$), particularly in those with LAM grades 2–4 compared with those with grade 1 and LAM negative (26.7%, 13.7%, 9.6%; $P = .005$). Mortality during hospitalization was 16.5% in patients with CD4 <200 cells/μL vs 6.3% in those with CD4 ≥200 cells/μL ($P = .002$). LAM-positive patients with CD4 <200 cells/μL had higher mortality during hospitalization than LAM-negative patients with CD4 <200 cells/μL (23.7% vs 13.0%; $P = .059$).

Among patients who survived hospitalization, mortality was higher in LAM positive with CD4 ≥200 cells/μL than LAM negative with CD4 <200 cells/μL: 40.6% (13/32) vs 16.9% (22/130), respectively ($P = .004$); there was no statistically significant difference among LAM-positive and LAM-negative patients with CD4 <200 cells/μL: 37.8% (17/45) vs 41.9% (49/117), respectively ($P = .634$).

Cumulative mortality at 6 months after admission was 40.1% (151/377), higher in LAM-positive patients (49/97, 50.5%) than in LAM-negative patients (100/276, 36.2%; $P = .013$) (Table 3). Mortality at 6 months was higher in LAM-positive patients with grades 2–4 than LAM-positive grade 1 or LAM-negative patients (27/46, 58.7%, vs 22/51, 43.1%, in

Table 2. LAM Positivity and LAM Grade in Patient Groups, Malawi, 2017 (n = 383)

	LAM Positive			
	All, n/N (%)[c]	Grade 2–4, n/N (%)	Grade 1, n/N (%)	*P* Value[d]
All (n = 383)	100/383 (26.1)	48/100 (48.0)	52/100 (52.0)	
CD4 <200 cells/μL (n = 202)	62/202 (30.7)	38/62 (61.3)	24/62 (38.7)	.013
CD4 ≥200 cells/μL (n = 174)	34/174 (19.5)	7/34 (20.6)	27/34 (79.4)	
Seriously ill[a] (n = 123)	39/123 (31.7)	23/39 (59.0)	16/39 (41.0)	.086
Not seriously ill (n = 260)	61/260 (23.5)	25/61 (41.0)	26/61 (59.0)	
Presumptive TB (n = 246)	74/246 (30.1)	39/74 (52.7)	35/74 (47.3)	.015
No presumptive TB (n = 134)	25/134 (18.7)	9/25 (36.0)	16/25 (64.0)	
Eligible for LAM as per 2019 WHO guide[b] (n = 364)	99/364 (27.2)	48/99 (48.5)	51/99 (51.5)	.034
Not eligible for LAM as per 2019 WHO guide (n = 19)	1/19 (5.3)	0/1 (0.0)	1/1 (100)	

Abbreviations: LAM, lipoarabinomannan; TB, tuberculosis; WHO, World Health Organization.

[a]Seriously ill: temperature >39°C, respiratory rate >30/min, heart rate >120/min, or unable to walk without help.

[b]Eligible for LAM as per 2019 WHO guidelines: ≥1 TB symptom recorded in the medical file (regardless of whether the clinician found the patient to have presumptive TB), serious illness, or CD4 <200 cells/μL.

[c]Row percentages: for LAM positive, all grades is the proportion of LAM positive among all patients in each patient group; LAM grade 2–4 is the proportion with grade 2–4 among LAM positive in each patient group; LAM grade 1 is the proportion with grade 1 among LAM positive in each patient group.

[d]*P* value for the chi-square test comparing the proportion of LAM positive in patients with CD4 <200 vs CD4 ≥200 cells/μL, seriously ill vs not, presumptive TB vs not, eligible for LAM as per 2019 WHO guidelines vs not.

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Grade 1; $P = .014$) (Figure 1). Mortality was higher in LAM-positive patients in whom the only positive TB laboratory test was LAM (other tests missing or negative) than in LAM-positive with other positive laboratory tests: 57.1% (44/77) vs 25% (5/20; $P = .010$). Among patients treated, mortality tended to be higher in LAM-positive patients compared with LAM-negative: 54.7% (29/53) among LAM-positive treated patients vs 38.2% (13/34) among LAM-negative treated patients ($P = .133$).

In patients with CD4 ≥200 cells/μL, cumulative mortality at 6 months was higher in LAM-positive patients than LAM-negative patients (44.1 vs 21.7%; $P = .008$). However, in patients with CD4 <200 cells/μL, there was no difference in cumulative mortality at 6 months by LAM result. LAM-positive patients who were not considered in need to be investigated for TB had double the mortality of LAM-negative patients (62.5% vs 30.2%; $P = .003$).

In multivariable analyses, the risk of mortality was higher in patients with an LAM-positive test (adjusted odds ratio [aOR], 2.5; 95% CI, 1.1–5.8; $P = .037$) and in those with CD4 <200 cells/μL (aOR, 2.7; 95% CI, 1.5–4.8; $P = .001$) (Table 4). The effect on mortality of having an LAM-positive test decreased when the CD4 count was <200 cells/μL. The marginal predicted probability of death was 47.9% (95% CI, 34.2%–61.7%) for LAM-positive patients and 51.2% (95% CI, 42.2%–60.3%) for LAM-negative patients among those with CD4 <200 cells/μL and 38.0% (95% CI, 20.7%–55.3%) for LAM-positive patients and 19.9% (95% CI, 12.9%–26.9%) for LAM-negative patients among those with CD4 ≥200 cells/μL. Patients included in the study during the first period did not have a higher risk of mortality compared with those included during the second period (aOR, 0.9; 95% CI, 0.5–1.4; $P = .583$). The marginal predicted probability of death was 35.6% (95% CI, 28.3%–42.9%) for patients included during the first period and 38.7% (95% CI, 30.1%–47.4%) for those included during the second period.

DISCUSSION

We found that in the medical wards of a resource-limited public hospital with high TB prevalence, a diagnostic strategy including systematic urine LAM for all HIV patients regardless of their TB symptoms or CD4 count identified a large proportion of patients with TB. One-third of patients with no other TB diagnostic results were found to have TB through LAM testing. These patients would have been missed without the use of LAM. Indeed, a high proportion of LAM-positive patients did not initiate TB treatment during the first period of the study (when LAM was not used for patient management). LAM testing identified patients at higher risk of dying during hospitalization and within 6 months of being hospitalized, particularly among patients with no other TB diagnostic results. However, a decrease in mortality was not observed when LAM was used to guide TB treatment.

Similar to other studies [3, 4], one-third of the patients could not produce sputum, preventing sputum microscopy and Xpert testing. Our study site additionally struggled with a lack of water and the inconsistent presence of x-ray technicians, which led to a considerable number of patients without x-ray results. LAM diagnosis was therefore of high utility in these patients, who might otherwise have been missed. TB prevalence (30%) in our study was similar to other cohorts of hospitalized HIV patients [3, 12, 13].

Some patients were not evaluated as requiring investigation for TB, yet they had at least 1 of the 4 TB screen symptoms recorded in the medical file. High levels of LAM positivity were found in these patients, who could benefit from systematic LAM testing or from systematic TB symptom screening followed by LAM testing in those with symptoms. As described in other studies [3, 7], a high proportion of the patients had symptoms of TB, and we found that 95% of the patients were eligible for LAM testing according to the latest guidance. Although LAM positivity was low in patients not eligible for LAM as per the 2019 WHO guidance, considering that some

Table 3. Mortality at 6 Months After Admission Stratified by LAM Result in Patient Groups, Malawi 2017

	LAM Negative	LAM Positive			
	n/N (%)	All, n/N (%)	Grade 2–4, n/N (%)	Grade 1, n/N (%)	*P* Value[a]
All patients (n = 373)[b]	100/276 (36.2)	49/97 (50.5)	27/46 (58.7)	22/51 (43.1)	.013
CD4 <200 cells/μL (n = 194)	67/135 (49.6)	31/59 (52.5)	20/36 (55.6)	11/23 (47.8)	.709
CD4 ≥200 cells/μL (n = 172)	30/138 (21.7)	15/34 (44.1)	4/7 (57.1)	11/27 (40.7)	.008
Seriously ill[c] (n = 120)	46/82 (56.1)	25/38 (65.8)	14/22 (63.6)	11/16 (68.8)	.315
Not seriously ill (n = 253)	54/194 (27.8)	24/59 (40.7)	13/24 (54.2)	11/35 (31.4)	.061
Presumptive TB (n = 240)	66/168 (39.3)	34/72 (47.2)	21/38 (55.3)	13/34 (38.2)	.253
No presumptive TB (n = 130)	32/106 (30.2)	15/24 (62.5)	6/8 (75.0)	9/16 (56.3)	.003

Abbreviations: LAM, lipoarabinomannan; TB, tuberculosis.

[a] *P* value for the chi-square test comparing mortality between LAM-positive and LAM-negative patients in each patient group.

[b] In total 377 patients had an outcome known at 6 months after admission, and among them 373 had an LAM test result.

[c] Seriously ill: temperature >39°C, respiratory rate >30/min, heart rate >120/min, or unable to walk without help.

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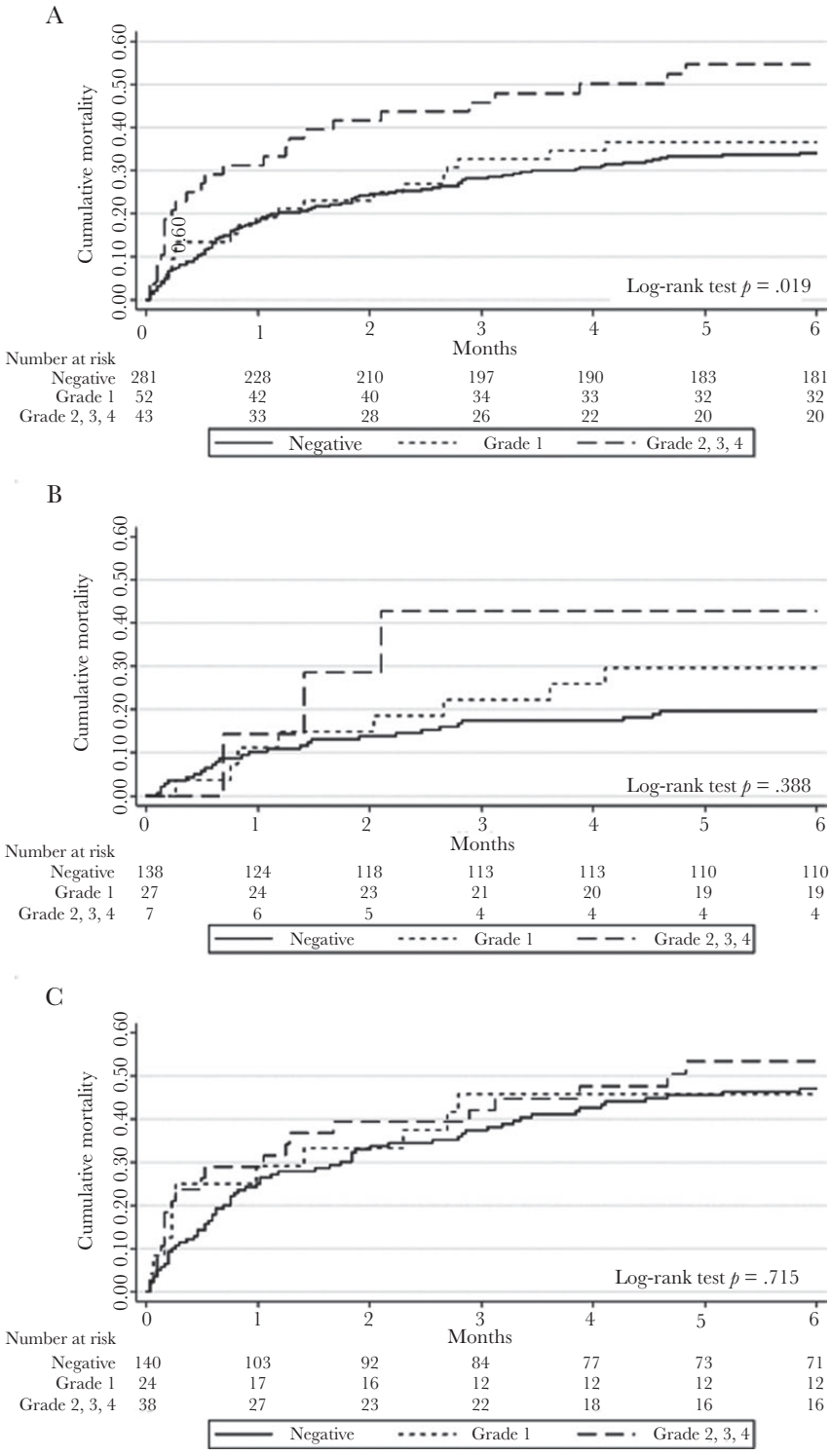

Figure 1. Mortality at 6 months by LAM result in all patients (A), in patients with CD4 ≥200 cells/μL (B), and in patients with CD4 <200 cells/μL (C), Malawi, 2017. Abbreviation: LAM, lipoarabinomannan.

of the patients with TB symptoms may not be identified as having presumptive TB and that CD4 count is currently not routinely done (or results may not be immediately available) in settings similar to this one, systematic LAM testing for all HIV patients in medical wards regardless of their symptoms or CD4 could simplify the use of LAM. This strategy would be practical and easily implementable [14] and would lead to rapid TB treatment.

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Table 4. Risk of Mortality at 6 Months in Hospitalized Patients—Multivariable Regression Model (n = 365)

	Adjusted Odds Ratio	95% CI	*P* Value
Age (per 1-y increase)	1.0	1.0–1.1	.006
Women	0.9	0.5–1.4	.576
Body mass index <17 kg/m^2	2.4	1.3–4.3	.004
Seriously ill	2.0	1.1–3.5	.021
Hemoglobin <12 gr/dL	2.9	1.4–5.7	.002
Included during first study period[a]	0.9	0.5–1.4	.583
CD4 <200 cells/μL	2.7	1.5–4.8	.001
LAM positive	2.5	1.1–5.8	.037
Interaction term between LAM positive and CD4 <200	0.4	0.1–1.0	.059

Abbreviation: LAM, lipoarabinomannan.

[a]During the first study period, LAM result was not used for patient management.

Cumulative mortality at 6 months after admission was very high (40%). In our study, as already described in others [15–19], LAM-positive patients had a higher risk of mortality. Moreover, we found that LAM-positive patients with no other TB diagnostic results had a higher mortality than those with other positive laboratory results. LAM is therefore a useful tool to identify patients at high risk of death. Mortality was particularly high for those with LAM grades 2–4, making LAM result intensity (grade) an additional indicator of higher mortality that should be taken into consideration. LAM-positive patients with CD4 <200 cells/μL had a higher risk of mortality than LAM-negative patients during hospitalization. However, it is important to note that LAM-positive patients with CD4 ≥200 cells/μL also had a higher risk of cumulative mortality at 6 months than LAM-negative patients. LAM could also help to identify patients with high risk of mortality among those with CD4 ≥200 cells/μL. These results indicate that LAM-positive patients (both with CD4 <200 and ≥200 cells/μL) should receive extra attention during hospitalization and after discharge.

In 2 clinical trials, LAM testing at admission followed by early treatment has been shown to decrease mortality in hospitalized patients with TB symptoms or low CD4 counts [6, 7]. In our study, we did not find a difference in the risk of mortality before and after LAM results were used for patient management. The probability of death at 6 months was very high in both periods. In addition, mortality remained higher among LAM-positive treated patients compared with LAM-negative treated patients. LAM is associated with high bacterial burden and low CD4 counts, known risk factors for death. It is important to note that an important proportion of the deaths occurred after hospital discharge. Adjunctive interventions during hospitalization and after discharge are therefore needed.

Xpert MTB/RIF remains a very important test to diagnose patients not captured by LAM and to detect rifampicin resistance among TB cases and should be requested in parallel to LAM testing. In contexts where Xpert MTB/RIF results are frequently delayed, LAM could guide treatment decisions while other results are in process. Even in settings with fast Xpert MTB/RIF turnaround times, LAM remains important for patients with low-quality or no sputum samples. We encourage proper LAM test performance, using the manufacturer-provided test scale and LAM grade reporting. In Malawi, hospital teams observed that at the end of the study, test scales were no longer being used and LAM positivity was based on the appearance of any indicator line, regardless of its intensity, a type of misinterpretation that has been observed in other contexts [14]. Future improved LAM tests such as FujiLAM are expected to be even more beneficial for this population [20–22], and further studies are needed to assess different LAM testing strategies (eg, systematic vs clinician-directed).

Strengths and Limitations

A strength is that this study was conducted in real-world conditions (no major study support was provided to the hospital, and similar patients and contexts are found in other Sub-Saharan, resource-constrained settings). In addition, outcomes at 6 months were available for most of the patients. However, the study results cannot reflect pure programmatic conditions, and further implementation studies are needed to assess the real uptake of LAM under nonstudy conditions. The study has also some limitations. *Mycobacterium* culture was not routinely performed, as it was not readily available in Malawi, and patients who could not produce sputum remained without an Xpert result. Therefore, some TB-confirmed cases may have been missed, and TB prevalence in this population could be higher. On the other hand, LAM was the only positive test in an important proportion of patients with a positive TB laboratory test, and although other studies have reported a high specificity of LAM [23], some of these results could be false positive. In addition, the number of patients in some study subgroups was limited, and mortality analysis for these groups should be cautiously interpreted. Finally, the lack of association between the period of recruitment (before or after LAM was used for patient management) and mortality should be interpreted with caution, as the study was not designed to assess the impact of LAM use on mortality and as data on comorbidities, patient treatment

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(other than TB), CD4 count, and viral load were not collected during follow-up.

CONCLUSIONS

In resource-limited hospital medical wards with high TB prevalence, a diagnostic strategy including systematic urine LAM in all HIV patients regardless of their TB symptoms or CD4 count is easily implementable and identifies high proportions of patients with TB. It also allows rapid TB treatment initiation and identifies patients with higher risk of intrahospital and postdischarge death.

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