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Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a high HIV prevalence setting

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Abstract

Background—Effective tuberculosis (TB) control in HIV-prevalent settings is hindered by absence of accurate, rapid TB diagnostic tests. We evaluated the accuracy of a urine lipoarabinomannan (LAM) test for TB diagnosis in South Africa.

Methods—Hospitalized adults with signs and/or symptoms of active TB were enrolled. Sputum smear microscopy and mycobacterial culture, mycobacterial blood culture, and HIV testing were performed. A spot urine specimen was tested for LAM.

Results—499 participants were enrolled; 422 (84.6%) were HIV-infected. In microbiologically-confirmed TB patients, the LAM test was positive in 114/193 (sensitivity 59%, [95% CI 52, 66]), including 112/167 (67% [59, 74]) who were HIV-infected. Among individuals classified as “not TB”, the LAM test was negative in 117/122 (specificity 96% [91, 99]), including 83/88 (94% [87, 98]) who were HIV-infected. In confirmed TB patients, the LAM test was more sensitive than sputum smear microscopy (42%, 82/193, $p < 0.001$) and detected 56% (62/111) of those who were sputum smear-negative. HIV-infection (AOR 13.4), mycobacteremia (AOR 3.21), and positive sputum smear (AOR 2.42) were risk factors for a positive LAM test.

Conclusions—The urine LAM test detected a subset of HIV-infected patients with severe TB in whom sputum smear microscopy had suboptimal sensitivity. The combination of urine LAM testing and sputum smear microscopy is attractive for use in settings with high HIV burden.

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Conflict of Interest

The authors have no conflicts of interest related to this study, its findings, or this manuscript. Inverness Medical Innovations donated Clearview TB ELISA kits and trained laboratory staff in urine specimen processing and testing, but had no role in the study concept, design, implementation, data analysis, results reporting, or decision to publish a manuscript.

Keywords

HIV; acquired immunodeficiency syndrome; tuberculosis; mycobacterium infections; diagnosis

Introduction

Tuberculosis (TB) incidence and mortality have increased dramatically as a result of the HIV epidemic. In southern Africa, TB is the leading cause of death among HIV-infected patients and approximately 50% of TB patients are HIV co-infected.^{1,2} Early treatment of TB is hindered by the lack of rapid, accurate diagnostic modalities that can be applied in resource-constrained settings.³ Mycobacterial culture is the laboratory standard for diagnosis of active TB, but is costly, requires access to specialized laboratories, and takes weeks to provide results. Sputum smear microscopy detects less than half of HIV-infected TB cases in many settings. The Global Plan to Stop TB has prioritized the development of simple, accurate, inexpensive tests for TB case detection in HIV-positive individuals.⁴

As a strategy for rapid TB diagnosis, the detection of *Mycobacterium tuberculosis* antigens has been explored over several decades.^{5–14} Lipoarabinomannan (LAM), a 17.5 kD glycolipid component of the outer cell wall of mycobacteria, is an attractive diagnostic target for several reasons. As a bacterial product it has the theoretical potential to discriminate active TB from latent TB infection independent of human immune responses. LAM is heat stable, cleared by the kidney, and detectable in urine.^{11–14} A urine test could facilitate TB diagnosis in patients in whom sputum is uninformative or not obtainable, and lacks the infection control risks associated with sputum production or blood collection. Finally, urine LAM detection may be amenable to simple, inexpensive, point-of-care platforms.

The Clearview™ TB ELISA assay (Inverness Medical Innovations, Waltham, Massachusetts, USA) is a direct antigen sandwich immunoassay in a 96-well plate format. We evaluated the accuracy of this urine LAM test for the diagnosis of active TB in patients admitted to 3 hospitals in South Africa with a presumptive diagnosis of TB.

Materials and Methods

Study Sites and Population

This study was nested in a prospective, multi-center cohort study to determine predictors and causes of death in hospitalized TB suspects. Sites were the Chris Hani Baragwanath Hospital, a large tertiary-care public hospital in Soweto; Selby Hospital, a nearby private hospital treating less severely ill patients requiring admission from the former hospital; and Tshepong Hospital, a provincial hospital. Potential participants were initially identified by review of admission intake logs by study personnel. Chart reviews and clinical interviews were then utilized to determine study eligibility. Eligibility criteria were kept broad to capture the full spectrum of pulmonary and extrapulmonary TB suspects. Inclusion criteria for the LAM diagnostic study component were age ≥ 18 years, signs and/or symptoms compatible with TB, urine sample available for testing, and informed consent. Patients who had prior hospitalization within two weeks or had been on TB therapy for > 2 months were excluded.

Demographic information and clinical history were obtained through interview and medical record review at enrollment. Study-directed testing at enrollment included one sputum for acid fast bacilli (AFB) smear microscopy and mycobacterial culture. One mycobacterial blood culture, serum HIV antibody testing (plus CD4 count for HIV-positive participants), and a spot urine sample were also taken. Additional diagnostic tests, including mycobacterial evaluation of CSF, pleural fluid or tissue, lymph node biopsies, and additional respiratory samples, were

also performed as part of routine clinical care at the discretion of the treating non-study clinician.. All treatments were prescribed at the discretion of the treating clinician. Results of study-directed tests except urine LAM were available to treating clinicians. A study interview was conducted at 2 months after enrollment to assess clinical status. This study was approved by review committees of the University of Witwatersand and Johns Hopkins Medical Institutions.

Laboratory Testing

Smear Microscopy and Mycobacterial Cultures—Sputum specimens were decontaminated with N-acetyl-L-cysteine-sodium hydroxide.¹⁵ After centrifugation, the pellet was suspended in buffer. A concentrated auramine-O smear was prepared, examined under x500 magnification using a fluorescent microscope, and graded.¹⁶ A 0.5-ml portion of processed sputum sediment was cultured using the BACTEC MGIT 960 system (BD Diagnostics Systems, Sparks, MD). MYCO/F LYTIC (BD Diagnostics Systems) tubes were used for mycobacterial blood cultures. Mycobacterial species identification was performed using GenoType Mycobacterium CM kits (Hain Lifescience, Nehren, Germany) for MGIT cultures or AccuProbe (Gen-Probe, San Diego, California) for MYCO/F LYTIC cultures.

Urine LAM test—Testing, using the Clearview™ TB ELISA kit was conducted at a single laboratory in South Africa. Urine specimens were transported to the laboratory, subjected to initial processing, then frozen within 24 hours of collection. Testing and interpretation were performed according to the manufacturer's instructions. An aliquot of each urine specimen was heated to 100°C for 30 minutes, then centrifuged at 10,000 rpm for 15 minutes. The supernatant was stored frozen at -20°C. ELISA assays were performed in batches. Each sample was thawed, and 0.1 ml was placed in duplicate wells of the 96-well plate. Positive and negative controls were placed in appropriate wells, and the plate was incubated at room temperature for one hour. Well contents were decanted and wells were washed. To each well was added 0.1 ml of rabbit anti-LAM antibody conjugated to horseradish peroxidase, and the plate was incubated at room temperature for one hour. Well contents were decanted and wells washed. To each well was added 0.1 ml of tetramethylbenzidine substrate and the plate was incubated at room temperature for 15 minutes followed by addition of 0.1 ml of 1M H₂SO₄. Optical density (OD) at 450nm was measured using an ELx800 microplate reader (BioTek Instruments, Winooski, Vermont). Duplicate samples with average optical densities of 0.1 OD greater than the negative control were considered positive.

Outcomes determination

Participants were categorized into one of the following four TB diagnostic categories based on microbiological and clinical criteria, and response to therapy at follow up. Except for urine LAM testing, the results of all clinically available specimens were utilized for outcomes categorization. LAM results were not used for diagnostic classification.

- **Confirmed TB**--*M. tuberculosis* cultured from any site, OR microscopical examination of any specimen revealing acid fast bacilli or granuloma(s) in the absence of a culture positive for any *Mycobacteria*
- **Possible TB**--no culture positive for *M. tuberculosis* AND presence of clinical response to empiric TB treatment as defined by subjective report of improvement in cough, weight loss, and/or fever at two month follow-up
- **Not TB**--cultures negative for *M. tuberculosis* AND ≥ 1 of the following: a) alternative definitive microbiological diagnosis, b) clinical improvement in the absence of TB treatment, c) failure to respond to empiric TB treatment
- **Indeterminate**--failure to meet criteria for any of the above diagnostic categories

Statistical analyses

Student's t-test was used to compare means. Two sample proportions were compared by χ^2 tests. McNemar's test was used to compare LAM and smear sensitivities. Simple and multiple logistic regressions were used to determine predictors of LAM test positivity. Nonparametric receiver operator characteristic (ROC) analysis was performed to evaluate sensitivity and specificity based on different OD cutoffs of positivity. Results for participants classified as "confirmed" or "not" TB, and sample OD calculated after subtracting the negative control OD were used to construct the ROC. A p value ≤ 0.05 was considered statistically significant and 95% confidence intervals (CI) were used. Statistical calculations were performed using Stata 10.1 (StataCorp, USA).

Results

Characteristics of the study population

499 participants were enrolled. Characteristics of the study population are shown in Table 1. HIV infection was diagnosed in 422 patients (85%). Final disease categorizations were as follows (Figure 1): 193 (39%) had confirmed TB (185 with positive cultures for *M. tuberculosis*, and 8 with positive AFB smears but negative cultures), 89 (18%) had possible TB, 122 (24%) did not have TB, and 95 (19%) were indeterminate. Among those with confirmed TB, 111/193 (58%) were sputum smear negative; *M. tuberculosis* was cultured from only sputum in 131 (71%), from sputum and blood in 25 (13%), and from only blood in 16 (8%).

LAM test performance among all participants

Figure 1 shows qualitative LAM results by final TB diagnostic classification. LAM test sensitivity was 59% (95% confidence interval [CI] 52, 66) in participants with confirmed TB, and 46% (40, 52) for confirmed TB plus possible TB groups combined. Among individuals categorized as "not TB", specificity was 96% (91, 99). Positive predictive value for confirmed TB (PPV) and negative predictive value (NPV) were, respectively, 73% (65, 80) and 34% (29, 39) among all participants, and 96% (90, 99) and 60% (52, 67) when indeterminate and possible TB patients were excluded. Twenty-three of 499 (4.6%) study participants were receiving ongoing TB treatment at the time of enrollment; 6 (26%) had confirmed TB, 7 (30%) had possible TB, 4 (17%) did not have TB, and 6 (26%) were indeterminate. Among these 23 participants, LAM test sensitivity was 33% (4.3, 77) in those with confirmed TB, and 15% (1.9, 45) for confirmed TB plus possible TB groups combined.

Quantitative LAM results are shown in Figure 2. Median (interquartile range [IQR]) ODs were as follows: not TB 0.012 (0.003, 0.03); indeterminate 0.02 (0.008, 0.075); possible TB 0.0175 (0.002, 0.059); confirmed TB 0.19 (0.026, 1.3). Median coefficient of variation for duplicate wells was 2.0% (IQR 0.8, 3.7).

LAM test performance stratified by HIV-infection status

LAM test sensitivity and specificity, stratified by HIV-infection status, are shown in Figure 1. Overall LAM sensitivity was 67% (59,74) and specificity was 94% (87,98) among HIV-positive participants with confirmed TB or no TB, respectively. For HIV-positive patients, LAM PPV for confirmed TB and NPV were, respectively, 75% (67, 82) and 30% (25, 36) among all participants, and 96% (90, 99) and 60% (51, 68) when indeterminate and possible TB patients were excluded. Among 47 HIV-negative participants the LAM test was positive in three, including 2/14 (14%) with confirmed TB and 1/5 (20%) indeterminate participants; specificity was 100% (23/23) in the small number of HIV-negative participants classified as "not TB".

Among HIV-positive participants with confirmed TB, LAM test sensitivity differed by CD4 category ($p<.001$). LAM sensitivity was 55% (41,69) for those with CD4 counts greater than 200, 14% (3,6, 58) for CD4 counts of 150–200, 56% (30, 80) for CD4 counts of 100–150, 71% (51,87) for CD4 counts of 50–100, and 85% (73, 93) for CD4 counts less than 50.

Factors associated with a positive urine LAM test

HIV-infection (AOR 13.4, $p<0.01$), positive mycobacterial blood culture (AOR 3.21, $p=0.01$), and positive sputum smear (AOR 2.42, $p<0.01$) were independently associated with a positive LAM test in confirmed TB patients (Table 2). In a separate analysis including only HIV-positive individuals with confirmed TB, independent predictors of a positive LAM test were positive sputum smear, (AOR 2.39, $p=0.03$), and CD4 count < 50 (AOR 4.04, $p<0.01$). Among HIV-positive participants with confirmed TB, several indicators of higher bacillary burden were associated with higher ODs. In multiple linear regression, those with CD4 count less than 50 had an OD of 0.80 (0.45, 1.15) greater than those with CD4 count greater than 200 ($p<0.001$); those with positive sputum smear had an OD of 0.42 (0.13, 0.71) greater than those with negative sputum smear ($p=0.004$); and those with positive mycobacterial blood cultures had an OD of 0.49 (0.15, 0.83) greater than those with negative cultures ($p=0.005$). Age, sex, and death at two months were not statistically significantly associated with a difference in OD.

LAM test performance compared to sputum smear microscopy in confirmed TB cases

Sensitivity of the LAM test was compared to that of sputum smear microscopy, a test with rapid turn-around-time (Table 3). Of 193 confirmed TB cases, 52 (27%) were positive by both the LAM test and smear microscopy, 49 (25%) were negative by both assays, 62 (32%) were positive by the LAM test alone, and 30 (16%) were positive by smear microscopy alone. The LAM test was more sensitive than sputum smear microscopy (42%, 82/193, $p<0.01$), and the LAM test was positive in 56% (62/111) of confirmed TB patients with a negative sputum smear. The combined sensitivity of sputum smear plus LAM test (either or both positive) was 75% (144/193, 95% CI 68, 81; $p < 0.01$ compared with smear alone, and $p<0.01$ compared with LAM test alone). LAM test sensitivity was higher than that of sputum smear microscopy for confirmed TB cases with HIV-infection (67% vs 40%, $p<0.01$) or who died (72% vs 48%, $p=0.03$).

Receiver operator characteristic (ROC) curve

Sensitivity and specificity were optimal at the manufacturer's recommended cut-off of OD 0.1 (on-line data supplement). Decreasing the OD cut-off below 0.1 resulted in marked reduction in sensitivity with little gain in specificity. Increasing the threshold for a positive test from an OD of 0.1 to 0.51 increased the specificity to 100% with a reduction in sensitivity to 38%.

Discussion

For the diagnosis of active TB in a setting of high HIV prevalence, the LAM test had a sensitivity of 59% in confirmed TB cases, and specificity of 96% among individuals classified as "not TB". LAM test sensitivity was higher in HIV-positive than HIV-negative TB patients, and was highest in the subgroup of HIV-positive TB patients with CD4 counts less than 50. HIV-related immunosuppression and high overall bacillary burden (as reflected by positive mycobacterial blood cultures and positive sputum smears) were associated with LAM test positivity among confirmed TB patients. An important attribute of the LAM test was its ability to detect over half of confirmed TB cases not detected by sputum smear microscopy. The combination of sputum smear plus LAM testing identified 75% of confirmed TB cases. Rapid detection of active TB is essential for managing patients with advanced HIV infection, and permits earlier initiation of TB therapy and institution of infection control procedures.

How does LAM test performance in our study compare with performance reported by other investigators? Boehme and colleagues used a prior version of the existing urine LAM assay (Chemogen, South Portland, Maine) to evaluate 231 TB suspects (69% HIV-positive) and 103 healthy controls in Tanzania.¹⁴ Sensitivity was 80.3% among individuals with *M. tuberculosis* isolated from sputum culture, and was unaffected by HIV status; specificity was 99% in healthy controls. Boehme et al. used unprocessed fresh urine whereas we used concentrated, frozen urine. Whether this was a major factor in the sensitivity difference between studies is unclear. Corbett and colleagues recently evaluated accuracy of the Clearview™ TB ELISA test in TB patients and suspects in Harare, and found sensitivity of 52% among HIV-infected, TB culture-positive individuals.¹⁷ In HIV-infected outpatients screened for TB during enrollment in an antiretroviral treatment program in Cape Town, Lawn and colleagues found Clearview™ TB ELISA test sensitivity of 38% overall in TB culture-positive individuals and 67% in the subgroup with CD4 < 50; specificity was 100%.¹⁸ These findings are in agreement with our finding that LAM sensitivity was highest in patients with the lowest CD4 counts.

In our study LAM test sensitivity was low in the group of participants designated as “possible TB”. There are several possible explanations. First, these individuals could have had TB disease with low mycobacterial burden that was insufficient to result in a positive LAM test. Alternatively, “possible TB” patients may not have had TB. Many received treatment directed against bacterial pathogens in addition to anti-TB treatment, and improvement could have been due to non-TB treatment. In addition, at 2-month follow-up we collected subjective information on clinical improvement; objective parameters such as chest radiographs may have been useful. In all likelihood, the “possible TB” group is a heterogeneous one that includes individuals with and without TB.

A new rapid TB diagnostic test with very high sensitivity is desperately needed, but elusive. The LAM test, with modest sensitivity, might nevertheless meet an important need in HIV-prevalent, resource constrained settings. Dowdy et al. used decision analysis to explore the potential cost-effectiveness of a hypothetical new point-of-care TB test.¹⁹ Cost-effectiveness depended most strongly on specificity and price, and was maximized in circumstances in which existing TB diagnostic capacity was poor (e.g. HIV-prevalent settings in which sputum smear microscopy has a low yield). The LAM test’s high specificity, potentially low price, and ability to detect TB in individuals with negative sputum smears are therefore attractive features. While a dipstick or other point of care test format would have advantages over the current test format, the current assay could be integrated into laboratories equipped for ELISA-based HIV testing.

Our study has important limitations. A definitive diagnosis could not be established in a substantial minority of study participants, a challenge not unique to our study or clinical practice in settings of high TB/HIV burden. To nevertheless maximize study interpretability, we report results for the “indeterminate” and “possible TB” groups despite uncertainties about final diagnosis. Second, the studied population had few individuals from whom non-tuberculous mycobacteria (NTM) were isolated, and therefore we were unable to assess whether the LAM test discriminates *M. tuberculosis* from NTM in clinical practice. In pre-clinical testing the current assay had highest analytical sensitivity for *M. tuberculosis* complex, with substantially less reactivity to NTM.¹⁴ Our study has several key strengths. Importantly, it was performed in a setting of high TB-HIV prevalence, and results are therefore generalizable to similar settings where the need for improved TB diagnostics is great. It should be noted, however, that the LAM test positive predictive value may be reduced in settings with lower TB prevalence. TB diagnostic accuracy was enhanced by the use of mycobacterial blood cultures, and HIV status was determined for almost all participants.

In conclusion, the urine LAM test detected a subset of HIV-positive patients with severe TB and high mortality in whom smear microscopy has suboptimal sensitivity. The combination of urine LAM testing and smear microscopy is attractive for use in settings with high HIV burden. However, the apparent low LAM test sensitivity in HIV-negative TB patients may limit this test's utility in settings of low HIV prevalence." Further studies are warranted to determine if implementation of LAM testing would result in improved clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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*Among the 95 indeterminate participants, 47 (49.5%) died without meeting other diagnostic criteria, 22 (23.1%) were lost to follow-up without meeting other diagnostic criteria, 16 (16.9%) had improvement at follow-up but either mycobacterial cultures were unavailable or treatment was unknown, and 10 (10.5%) had no confirmed diagnosis and worsened or had no improvement with prescribed non-TB treatment.

Figure 1.

Flow chart of final TB diagnostic classification, and LAM test sensitivity and specificity.

Figure 2.

Box plot of LAM test results, by final TB diagnostic classification. Horizontal lines within boxes represent medians. The lower and upper bounds of the boxes represent the first and third quartiles, respectively. Values > 1.5 interquartile range below the first quartile or 1.5 interquartile range higher than the third quartile were considered outliers (●). Whiskers represent the smallest and largest values not considered outliers. The asterisk (*) in the Confirmed TB category represents a single value of OD 4.87, not shown to preserve scale.

Table 1

Characteristics of Study Participants

Characteristic	N	%
Male	169	34
Median age in years (SD)	37 (10)	
Age range in years	18–77	
Enrollment Site		
Chris Hani Baragwanath Hospital	182	36
Selby Hospital	168	34
Tshepong Hospital	149	30
HIV status		
Positive	422	85
Negative	47	9
Unknown	30	6
Median CD4* (IQR) cells/ml ³	79 (24–186)	
Any sputum smear positive for AFB	82	16
Any sputum culture positive for <i>M. tuberculosis</i>	161	32
Any sputum culture positive for non-tuberculous mycobacteria [†]	9	2
Blood culture positive for <i>M. tuberculosis</i>	43	9
Blood culture positive for non-tuberculous mycobacteria	2	0.4
Other culture positive for <i>M. tuberculosis</i> ^{††}	15	3
Any specimen culture positive for <i>M. tuberculosis</i>	185	37

Abbreviations: SD, standard deviation; IQR, interquartile ratio; AFB, acid fast bacilli

* among HIV-positive participants

[†] 4 *M. avium-intracellulare*, 1 *M. kansasii*, 2 *M. gordonae*, 1 *M. chelonae*, 1 unable to speciate

^{††} pleural fluid or biopsy, 11; biopsy of lymph node or other soft tissue, 4

Table 2
LAM test results according to patient characteristics for 193 individuals with confirmed TB

Risk Factor	Total	LAM positive	All participants		HIV-infected participants only	
			OR	Adjusted OR [†]	Adjusted OR ^{††}	
Sex						
Female	121 (64)	76 (63)	ref	ref	ref	
Male	67 (36)	35 (52)	0.65 (0.35, 1.19)	0.96 (0.46, 1.99)	1.06 (0.48, 2.39)	
Age						
<30	57 (30)	33 (58)	ref	ref	ref	
30–39	64 (33)	44 (69)	1.6 (0.76, 3.37)	1.48 (0.64, 3.42)	1.43 (0.57, 3.61)	
40–49	45 (23)	23 (51)	0.76 (0.35, 1.67)	0.65 (0.26, 1.61)	0.51 (0.19, 1.38)	
>50	27 (14)	14 (52)	0.78 (0.31, 1.97)	1.51 (0.41, 5.60)	1.30 (0.32, 5.27)	
HIV status						
Negative	14 (7)	2 (14)	ref	ref	N/A	
Positive	167 (87)	112 (67)	12.2 (2.64, 56.5) [*]	13.4 (2.59, 69.9) [*]		
Sputum smear						
Negative	111 (58)	62 (56)	ref	ref	ref	
Positive	82 (42)	52 (63)	1.37 (0.76, 2.46)	2.42 (1.18, 4.97) [*]	2.39 (1.09, 5.23) [*]	
Blood culture						
Negative	150 (78)	79 (53)	ref	ref	ref	
Positive	43 (22)	35 (81)	3.93 (1.71, 9.04) [*]	3.21 (1.31, 7.89) [*]	2.41 (0.89, 6.49)	
2-Month mortality						
Alive at 2 months	150 (78)	83 (55)	ref	ref	ref	
Death by 2 months	43 (22)	31 (72)	2.09 (0.99, 4.4) [*]	1.62 (0.70, 3.76)	1.60 (0.64, 3.98)	
CD4 (cells/mm ³) ^{**}						
>200	56 (34)	31 (55)	ref		ref	
150–200	7 (4)	1 (14)	0.13 (0.02, 1.19)		0.11 (0.01, 1.10)	

Risk Factor	Total N=193	LAM positive N=114 (59%)	All participants		HIV-infected participants only	
			OR	Adjusted OR [†]	Adjusted OR ^{††}	Adjusted OR ^{††}
100–149	16 (10)	9 (56)	1.03 (0.34, 3.18)	not included	0.86 (0.26, 2.85) 1.30 (0.44, 3.82) 4.04 (1.58, 10.34)*	
50–99	28 (17)	20 (71)	2.02 (0.76, 5.34)			
<50	60 (36)	51 (84)	4.57 (1.89, 11.1)*			

Abbreviations: OR, odds ratio; N/A, not applicable

*
p ≤ 0.05

**
HIV status of 12 participants was unknown

†
Adjusted odds ratios calculated from multiple logistic regression with sex, age, HIV status, smear status, blood culture status, and survival included in the model.

††
Adjusted odds ratios calculated from multiple logistic regression with sex, age, smear status, blood culture status, survival, and CD4 count included in the model.

Table 3
Performance of sputum smear microscopy versus urine LAM test in confirmed TB patients

Group	Total n (%)	Sputum smear microscopy positive n (%)	LAM positive n (%)	p value (LAM versus sputum smear microscopy)	Combination LAM plus sputum smear microscopy [*] n (%)	p value (combination versus sputum smear microscopy alone)
Sputum smear microscopy						
Positive	82 (42)		52 (63)			
Negative	111 (58)	--	62 (56)	--	--	--
All confirmed TB patients	193 (100)	82 (42)	114 (59)	<0.01	144 (75)	<0.01
Sputum culture positive	161 (83)	73 (45)	94 (58)	0.01	120 (75)	<0.01
Blood culture positive	43 (22)	13 (30)	35 (81)	<0.01	36 (84)	<0.01
Death by follow-up	43 (22)	21 (49)	31 (72)	0.03	37 (86)	<0.01
HIV positive	167 (87)	66 (39)	112 (67)	<0.01	128 (77)	<0.01

^{*} either a positive urine LAM test or a positive sputum smear microscopy result, or both, considered to represent a diagnosis of TB