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Value of Urine Lipoarabinomannan Grade and Second Test for Optimizing Clinic-based Screening for HIV-associated Pulmonary Tuberculosis

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Abstract

Background—We assessed the role of urine LAM (lipoarabinomannan) grade and a second LAM test for HIV-associated pulmonary tuberculosis (TB) screening in outpatient clinics in South Africa.

Methods—We enrolled newly-diagnosed HIV-infected adults (≥ 18 years) at 4 clinics, excluding those on TB therapy. Participants provided sputum for AFB microscopy and culture. Nurses conducted two rapid urine LAM tests at the point-of-care, and graded positive results from low (“faint”) to high (5+). Culture-confirmed pulmonary TB was the gold standard. We used area under receiver operating curves (AUROC) to compare screening strategies.

Results—Among 320 HIV-infected adults, median CD4 was 248/mm³ (IQR 107–379/mm³); 54 (17%) were TB culture-positive. 52 (16%) of all participants were LAM-positive by either test; correlation between LAM tests was high. Among 10 “faint” positive results, 2 (20%) had culture-

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Conflict of Interest Statement

We declare that we have no conflicts of interest.

positive TB. Using 1+ LAM grade as positive, one LAM test had sensitivity of 41% (95% CI 28–55%) and specificity of 92% (95% CI 88–95%). A 2 LAM test strategy had a sensitivity of 43% (95% CI 29–57%). One LAM test 1+ grade (AUROC=0.66; 95% CI 0.60–0.73) was significantly better than sputum AFB alone. The optimal strategy was sequentially performing one LAM test followed by sputum AFB if LAM grade <1+ (AUROC=0.70; 95% CI 0.63–0.77), which had sensitivity of 48% (95% CI 34–62%) and specificity of 91% (95% CI 87–94%).

Conclusions—In this clinic-based study, “faint” line was a false-positive, second urine LAM test added no value, and an optimal screening strategy was one LAM test followed by sputum AFB microscopy for urine LAM-negative people.

Keywords

Tuberculosis; HIV/AIDS; Lipoarabinomannan (LAM); urine; screening; South Africa

Introduction

Mycobacterium tuberculosis remains the leading cause of AIDS-related deaths worldwide.¹ Since anti-TB therapy should optimally be started weeks before antiretroviral therapy among HIV and tuberculosis (TB) co-infected patients,¹ an ideal diagnostic test for HIV-associated TB would be an easily performed point-of-care test.² A rapid, clinic-based diagnostic test to identify HIV-associated TB at the time of HIV diagnosis might be used to accelerate TB treatment initiation, reduce loss to follow-up, and improve patient outcomes.

Symptom-based screening has proven unreliable by missing asymptomatic TB-infected persons and due to poor specificity identifies many people in need of additional testing, while existing tests for diagnosing HIV-associated TB have been suboptimal.^{3,4} Sputum smear microscopy for acid-fast bacilli (AFB) requires a trained microscopist and has poor diagnostic sensitivity among HIV-infected adults with culture-confirmed pulmonary TB.^{5–7} Mycobacterial sputum culture is very time and labor intensive, and has poor availability in resource-limited settings.^{8,9} The Xpert MTB/RIF assay is an improvement in diagnosing HIV-associated TB, but the assay's high cost, 2-hour operator time, and reliance on electricity have thus far rendered it impractical for use at the clinical point-of-care in many settings.^{10,11} Therefore, an inexpensive, rapid, clinic-based point-of-care test for HIV-associated TB remains a high global priority.¹²

Lipoarabinomannan (LAM) is a lipopolysaccharide in the cell wall of *M. tuberculosis* that is released from metabolically active or degrading organisms and excreted in urine.¹³ A laboratory-based urine LAM ELISA test had high diagnostic specificity for detecting HIV-associated TB.^{14–16} A novel lateral flow assay for detecting LAM in urine does not require laboratory equipment or reagents, returns test results in 25 minutes, and can be conducted at the clinical point-of-care.¹⁷ Studies among hospitalized patients in sub-Saharan Africa have suggested that a darker band intensity may be a more appropriate threshold for the urine LAM test,^{18–20} but no studies have reported additional gains in diagnostic sensitivity by conducting a second LAM test. Since we initially reported a low diagnostic sensitivity of a single rapid urine LAM test with a binary (positive/negative) result,²¹ we sought to use a different cohort to determine the value of the urine LAM test grade and a second LAM test

in screening for TB among newly-diagnosed HIV-infected adults in outpatient clinical settings in South Africa.

Methods

Study sites and participants

We conducted a prospective clinic-based study of adults who presented for voluntary HIV testing from May 2012 to January 2013 in KwaZulu-Natal, South Africa. We enrolled consecutive newly-diagnosed HIV-infected persons in the outpatient clinical areas of McCord Hospital, St. Mary's Hospital, and two municipal health clinics. Both McCord Hospital and St. Mary's Hospital operated high-volume outpatient HIV clinics that served a resource-limited population in urban and peri-urban area of Durban. The two municipal health clinics, Tshelimnyama and Mariannridge, are primary health care clinics located within the peri-urban catchment area of St. Mary's Hospital. Throughout the study, all four clinical sites offered free HIV counseling and rapid HIV testing during normal business hours.

We enrolled adults (≥ 18 years) on the same day of their HIV test, regardless of the presence of TB-related symptoms. We excluded people already known to be HIV-infected, women known to be pregnant, and those unwilling to share their HIV test result with our research team. All participants provided written informed consent either in English or Zulu. The ethics committees of McCord Hospital [IRB00005803] and St. Mary's Hospital in Durban, and Partners HealthCare in Boston [Protocol #: 2006-P-001379/40] approved the study. The diagnostic test manufacturer (Alere Inc.) played no role in the study design, data analyses, or interpretation of results from this study.

Data collection

Prior to the start of the study, a representative from Alere Inc. conducted a training session for all study nurses, each of whom had previously received training in the diagnosis, treatment, and care of TB-infected patients. The training session reviewed the detailed procedures and interpretation of the Determine™ TB LAM test (Alere Inc., Waltham, USA). Each study nurse practiced performing and interpreting the urine LAM test with direct supervision from the representative and project managers until they felt comfortable performing and reading the assay. Before enrollment of participants in this study, all study nurses had over 8 months of experience performing the Determine™ TB LAM test and interpreting test results in an outpatient clinical setting.

Upon participant enrollment, study nurses collected demographic details, self-reported history of prior TB care and treatment, and current use of a diuretic medication. Participants were asked to provide an expectorated respiratory sputum sample and a urine specimen, each in a sterile container. Participants unable to provide an expectorated respiratory sputum sample received sputum induction with nebulized 3% hypertonic saline using a portable machine (WH-802, Yuehua Medical Instrument Factory Co.; Guangdong, China). All participants were offered baseline CD4 count testing.

Trained study nurses performed all urine LAM testing and interpretation of test results on fresh urine samples at the point-of-care in a designated clinical room in an outpatient clinic, and in accordance with the manufacturer's specifications. The urine LAM test kits were maintained in a sealed pouch and stored out of direct sunlight at room temperature (15–26°C), which was within the manufacturer's required range. LAM tests used were from Manufacturer Lot Numbers 110512, 120215, and 120222. All urine samples were tested immediately after urine collection and results were interpreted between 25 and 35 minutes. Each nurse conducted two urine LAM tests from the urine specimen provided by each participant. LAM tests that did not have a positive control line were considered 'indeterminate' and were repeated with the same urine sample. Urine specimens were considered positive if bands were visible at both the control and participant test lines. Positive LAM tests were graded from low band intensity (1+) to high band intensity (5+), according to the manufacturer's original reference card with 5 positive categories. Based on nurses' feedback from our previous study, nurses could grade a test as "faint" if a line was visible, but not dark enough to be considered a 1+ grade. Therefore, we had 6 distinct categories for a positive test. Urine LAM test results were not used to guide therapeutic decisions.

Certified technologists performed sputum smear microscopy for AFB and both solid and liquid mycobacterial culture from respiratory samples in a reference laboratory at the University of KwaZulu-Natal. Smear microscopy was performed on decontaminated samples using both Ziehl-Neelson and Auramine stains, and considered positive if either stain revealed AFB. Mycobacterial culture was performed by inoculating Middlebrook 7H11 solid agar medium, and inoculating 0.5 ml in liquid mycobacterial growth indicator tubes (MGIT™) in an automated Bactec™ 960 instrument (BD; Franklin Lakes, USA). Culture plates were read at 3 and 6 weeks, and *M. tuberculosis* was identified from solid or liquid cultures using niacin and nitrate testing. Participants were considered culture-positive with growth from either the solid or liquid culture.

As part of the usual routine care, all participants were evaluated by a non-study clinician and received additional diagnostic evaluations, such as a chest X-ray or abdominal ultrasound, as indicated. The non-study clinician could decide to empirically start a participant on anti-TB therapy with sufficient clinical suspicion, which was generally based on TB-related symptoms and/or radiography. All HIV and TB care and treatment were provided in accordance with South African Department of Health guidelines.²² All participants were followed by routine care and the study team for 9 months to allow ample time for anti-TB therapy initiation resulting from negative microbiological testing but heightened clinical suspicion.

Statistical Analyses

We excluded participants from the analysis who were taking anti-TB therapy at the time of LAM testing, unable to produce a sputum or urine sample, or without a culture result or urine LAM grade. We compared sputum AFB and urine LAM results to "culture-confirmed pulmonary TB", which we defined as positive sputum culture for *M. tuberculosis*, the accepted gold standard test. However, since mycobacterial culture is an imperfect gold

standard test,²³ we also compared sputum AFB and urine LAM results to “culture-confirmed or clinically suspected TB”, which we defined as either culture-confirmed pulmonary TB or having been initiated on anti-TB therapy by a non-study clinician within the 9 month follow-up period.

We used Spearman’s correlation coefficient to compare test results and grades between the 2 urine LAM tests using, Fisher’s exact test to compare categorical variables, and McNemar’s test to compare diagnostic sensitivities. We calculated LAM test sensitivity, specificity, predictive values (positive and negative) for sputum AFB and urine LAM tests, alone and in combination, for diagnosing sputum culture-confirmed pulmonary TB. Since point-of-care CD4 testing could be employed in the future for newly-diagnosed HIV-infected adults in clinics, we calculated diagnostic test characteristics above and below CD4 100/mm³. We evaluated diagnostic characteristics of urine LAM using the secondary outcome, “culture-confirmed or clinically-suspected TB.” We also evaluated various screening strategies using either a single test, a combination of tests, or a sequential strategy for one or two urine LAM test and sputum AFB microscopy using area under receiver operating curves (AUROC). We compared AUROC estimates using the DeLong method,²⁴ and denoted ‘optimal strategies’ to be those with the highest AUROC. We calculated exact 95% confidence intervals (CI) for estimates, reported two-tailed p-values using $\alpha=0.05$, and conducted analyses using SAS version 9.2.

Results

We enrolled 351 newly-diagnosed HIV-infected adults, and excluded 31 due to missing TB culture result, missing a LAM test result, or missing a LAM test grade. Among 320 HIV-infected adults, the mean age was 33 years (standard deviation ± 9 years) and 162 (51%) participants were male (Table 1). Twenty-eight (9%) people reported a previous history of a TB infection, and 90 (28%) people were current smokers. No participants reported using diuretic medications for hypertension. Two hundred eighty-eight (90%) underwent CD4 cell count testing, and among those the median CD4 was 248/mm³ [Interquartile range (IQR) 107–379/mm³]. Overall, fifty-four participants had sputum culture-confirmed pulmonary TB, and an additional 14 people were sputum culture-negative but started on anti-TB therapy due to clinical suspicion. Based on this sample, the estimated sputum culture-confirmed TB prevalence was 17% [95% confidence interval (CI) 13–21%], and the estimated sputum culture-confirmed or clinically-suspected TB prevalence was 21% (95% CI 17–26%). Ten (3%) participants were sputum AFB positive.

Concordance among urine LAM tests

Overall, 52 (16%) participants were urine LAM-positive by either test using a “faint” band as a threshold for positivity; 50 participants by the first LAM test and 48 participants by the second LAM test. The correlation between the two LAM tests was high ($r=0.91$; $p<0.0001$) (Table 2). Almost all discordance occurred among tests with a “faint” positive or 1+ grade result. Among 7 participants with a “faint” positive result with the first LAM test, the second LAM test was negative for 2 participants, “faint” for 2 participants, 1+ for 2 participants,

and 2+ for one participant. When using a grade of 2+, there was near universal agreement on test results and the test grade.

Diagnostic accuracy for culture-confirmed TB

Overall, the first urine LAM test had a diagnostic sensitivity and specificity of 41% (95% CI 28–55%) and 89% (95% CI 85–93%) for detecting culture-confirmed pulmonary TB (Table 3). All 7 “faint” positive results for the first LAM test occurred among TB culture-negative participants. Therefore, when using a LAM grade 1+ threshold, diagnostic specificity of the first LAM test alone improved to 92% (95% CI 88–95%). Using a LAM grade 2+ threshold decreased sensitivity to 28% (95% CI 16–42%), and improved specificity to 94% (95% CI 90–97%). Using greater band intensities for a positive LAM test threshold reduced diagnostic sensitivity, but improved specificity.

The 2 LAM test strategy had a diagnostic test sensitivity of 43% (95% CI 29–57%) and specificity of 89% (95% CI 85–93%). When requiring both LAM test to meet a grade threshold 1+, the test sensitivity decreased marginally to 37% (95% CI 24–51%), but the specificity improved to 92% (95% CI 89–95%). A single LAM test with a 1+ grade identified an additional 26% of participants with culture-confirmed pulmonary TB, as compared to sputum AFB testing alone ($p=0.004$).

Diagnostic characteristics of the urine LAM test, but not sputum AFB, were significantly different for highly immunocompromised adults (Table 4). Among adults with $CD4 < 100$ cells/mm³, one urine LAM test (grade 1+) had a diagnostic sensitivity of 56% (95% CI 35–75%) and specificity of 80% (95% CI 64–91%). The diagnostic sensitivity of urine LAM among adults with $CD4 < 100$ cells/mm³ was 2.3-fold higher than those with a $CD4 \geq 100$ cells/mm³ (24%; 95% CI 9–45%; $p=0.03$).

Diagnostic accuracy for culture-confirmed or clinically-suspected TB

Diagnostic accuracy of urine LAM for participants being either sputum culture-positive or started on anti-TB therapy due to a clinical diagnosis of active pulmonary TB was similar. All of the 14 people started on anti-TB therapy due to clinical suspicion occurred a mean of 21 days (range 5–87 days) from diagnostic testing. Using this expanded TB definition, the first LAM test alone had a slightly higher diagnostic specificity of 90% (95% CI 86–94%). Using a LAM grade 1+ threshold for one urine LAM test, diagnostic sensitivity and specificity were 38% (95% CI 27–51%) and 93% (95% CI 89–96%). As before, greater band intensity for a positive LAM test threshold reduced diagnostic sensitivity and improved specificity. The second LAM test had similar diagnostic performance and no appreciable change in detecting more people with culture-confirmed or clinically-suspected TB. A single LAM test identified an additional 26% of participants with culture-confirmed or clinically-suspected pulmonary TB, as compared to AFB testing alone ($p=0.0005$).

Diagnostic screening strategies in an outpatient clinic

We evaluated various diagnostic screening strategies with sputum AFB and urine LAM testing at initial HIV diagnosis in an outpatient clinic setting (Table 5). Sputum AFB testing alone had an AUROC of 0.57 (95% CI 0.52–0.62). A screening strategy of 1 LAM test with

grade 1+ (AUROC=0.66; 95% CI 0.60–0.73) or a 2-test strategy (AUROC=0.66; 95% CI 0.59–0.73) each significantly increased the AUROC value when compared to AFB screening alone. A dual screening strategy in which both sputum AFB and urine LAM must be positive improved diagnostic specificity to 100% (95% CI 99–100), but decreased sensitivity to 7% (95% CI 2–18%), and lowered the overall AUROC (0.54; 95% CI 0.50–0.57) compared to sputum AFB alone. Using a 2-test strategy, in which either sputum AFB or LAM 1+ grade could be positive, resulted in an AUROC 0.70 (95% CI 0.63–0.77). Sequential test strategies with a higher grade threshold had lower AUROC values but higher specificity, while a sequential test strategy with 2 LAM tests had an AUROC similar to a 1 LAM test strategy (AUROC=0.69; 95% CI 0.62–0.76). The highest AUROC was a sequential screening strategy of first performing 1 urine LAM test, and if the grade was “faint” (<1+) or negative performing sputum AFB smear (AUROC=0.70; 95% CI 0.63–0.77), which had a diagnostic sensitivity of 48% (95% CI 34–62%) and specificity of 91% (95% CI 87–94%).

For clinics implementing point-of-care CD4 count testing at the time of HIV diagnosis, screening with sputum AFB smear alone had an AUROC of 0.57 (95% CI 0.51–0.64) among participants with CD4 <100/mm³. A sequential strategy of sputum AFB if LAM grade <1+ (AUROC=0.70; 95% CI 0.58–0.81) increased the AUROC value when compared to sputum AFB screening alone (p=0.036).

Discussion

In this clinic-based study of TB screening among newly-diagnosed HIV-infected adults, trained nurses were able to successfully perform and interpret the rapid urine LAM test at the clinical point-of-care. Overall, a darker band intensity of the urine LAM test had improved specificity for diagnosing culture-confirmed pulmonary TB. A “faint” test line was generally a false-positive result, but this may prompt a clinician to consider additional testing. While it is unreasonable to expect patients to provide two distinct urine samples during one visit, performing two urine LAM tests on the same specimen had a high degree of correlation and the second urine LAM test had no additional diagnostic value. In this cohort, a single urine LAM test had improved sensitivity and area under the receiver operator curve compared to sputum AFB, and the optimal screening strategy was one urine LAM test followed by sputum AFB microscopy for people urine LAM-negative (grade <1+).

The diagnostic accuracy of the urine LAM testing performed by nurses in our outpatient clinics was similar to previous studies. We previously reported an overall diagnostic sensitivity of 28% using a grade 1+ threshold,²¹ and a laboratory-based study on thawed (not fresh) urine samples also reported test sensitivity of 28% for detecting HIV-associated pulmonary TB among adults in Cape Town.²⁵ Studies conducted among HIV-infected adults presenting with multiple TB-related symptoms have reported higher diagnostic sensitivity.^{18–20,26,27} In several other studies, including two of our own studies, diagnostic specificity of the urine LAM tests grade 1+ threshold has been approximately 85–92%.^{20,21,26,27} One Cape Town study reported a higher diagnostic specificity (98%), which may be related to collecting multiple sputa samples from most (95%) participants.²⁵ We also

found higher sensitivity among people with a CD4 <100 cells/mm³, as has been reported.²⁵ However, this was associated with a lower diagnostic specificity (or greater false positive rate). Our study builds upon previous studies by evaluating urine LAM testing as performed by nurses in an outpatient clinical setting, and determining the value of the test band intensity for determining the urine LAM grade and the utility of conducting a second urine LAM test. Our data also support an expert panel's decision to use 2+ as a diagnostic threshold, and this approach when combined with sputum AFB if LAM-negative was better than sputum AFB testing alone.²⁸

Using results generated from nurses performing TB screening in real-world outpatient clinics, we compared various screening strategies. Compared to sputum AFB smear, the urine LAM test identified more people with culture-confirmed pulmonary TB, but also had more false positive results. Using a stronger band intensity for a positive urine LAM test improved test specificity, but decreased test sensitivity. In a retrospective study, combining urine LAM and sputum AFB testing increased sensitivity to 44%, which was similar to our results, while having minimal impact on specificity.²⁵ Others have reported urine LAM testing to complement sputum AFB testing among symptomatic patients.^{29,30} Given that the implementation of clinic-based urine LAM testing is likely easier and less expensive than clinic-based sputum AFB testing, we evaluated a sequential screening in which the urine LAM test would be performed first. Then, the optimal screening strategy was either a single urine LAM test or one urine LAM test followed by sputum AFB for a negative (grade <1+) LAM test. These diagnostic strategies detected 41% and 48% of culture-confirmed pulmonary TB cases, respectively, but unlike previous studies we found a 7–8% decrease in diagnostic specificity.

Urine LAM may be a useful pathogen biomarker for an active HIV-associated TB infection. The increased specificity with a darker band intensity of the urine LAM test suggests higher band intensities may be associated with a greater bacillary load of TB. We have previously shown LAM decreases among patients receiving anti-TB therapy.²⁷ Therefore, while the test specificity of urine LAM was lower than sputum AFB, which may lead to overtreatment of active TB, this may have been related to incomplete detection of active TB infections. Perhaps a more comprehensive assessment for an active pulmonary or extrapulmonary TB infection would have resulted in higher urine LAM test specificity (or lower false positive rate). However, urine LAM screening identified significantly more people with active TB, has a far lower occupational risk to health workers, and may be easier and cheaper to implement than sputum AFB microscopy. Since a primary problem in TB-endemic settings has been identifying TB-infected people,¹² perhaps a small percentage of calculated overtreatment due to false positive LAM screening may be acceptable for larger gains in rapidly identifying TB-infected people.

Our study has several strengths and limitations. A primary strengths of this study were evaluating trained nurses performing urine LAM testing in an outpatient clinic and testing patients regardless of symptoms, which best approximate a real-world application of this test as a diagnostic screening tool. While evaluation of the test at the clinical point-of-care was deliberate, having nurses to interpret test results in a non-laboratory setting may produce inaccuracies. Limitations included not measuring the bacillary burden of TB, not conducting

mycobacterial blood cultures, not having comprehensive information about extrapulmonary TB, and obtaining one sputum sample for mycobacterial culture, all of which may have missed patients with active TB. A more comprehensive evaluation for extrapulmonary TB may have revealed more TB cases among LAM-positive patients, thereby increasing diagnostic specificity. Use of diuretics may affect the urine LAM test performance, but too few people were taking diuretic medications to assess this relationship. We did not obtain a CD4 count on all participants, and the sample size was low to draw conclusions about using a CD4 count threshold to guide urine LAM screening. We also evaluated the rapid LAM testing as an outpatient screening test among HIV-infected adults in a TB-endemic region, so these results may not be generalizable to other populations.

In conclusion, rapid urine LAM testing can be readily performed by nurses in an outpatient clinical setting and may be most beneficial in settings with limited capacity for sputum culture or when a timely diagnosis of TB is paramount. However, since the optimal clinic-based screening strategy identified only one-half of cases, additional more sensitive laboratory-based diagnostic methods should continue to be utilized. Since urine LAM tests were relatively inexpensive (~US \$3.05/test in this study), operational studies might be helpful to measure the clinical impact, including accelerated time to treatment and reduced risk for occupational transmission, when implementing clinic-based urine LAM screening at initial HIV diagnosis.²⁸ In the absence of a highly accurate clinic-based test for HIV-associated TB, rapid urine LAM testing offers a simple, inexpensive option that improves upon sputum AFB smear for outpatient clinics in TB-endemic, resource-limited settings.

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Table 1

Cohort characteristics of newly-diagnosed HIV-infected adults (N=320).

	Mean $\pm$ SD or N (%)
Demographics	
Age (years) (N=316)	33.1 $\pm$ 9.4
Male gender	162 (50.6)
Tuberculosis History	
Prior TB infection	28 (8.9)
Currently Smoke	90 (28.1)
Current Diuretic Use	
Yes	0 (0)
No	313 (97.8)
Don't know or missing	7 (2.2)
CD4 Cell Count (median/IQR)/mm ³ (N=288)	248 [107, 379]
350 cells/mm ³	91 (31.6)
200–349 cells/mm ³	83 (28.8)
100–199 cells/mm ³	47 (16.3)
<100 cells/mm ³	67 (23.3)
Sputum AFB Smear Testing	
Sputum AFB smear positive	10 (3.1)
Tuberculosis Outcomes	
Culture-confirmed pulmonary TB positive	54 (16.9)
Culture-confirmed pulmonary TB or started on therapy due to clinical suspicion	68 (21.3)
Urine LAM Testing	
LAM test #1 positive	50 (15.6)
LAM test #2 positive	48 (15.0)
Either urine LAM test was positive	52 (16.3)
Both urine LAM tests were positive	46 (14.4)

AFB=acid-fast bacilli; IQR=interquartile range; LAM=lipoarabinomannan; SD=standard deviation; TB=tuberculosis.

Table 2

Correlation between two urine LAM test results by test grade (N=320).

Urine LAM Test #2								
Urine LAM Test #1	Negative	"faint"	1+	2+	3+	4+	5+	Total
Negative	268	2	--	--	--	--	--	270
"faint"	2	2	2	1	--	--	--	7
1+	2	1	9	--	--	--	--	12
2+	--	--	--	12	--	--	--	12
3+	--	--	--	--	6	--	--	6
4+	--	--	--	--	--	6	--	6
5+	--	--	--	--	--	--	7	7
Total	272	5	11	13	6	6	7	320

Table 3

Diagnostic accuracy of sputum AFB smear and urine LAM for diagnosing culture-confirmed pulmonary tuberculosis (N=320).

	Sensitivity		Specificity		Positive PV		Negative PV	
	Positive/ Total	% (95% CI)	Negative/ Total	% (95% CI)	% (95% CI)		% (95% CI)	
Sputum AFB Smear	8/54	15 (7-27)	264/266	99 (97-100)	80 (44-97)		85 (81-89)	
Urine LAM – Test #1								
”faint”	22/54	41 (28-55)	238/266	89 (85-93)	44 (30-59)		88 (84-92)	
1 +	22/54	41 (28-55)	245/266	92 (88-95)	51 (35-67)		88 (84-92)	
2+	15/54	28 (16-42)	250/266	94 (90-97)	48 (30-67)		87 (82-90)	
3+	10/54	19 (9-31)	257/266	97 (94-98)	53 (29-76)		85 (81-89)	
4+	8/54	15 (7-27)	261/266	98 (96-99)	62 (32-86)		85 (81-89)	
5+	3/54	6 (1-15)	262/266	99 (96-100)	43 (10-82)		84 (79-88)	
Urine LAM – Test #2								
”faint”	22/54	41 (28-55)	240/266	90 (86-94)	46 (31-61)		88 (84-92)	
1 +	20/54	37 (24-51)	243/266	91 (87-94)	47 (31-62)		88 (83-91)	
2+	15/54	28 (16-42)	249/266	94 (90-96)	47 (29-65)		86 (82-90)	
3+	10/54	19 (9-31)	257/266	97 (94-98)	53 (29-76)		85 (81-89)	
4+	8/54	15 (7-27)	261/266	98 (96-99)	62 (32-86)		85 (81-89)	
5+	3/54	6 (1-15)	262/266	99 (96-100)	43 (10-82)		84 (79-88)	
Both urine LAM tests								
Either test positive (”faint”)	23/54	43 (29-57)	237/266	89 (85-93)	44 (30-59)		88 (84-92)	
Either test 1 +	22/54	41 (28-55)	242/266	91 (87-94)	48 (33-63)		88 (84-92)	
Both tests 1 +	20/54	37 (24-51)	246/266	92 (89-95)	50 (34-66)		88 (83-91)	
Either test 2 +	15/54	28 (16-42)	249/266	94 (90-96)	47 (29-65)		86 (82-90)	
Both tests 2 +	15/54	28 (16-42)	250/266	94 (90-97)	48 (30-67)		87 (82-90)	

AFB=acid-fast bacilli; CI=confidence interval; LAM=lipoarabinomannan; PV=predictive value.

Diagnostic accuracy of sputum AFB smear and urine LAM for diagnosing culture-confirmed pulmonary tuberculosis by CD4 count (N=288).

Table 4

	Sensitivity		Specificity		Positive PV		Negative PV	
	Positive/ Total	% (95% CI)	Negative/ Total	% (95% CI)	% (95% CI)		% (95% CI)	
Sputum AFB Smear								
100 cells/mm ³	4/25	16 (5–36)	194/196	99 (96–100)	67 (22–96)		90 (85–94)	
<100 cells/mm ³	4/27	15 (4–34)	40/40	100 (91–100)	100 (40–100)		63 (50–75)	
Urine LAM – Test #1 1+ grade								
100 cells/mm ³	6/25	24 (9–45)	186/196	95 (91–98)	38 (15–65)		91 (86–94)	
<100 cells/mm ³	15/27	56 (35–75)	32/40	80 (64–91)	65 (43–84)		73 (57–85)	
Urine LAM – Test #1 2+ grade								
100 cells/mm ³	4/25	16 (5–36)	190/196	97 (94–99)	40 (12–74)		90 (85–94)	
<100 cells/mm ³	10/27	37 (19–58)	32/40	80 (64–91)	56 (31–78)		65 (50–78)	

AFB=acid-fast bacilli; CI=confidence interval; LAM=lipoarabinomannan; PV=predictive value.

Table 5

Screening strategies for sputum AFB and urine LAM for diagnosing culture-confirmed pulmonary tuberculosis (N=320).

	AUROC (95% CI)	p-value vs. Sputum AFB smear	Sensitivity Positive/ Total	% (95% CI)	Specificity Negative/ Total	% (95% CI)
Single Test Strategies						
Sputum AFB smear	0.57 (0.52–0.62)	--	8/54	15 (7–27)	264/266	99 (97–100)
1 Urine LAM Test with 1+ grade	0.66 (0.60–0.73)	0.022	22/54	41 (28–55)	245/266	92 (88–95)
1 Urine LAM Test with 2+ grade	0.61 (0.55–0.67)	0.284	15/54	28 (16–42)	250/266	94 (90–97)
2 Urine LAM Tests	0.66 (0.59–0.73)	0.035	23/54	43 (29–57)	237/266	89 (85–93)
Two Test Strategies - Both Positive						
Sputum AFB and 1 LAM Test with 1+ grade	0.54 (0.50–0.57)	0.067	4/54	7 (2–18)	266/266	100 (99–100)
Sputum AFB and 1 LAM Test with 2+ grade	0.54 (0.50–0.57)	0.067	4/54	7 (2–18)	266/266	100 (99–100)
Sequential Two Test Strategies – One Positive						
Urine LAM first, if grade <1+ then AFB smear	0.70 (0.63–0.77)	<0.001	26/54	48 (34–62)	243/266	91 (87–94)
Urine LAM first, if grade <2+ then AFB smear	0.64 (0.58–0.71)	0.012	19/54	35 (23–49)	248/266	93 (90–96)
Urine LAM first, if grade <3+ then AFB smear	0.63 (0.56–0.69)	0.022	16/54	30 (18–44)	255/266	96 (93–98)
2 Urine LAM tests, if both grade <1+ then AFB smear	0.69 (0.62–0.76)	<0.001	27/54	50 (36–64)	235/266	88 (84–92)
Test Strategies among CD4 <100/mm³						
Sputum AFB smear	0.57 (0.51–0.64)	--	4/27	15 (4–34)	40/40	100 (91–100)
1 Urine LAM Test with 1+ grade	0.68 (0.56–0.79)	0.104	15/27	56 (35–75)	32/40	80 (64–91)
Urine LAM first, if grade <1+ then AFB smear	0.70 (0.58–0.81)	0.036	16/27	59 (39–78)	32/40	80 (64–91)
Urine LAM first, if grade <2+ then AFB smear	0.60 (0.49–0.72)	0.580	11/27	41 (22–61)	32/40	80 (64–91)
2 Urine LAM tests, if both grade <1+ then AFB smear	0.67 (0.56–0.79)	0.104	16/27	59 (39–78)	30/40	75 (59–87)

AFB=acid-fast bacilli; AUROC=area under receiver operating curve; CI=confidence interval; LAM=lipoarabinomannan.