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Specificity and Sensitivity of Lipoarabinomannan (LAM) Determine Strip Test Using Urine from HIV Patients with Signs of Tuberculosis in Western Kenya

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Abstract: Tuberculosis continues to be a major problem especially in Sub-Saharan Africa where the spread is enhanced by HIV infection. TB/HIV co-infection has a high morbidity and mortality, therefore a quick TB diagnosis for early initiation of therapy is necessary. The application of Determine TB LAM strip test for non-sputum clinical samples in the diagnosis of suspected tuberculosis in Western Kenya population has not been evaluated. We are reporting on the use of urinary LAM test for presumptive TB patients who are -HIV-1 infected in MTRH, Kenya. This was a cross-sectional analyses of morning urine samples from 140 suspected HIV-1/TB co-infected adults who are not on medication with CD4+ count <250 cells/mm³ for the presence of Mycobacterium tuberculosis (MTB) LAM in urine. One hundred and forty patients were recruited; 37 (27.8%) tested positive for tuberculosis based on LAM test. Diagnostic accuracy was based on urine culture and sputum microscopy which was included for comparison. The sensitivity of LAM test against Sputum Microscopy was 36.4%, with a PPV of 22.0% while the specificity of LAM test was 73.9%, with a NPV of 85.0%. Sensitivity increased to 60% for those with CD4≤100 cells/mm³ whereas the specificity slightly increased to 76.4% for those with CD4>100cells/mm³. The comparison of LAM test against urine culture for TB were similar and it increased the sensitivity and specificity to 100% and 80.7% respectively. Stratified by CD4 categories, LAM test against urine TB culture increased the sensitivity to 100% and specificity to 85.5% for HIV-infected persons with CD4 >100cells/mm³. This study showed that urinary LAM can be used as an adjunct test for diagnosis of active TB and in combination with other tests in the diagnosis platform.

Keywords: Urine, mycobacterium, lipoarabinomannan, Sensitivity, Specificity, Kenya.

INTRODUCTION

Tuberculosis (TB) is an infective disease that is caused by diverse types of the genus *Mycobacteria* which is also known of the Koch's bacilli, which has the ability to affect any organ or tissue in the body. Tuberculosis is one of the biggest killers in the World when combined with human immunodeficiency virus infection (HIV)/Acquired Immunodeficiency Syndrome (AIDS) [1].

Early death due to tuberculosis (TB) and HIV co-infection and the reduced performance of microscopy has led health care workers to use presumptive treatment as a diagnostic method for tuberculosis leading to over-prescription and administration of anti-TB drugs, overburdened

treatment programs, and missed opportunity to detect other co-morbidities in HIV infected patients [2,3]. Better tests are needed that are more sensitive, faster to yield results and simpler to use. To improve the detection accuracy of active TB among symptomatic individuals and reduce the period between onset of symptoms and initiation of therapy, compared to sputum, urine as a biological sample for diagnostic testing of MTB is appealing, easy to collect, readily available and has a low infection risk to staff during collection. Detection of antigens of many infectious agents in urine has been widely employed and TB diagnosis is no exception. A number of *M. tuberculosis* antigens have been evaluated in urine for the TB diagnosis. Of the 12 TB antigens that have been

evaluated, lipoarabinomannan (LAM) is the most extensively evaluated and promising [4].

In Kenya, From the TB Epidemiological and Impact Analysis Report of 2014, various trends were noted. Analysis of the trends in estimates of TB incidence suggests a consistent decline in new TB cases over time. The decline in TB cases started in 2005 following the decline in TB/HIV cases, which started in 2004. Furthermore, after a peak in 2006, the TB prevalence declined and thereafter plateaued from 2009. TB mortality estimates suggest an increase in TB deaths in 2011-2012. However, the wide confidence intervals indicate considerable uncertainty in the estimates, suggesting the need for other more direct methods to measure prevalence and mortality.

The search for a rapid TB diagnostic tool for the detection of *M. tuberculosis* has been explored over years and is still going on. It is important to consider the biology of *M. tuberculosis* since the cell wall of *M. tuberculosis* is highly impermeable and plays a protective role in establishing infection; hence will be able to deal with this disturbing and difficult to treat disease. LAM is a glycolipid that forms one of the main components of the outer cell wall of mycobacterial species, and is a heterogeneous immune-reactive glycol conjugate. It is heat-stable 17.5kD and accounts for up to 15% of the total bacterial weight. LAM is an important virulence factor of *M. tuberculosis* [5-7]. LAM consists of three distinct structural domains, including a phosphatidylinositol (PI) anchor, a branched mannan, and a branched arabinan [8].

The different types of LAM capping determine the ability of LAM to modulate immune responses; Man LAM is the commonest form in *M. tuberculosis* and is a very potent anti-inflammatory molecule and virulence factor [9]. The mannose caps, as recently discovered, may be involved not only in attenuating host immune response, but also in mediating the binding of mycobacteria and subsequent entry into macrophages [10]. This includes the modulation of several of host immune responses including: cytotoxic oxygen free-radical scavenging; inhibition protein kinase C activity and; prevent interferon gamma transcription in macrophages and T-cells. The inhibition of macrophage activation, abrogation of T-cell activation and blockage of the cytotoxic activities contributes immensely to the persistence of *M. tuberculosis* within the mononuclear phagocytes and their dissemination to other parts of the body. This shows that Man LAM also possesses much less potency in evoking TNF-alpha and other responses and is an immunogenic virulence factor of much clinical and diagnostic significance [11, 12]. LAM can be detected in the urine of patients with active TB. LAM circulates in the bloodstream and passes through the renal filtration barrier without major changes and is thus detectable in an antigenically intact form in urine [13].

Diagnosis of TB using urine could be useful in patients who cannot produce sputum.

METHODOLOGY

Study design: This was a cross-sectional study.

Study Site

The study was carried out at MTRH clinics at Eldoret, Kenya (catchments population – 16 million; HIV prevalence – 7%). MTRH is the 2nd National Hospital in Kenya and serves as a referral center for the western Kenya region. It also serves as a teaching hospital for Moi University College of Health Sciences. The hospital has a bed capacity of 720.

Study population

The study was carried consecutively on participants who are MTRH patients; HIV-infected who are who are suspected of having tuberculosis between 2012 - 2014.

INCLUSION CRITERIA

Subjects who fulfilled the following criteria were included in the study: (1) HIV positive patients; (2) CD4⁺ less than 200 cells/mm³; (3) age >18 years ; (4) the next of kin signed the study informed consent form; (5) The participant's adult clinical summary was present; (6) Untreated TB suspect and ; (7) Both smear positive and smear negative TB patients.

EXCLUSION CRITERIA

Subjects who did not fulfilled the following criteria were excluded in the study: (1) Treated TB cases more than 90 days ; (2) not HIV-infected; (3) not enrolled in any MTRH clinic; (4) age <18 years ; (5) absence of the next of kin signed informed consent form and; (6) The participant's MTRH adult clinical summary was missing.

Human subjects' protection

The Moi University School of Medicine (MUSoM)/Moi Teaching and Referral Hospital (MTRH) Institutional Review and Ethics Committee (IREC) and the Indiana University School of Medicine (IUSOM) Institutional Review Board (IRB) approved the study.

Study Procedures

Morning urine samples were collected from HIV infected patients suspected of TB infection during their first visit to MTRH TB clinic. Samples were analyzed for the presence of Mycobacterium tuberculosis DNA. Other laboratory assays included Acid-fast staining and culture of urine. Clinical symptoms and radiological findings were also evaluated. Host factors (age, gender, and patient category, site of TB, HIV status, and CD4+ count) were obtained.

Sample collection and handling

Sputum samples were collected from patients who were able to expectorate. In case EPTB was suspected, the collection of 1–2 non-sputum samples from clinically involved sites (e.g. urine) was also obtained. Further details of biological samples were collected for TB culture as provided. Smear microscopy was performed on processed sputum, which was also cultured using the MGIT 960 liquid culture system (BD Diagnostics, USA). The reference standard for definite-TB was liquid culture positivity for *M. tuberculosis*.

Urine sampling and LAM methodology

All study patients were required to give 10–30 ml mid-stream urine in a fresh standard, sterile container after recruitment. Prior to urine collection, patients were asked to clean the urogenital area with a clean wipe. Alere Determine™ TB LAM Ag was performed on thawed urine. All thawed samples were centrifuged at 10,000g for 5 minutes at room temperature and the 60uL test sample was carefully collected from the supernatant. Fresh urine sample was used if the sample was kept within 8 hours at room temperature. If the test sample was to be run within 3 days of collection, urine sample was stored at 2–8°C and if the testing was delayed for more than 3 days, urine was frozen and stored at –20°C for later batch testing.

Acid fast-staining/microscopy

Direct smear microscopy also known as Acid-fast microscopy is still the basis of TB diagnosis in the majority of high burden settings and in mycobacteriology. The acid-fast stain is a differential stain used to identify acid-fast organisms such as members of the genus *Mycobacterium*. Acid-fast organisms are characterized by wax-like, nearly impermeable cell walls; they contain mycolic acid and large amounts of fatty acids, waxes, and complex lipids. A typical AFB stain procedure involves dropping the cells in suspension onto a slide, then air-drying the liquid and heat fixing the cells. The slide is flooded with Carbol Fuchsin, which is then heated to dry and rinsed off in tap water. The slide is then flooded with a 1% solution of hydrochloric acid in isopropyl alcohol (or methanol) to remove the Carbol Fuchsin, thus removing the stain from cells that are unprotected by a waxy lipid layer. Thereafter, the cells are stained in methylene blue and viewed on a microscope under oil immersion.

Urine culture

A urine culture is a test to find and identify germs (usually bacteria) that may be causing a urinary tract infection (UTI). Urine in the bladder normally is sterile-it does not contain any bacteria or other organisms (such as fungi). But bacteria can enter the urethra and cause an infection. Urine culture is the gold standard for establishing the diagnosis for renal tuberculosis. Morning midstream urine specimens was sent to the laboratory for culture so as to maximize the

likelihood of a positive result; false negative results may occur if the patient is receiving anti-tuberculous therapy or broad spectrum antibiotics hence the study did not recruit patients on treatment which may inhibit mycobacterial growth because of the high urinary concentrations obtained. Bacilli are shed into the urine intermittently; as a result, only 30 to 40 percent of single specimens are positive in patients with active disease. The laboratory utilizes the Bactec MGIT 960 TB System for detection of AFB in urine specimens, and performance of susceptibility testing. Identification of *M. tuberculosis* from culture is as soon as possible, but within 14-21 days from specimen receipt while susceptibility results for *M. tuberculosis* are obtained as soon as possible, but within 15-30 days of specimen receipt. The Bactec MGIT 960 TB monitors growth. Patients sample that did not show any evidence of bacterial growth between days 1 to day 42 of incubation period were termed as negative according to the working protocol.

Statistical Analysis

The primary outcome is Tuberculosis (TB) positivity based on Determine TB LAM strips. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were used to assess the validity of LAM Determine strip test against Sputum Microscopy in identifying TB cases among HIV-infected persons. The likelihood ratios combine sensitivity and specificity into a single figure that indicates by how much the test result will reduce the uncertainty of a given diagnosis (AFC Primer). Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Between 2012-2014, 140 HIV infected participants, 72 (54.5%) females, were enrolled. The mean and standard deviation, mean (SD), for age was 39.4 (SD: 9.3) and 37.7(SD: 8.5) among those who tested positive and negative for Tuberculosis using LAM Determine strip test, respectively. The median age was similar for those with lower CD4 cells (≤ 100) compared to those with CD4 >100 [38.3 (SD: 8.1) vs 39.2 (SD: 9.6)]. Among the female, 15% were positive based on LAM determine strip test with a majority (71%) having CD4 >100 cells/mm. Among patients who were in WHO stage III & IV about a sixth had CD4 >100 cells/mm³. These results are summarized in Table 1.

Of the 140 patients; 37 (27.8 %), 22 (16.5 %), 14 (10.5 %) were identified as positive for tuberculosis based on, LAM determine strip test, Sputum Microscopy and Urine Culture respectively (Table 2).

The sensitivity of LAM Determine strip test against Sputum Microscopy was 36.4%, with a positive predictive value of 21.6%. On the other hand, the

specificity of LAM Determine strip test against Sputum Microscopy was 73.9%, with a negative predictive value of 85.4%. This implies that, LAM Determine strip test has a probability of 0.36 to positively diagnose a person who has TB and a likelihood ratio of 0.86 to correctly identify those who do not have TB. Putting CD4 stratification into consideration, sensitivity increased to 60.0% for those with CD4 \leq 100 cells/mm³ whereas the specificity slightly increased to 76.4% for those with CD4 $>$ 100cells/mm³. The comparison of LAM Determine strip test against urine culture was similar and it increased the sensitivity and specificity to 100% and 80.7% respectively. When stratified by CD4 categories, the comparison of LAM Determine strip test against urine culture increased the sensitivity to 100% but only increased specificity to 85.5% for persons with CD4 $>$ 100cells/mm³.

The negative and positive likelihood ratios for LAM determine strip test against Sputum Microscopy were 0.86 and 1.39 respectively. The positive likelihood ratio implies that a person with TB is 1.39 times more likely to have a positive result based on LAM determine strip test than a person without TB. Conversely, the negative likelihood ratio shows that a person without TB is 0.8 times more likely to have a negative test based on LAM determine strip test compared with a person with TB. When stratified by CD4 categories, the negative and positive likelihood ratios for LAM determine strip test against Sputum Microscopy were 0.56 and 1.95 respectively for CD4 \leq 100 cells/mm³ and 1.09 and 0.71 respectively for CD4 $>$ 100cells/mm³. These results are shown in Table 3.

Table-1: Demographic and clinical characteristics among HIV-infected patients in MTRH, 2011-2013

Characteristics	LAM strip test		CD4 count, cell/mm ³	
	Positive	Negative	\leq 100 cell/mm ³	$>$ 100 cell/mm ³
Gender (Female)	19 (51.4)	53 (55.8)	24 (33.3)	48 (66.7)
Age (years), Mean (SD)	39.4 (9.3)	37.7 (8.5)	38.3 (8.1)	39.2 (9.6)
WHO stage				
Stage I & II	6 (26.1)	17 (73.9)	4 (17.4)	19 (82.6)
Stage III & IV	28 (31.1)	62 (68.9)	39 (43.3)	51 (56.7)

Table-2: Urine LAM strip test results versus Sputum Microscopy from HIV patients with signs of Tuberculosis MTRH in Western Kenya

Characteristics	Sputum microscopy		Urine culture		Total
	Positive	Negative	Positive	Negative	
LAM strip test					
Positive	8 (36.4)	29 (26.1)	14 (100.0)	23 (19.3)	37 (27.8%)
Negative	14 (63.6)	82 (73.9)	0 (0.0)	96 (80.7)	96 (72.2%)
Total	22 (16.5%)	111 (83.5%)	14 (10.5%)	119 (89.5%)	

Table-3: Sensitivity and specificity of LAM strip test using urine from HIV infected patients with signs of tuberculosis MTRH in Western Kenya

Indicator	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Likelihood Ratio*	
					Negative	Positive
LAM strip test vs Sputum microscopy						
Overall	36.4	73.9	21.6	85.4	0.86	1.39
CD4 \leq 100	60.0	69.2	33.3	87.1	0.58	1.95
CD4 $>$ 100	16.7	76.4	10.5	84.6	1.09	0.71
LAM strip test vs Urine culture						
Overall	100.0	80.7	37.8	100.0	0.00	5.17
CD4 \leq 100	100.0	72.1	33.3	100.0	0.00	3.58
CD4 $>$ 100	100.0	85.5	42.1	100.0	0.00	6.91

* The negative likelihood ratio is calculated as (1-sensitivity) \div specificity, and the positive likelihood ratio as sensitivity \div (1-specificity).¹

DISCUSSION

The aim of this study was to determine the sensitivity and specificity of Determine TB LAM strip test in HIV infected patients suspected of having tuberculosis and determine its applicability in this

setting. The study found that urine LAM is a sensitive tool in detecting tuberculosis in urine. The sensitivity of urinary LAM increases as the immunity decreases. These findings are in agreement with previous study which has revealed improved sensitivity with an

increase in immunosuppression [14]. Lawn had done work on pathogen and host factor potentially impacting the detection of LAM in urine while Shah [13] reported on HIV-infection, mycobacteremia, and positive sputum smear were risk factors for a positive LAM test. This is a group in which sputum microscopy is of low yield hence this group with advanced immunosuppression may be a target population for whom the urine LAM test would be particularly useful as they found that among HIV-infected patients, individuals with CD4 counts of <50 had an average OD that was 1.05 OD units higher than that for individuals with CD4 counts of >150 ($P < 0.0001$). This implies that urinary LAM is associated to host immune factors [15].

This study also revealed that the sensitivity of urine LAM strip determine is not accurate when used alone for identifying TB positive persons but improves combined with other diagnostic methods in the diagnostic platform. Our findings are in agreement with those findings described in a systematic review of seven studies that evaluated test precision using only microbiologically confirmed cases sensitivity was 13%–93% and specificity 87–99%. Also Dheda *et al* disclosed in his study that the diagnostic practicality of urine-LAM is partial, as a rule-in test, to a particular patient subgroup [16]. Also Boehme and colleagues indicated that using an earlier version of the present urine LAM assay (Chemogen, South Portland, Maine) to evaluate 231 TB suspects (69% HIV-positive) and 103 healthy controls in Tanzania also maintained that the role of urine LAM in the diagnosis of tuberculosis as they found among 69 cases of sputum or blood culture confirmed tuberculosis, LAM sensitivity was 65% and specificity 86% compared to 36% and 98% for the sputum smear [17].

Dissimilarities seen in the test features might possibly be as a result of diverse LAM testing approaches. Urine collection and processing may influence the test precision, although analysis of subgroups in which the urine used in the assay was either fresh or previously frozen found no statistically significant differences between these groups. In our study, most assays were conducted on frozen samples hence we were not able to compare.

In our study the combination of sputum smear plus LAM testing identified 88.2% of confirmed TB cases. Shah *et al.* in their work reported that 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 and the combination of urine LAM testing and sputum smear microscopy identified 75% of confirmed TB cases.

Presence of LAM in urine suggests that renal tuberculosis may arise more frequently in progressive HIV infection especially in patients with disseminated

tuberculosis. However other studies have demonstrated that LAM can also be detected in patients with disseminated tuberculosis without renal association. This indicates that there are other mechanisms that contribute to the presence of LAM in urine. A study done in Ugandan HIV patients demonstrated urinary LAM-antigen testing to renal histology in an autopsy cohort of hospitalized patients [18]. There is need to understand more on the mechanisms involved so as to give a better insight to this issue since it is not yet known if LAM is as a result of live replication or if LAM is from dying mycobacteria.

Limitations

Some of the limitations of this study are that LAM strip test results were not used to make medical conclusions hence clinical significance could not be determined. Additional samples may be required since LAM strip test does not have information on the susceptibility test. For the LAM strip test evaluation, our study did not use fresh urine samples but instead used frozen urine sample which may possibly have obstructed the performance of the test. LAM strip test was restricted to patients with HIV infection with progressive immunosuppression and who are suspected of having tuberculosis. However the data is very important since it depicts the usefulness of the test in our setting and its potentiality in improving the diagnosis of TB using urine samples.

CONCLUSION

In conclusion, there is need for a new diagnostic tool, which has a high sensitivity. Although the sensitivity of LAM determine strip test is not outstanding, it may be important in settings with poor resources where the necessity for better diagnosis is unlimited. LAM Determine strip test was related to severe immunosuppression hence a capable diagnostic tool in HIV positive patients with low CD4 counts. Presence of LAM in urine suggests that renal tuberculosis may arise more frequently in progressive HIV infection.

RECOMMENDATION

There is need to conduct research using larger quantities of urine so as to increase sampling probabilities.

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Authors Contributions

This work was carried out in collaboration between all authors. Author IMA designed the study, wrote the protocol and interpreted the data. Authors IMA, FFS and KKA anchored the field study, gathered the initial data and performed preliminary data analysis.

Authors IMA, CMK, AMS and OAO managed the literature searches and produced the initial draft. All authors read and approved the final manuscript.

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