Systematic Review

A Systematic Review of Utility of Urine Lipoarabinomannan in Detecting Tuberculosis among HIV-Positive Tuberculosis Suspects

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ABSTRACT

Sputum smear microscopy (SSM), though regarded as an inexpensive and popular method for detecting tuberculosis (TB), lacks adequate sensitivity, specifically in adult people living with HIV/AIDS (PLHIV). Urine lipoarabinomannan (LAM) is a promising diagnostic tool among PLHIV with CD4 cell count < 200 cells/μl. We attempted to review all the studies undertaken in identifying the utility of urine LAM in diagnosing TB, especially among PLHIV. We searched PubMed, Google Scholar, and MEDLINE databases for studies reporting diagnostic utility of urine LAM status in PLHIV, published in the last 20 years till December 2019. The keywords used for searching were "Tuberculosis," "HIV/AIDS," "Diagnosis," "Screening" "Lipoarabinomannan," and "Urine." Our search resulted in 137 shortlisted citations, of which 67 related manuscripts were identified for detailed study. Based on inclusion and exclusion criteria, 37 studies were reviewed in detail. Average sample size of these studies was 464 (range = 81–2528; SD = 427). Crude average sensitivity of urine LAM in culture-confirmed TB cases was 44.1% (range = 8.3–93) while that of SSM was 38.6% (range = 14–65). However, sensitivity of urine LAM + SSM was 60.4% (range = 38.3–92.7), demonstrating the utility of SSM + urine LAM combination for detecting TB. Specificity was similar between urine LAM and SSM with 92.7% (range = 76–100) and 97.9% (range = 93.9–100), respectively. Majority of the studies demonstrated higher sensitivity of urine LAM in those with lesser the CD4 count, with immunocompromised and with debilitation who cannot produce self-expectorated sputum. We conclude that urine LAM is a potential diagnostic test in the algorithms involving immunocompromised, debilitated patients and specifically in PLHIV whose CD4 count is ≤100 cells/μl.

KEY WORDS: Tuberculosis, HIV/AIDS, diagnosis, screening, lipoarabinomannan, and urine

INTRODUCTION

Even today, tuberculosis (TB) is one of the key public health challenges worldwide. According to the World Health Organization (WHO), globally, an estimated 10.0 (range, 9.0–11.1) million people developed TB in 2018. There were an estimated 1.2 (1.1–1.3) million

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TB deaths among HIV-negative people in 2018 and an additional 251,000 deaths (223,000–281,000) among people living with HIV/AIDS (PLHIV).[1] TB is considered as the most common and serious opportunistic infection in PLHIV and is the manifestation of AIDS in more than 50% of cases in developing countries.[2-4] On the other hand, diagnosis of incidental HIV has been on rise among the presumptive TB patients who walk-in for the diagnosis of TB as it is one of the most common opportunistic infections among PLHIV. TB shortens the survival of PLHIV, which will be accelerating the progression of HIV and is the cause of death in one-third of PLHIV worldwide.[5] Delay in diagnosis may lead to progression of disease, increased hospitalization, and increased costs to the health system and patient. Smear negative pulmonary TB (PTB) cases have been in an increasing trend following the TB-HIV coepidemic. It is often difficult to distinguish other HIV-related pulmonary disease from PTB. Hence, the extent of overdiagnosis of smear-negative PTB is uncertain. It is important to follow the diagnostic algorithm outlined for the diagnosis of PTB even in PLHIV to diagnose smear-negative TB.[6]

AVAILABLE DIAGNOSTIC OPTIONS

Diagnosis of TB mostly depends on sputum smear microscopy (SSM), which is regarded as an inexpensive and popular method for the diagnosis of TB and for the evaluation of the response to treatment. However, this method lacks adequate sensitivity, especially in adult PLHIVs, in children and other immunocompromised presumptive TB cases, and fails to differentiate the *Mycobacterium tuberculosis (MTb)* complex from nontuberculosis mycobacterium (NTM).[7,8] Therefore, culture (solid and liquid media) is considered as the standard method not only for differentiation between these two groups of mycobacteria but also for the confirmation of growth of live *MTb* as well as its drug sensitivity and resistance status. Despite its benefits, culture is time-consuming and cannot be performed in the absence of highly trained personnel, a well-designed transport system, and an equipped laboratory.[9] On the other hand, the absence of clinical symptoms or abnormal findings on chest X-ray, along with negative acid-fast bacilli (AFB) smear, results in HIV-positive patients with PTB.[9-11] Molecular diagnosis in TB had enabled rapid detection of *MTb* from clinical specimens; molecular methods had become important tools for the identification of mycobacterial species and also for the detection of drug resistance for epidemiological investigation.[12]

SCOPE OF URINE LIPOARABINOMANNAN IN TUBERCULOSIS DIAGNOSIS

Urine LAM is one of the promising diagnostic tools among PLHIV with TB whose CD4 cell counts are <200 cells/µL in different clinical settings.[13] Mycobacterial cell wall contains a glycolipid called lipoarabinomannan. Studies established a proof of concept[14] for using urine sample in detecting

ELISA in 2001, which later was marketed by Alere, USA, as "Determine TB-LAM."[15,16] Main advantages of the test are a point-of-care utility, cheap (<3 USD), and quick (<25 min). The WHO in 2015 policy guidelines[17] on LF-LAM assays suggests that the test may be used to assist the detection of *MTb* in presumptive TB PLHIV patients with CD4 count ≤ 100 cells/µL or who are seriously ill (present with any one of four "danger signs"). Furthermore, the test may be useful in children due to difficulty in obtaining sputum.[18,19]

RESEARCH GAPS

There has been considerable work on the technology of urine LAM in diagnosis of *MTb* as well as its association with mortality related to TB. However, the research is mostly limited to few Western countries. We attempted to review the studies undertaken in all the countries toward identifying the utility of urine LAM in diagnosing TB, especially among PLHIV patients with presumptive TB.

REVIEW OF EXISTING KNOWLEDGE BASE

We searched PubMed, Google Scholar, and MEDLINE databases for studies reporting diagnostic utility of urine LAM status in PLHIV, published in the last 20 years between May 1st, 1999, and December 1, 2019. The keywords used for searching were "Tuberculosis," "HIV/AIDS," "Diagnosis," "Screening" "lipoarabinomannan," and "Urine." We also searched the references of relevant articles and "related studies." The identified studies were compiled into a database, and titles and abstracts were compared thoroughly for removing duplicates. Full texts of the shortlisted abstracts were used for the review in reporting the results. Institutional ethics committee was intimated about the research, but no specific permission was taken as it involved only secondary data analysis of published and anonymized data.

STUDY SELECTION

Studies, which discussed the diagnostic value of urine LAM in PLHIV, were included for the systematic review. Studies which reported mortality or prognostic significance of urine LAM were excluded if they did not discuss about the diagnostic value of urine LAM in detecting TB. There was no geographic limit to incorporate in the review. Studies were also excluded if the reporting of diagnostic value was limited to HIV-negative subjects without involving PLHIV. Studies including both PLHIV and HIV-nagative subjects were reviewed only for the diagnostic value of urine LAM among PLHIV. Abstracts of non-English journals providing sufficient information were included in the review.

DATA EXTRACTION AND ANALYSIS

Information was collected, compiled, and analyzed separately by two researchers by collating the data into databases. The information collected consisted of study

citation, year of publication, number of subjects in the study, subjects' age group, methods of urine LAM testing, hospital/clinic settings, results of the studies, etc., Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were assessed based on the available data in the selected publications. Multivariate analysis results, whenever available, were reviewed carefully. Data analysis was done using IBM SPSS Statistics Package version 20.0 as needed.

GEOGRAPHIC MAPPING OF PUBLICATIONS

One hundred and thirty-seven citations were shortlisted using the keyword search in different databases. Of them, 67 full manuscripts were selected for complete exploration. Thirty-seven studies were included in detailed review [Table 1] after excluding the studies as per the exclusion criteria [Figure 1]. Majority of the studies were conducted in Sub-Saharan Africa and enrolled adult patients with ≥18 years of age. Of the 37 studies reviewed, only 5 were from Asia with one each from India and Myanmar and two from Thailand. The fifth study had a subset samples from Bangladesh and Vietnam. All the remaining 32 studies were from Africa with majority (18/32; 56%) involving South Africa. There were four multinational studies involving South Africa, Tanzania, Zimbabwe, Uganda, Peru, Bangladesh, and Vietnam. Other African countries reported were Ethiopia, Ghana, Mozambique, and Kenya [Table 2]. These studies were reported between 2005 and December 1, 2019. The publications on utility of urine LAM have been in increasing trend since 2013, though there was initial peak in 2009, which reflects on the potential importance of the topic [Figure 2].

All the studies reviewed are prospective cohort studies involving HIV-infected individuals. Almost all studies (34/37) recruited subjects with ≥18 years of age, while two studies reduced the age limit to ≥15 years and one study exclusively recruited children of ≤12 years of age. Majority of the studies recruited subjects in outpatient
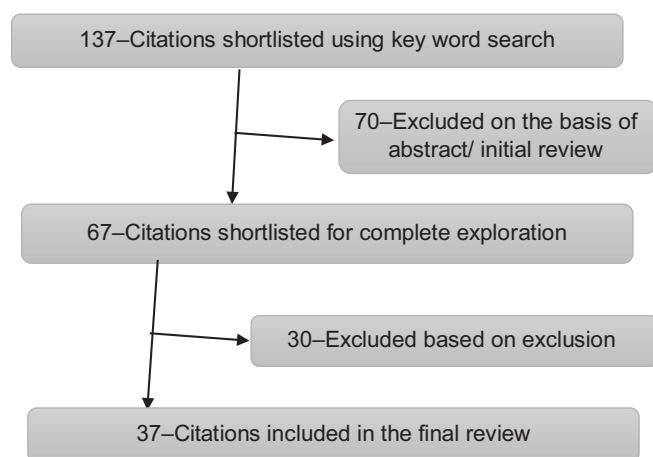
settings (23/37), while 9 of 37 studies recruited hospitalized subjects. The remaining five studies had subjects from both hospitalized and outpatient settings. Majority (21/37; 57%) of studies used fresh urine sample for urine LAM test, while frozen urine was used in 40% (15/37) studies and one study used both fresh and frozen samples [Table 1].

UTILIZATION OF LIPOARABINOMANNAN IN TUBERCULOSIS DIAGNOSIS AND ITS EVOLUTION

LAM-ELISA (Chemogen, So. Portland, Maine, USA) kit was used in the initial four studies during 2005–2009, which later was renamed to Clearview™ TB ELISA kit and used till 2012. In 2012, studies started using Determine™ TB LAM test (Alere Inc., Waltham, USA) kit. In 2012, one study attempted to compare the Clearview kit with Determine kit and demonstrated almost equal efficacy with marginal improvement (Determine 24/85 vs. Clearview 23/85) in detecting urine LAM with Determine [Table 1]. All the studies followed the manufacturers' guidelines in reading the output of urine LAM test and the OD was read immediately at 450 nm. Studies have considered OD at least 0.1 above the negative control as positive reading. Except for 4 studies,[19,38,50,51] 88% of the studies used 2+ as the cutoff in reading urine LAM test as positive. Besides urine LAM, other diagnostic tests included by these studies are SSM using ZN staining and auramine staining, culture of MTb using solid (LJ medium) culture and liquid (BACTEC MGIT) culture, Xpert MTB/Rif using sputum, chest X-Ray (CxR), tuberculin skin test (TST), and blood culture. Except for one study[48] which used Xpert MTB/Rif as a standard for comparing urine LAM results, all other studies used either solid culture (5/36) or liquid culture (25/36) or both (6/36) as gold standard to determine TB infection in the subjects. SSM was performed using either ZN staining (15/34) or auramine staining (13/34) or both (6/34) as a primary diagnostic tool, while 3 studies did not include SSM in the list of tests [Table 1].

STUDY POPULATION

Samples sizes of the studies ranged from 81 to 2528 with an average of 464 patients and standard deviation of 428. The sensitivity of detecting *MTb* in culture-confirmed
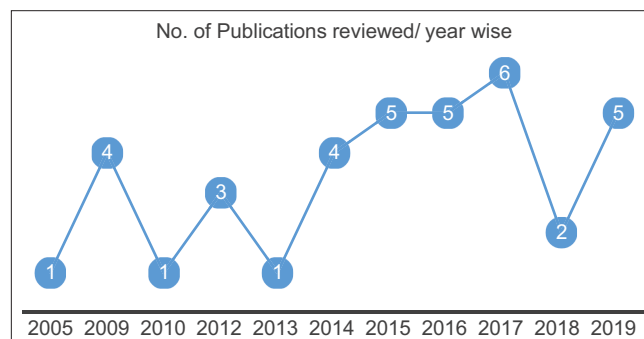

Figure 1: Flowchart depicting selection process of studies for review

Figure 2: Year-wise distribution of studies under review

Table 1: Studies in chronological order assessing utility of urine lipoarabinomannan in detecting *Mycobacterium tuberculosis*

Year of publication	Lead author	Country	Urine sample type	Tests conducted	LAM assay used	Age group	Patient setting
2005	Boehme *et al*.[20]	Tanzania	Fresh urine	SSM (ZN), LJ, LAM-ELISA, CxR	LAM-ELISA by Chemogen	≥18 years	OP
2009	Lawn *et al*.[21]	South Africa	Frozen urine	SSM (Aur), MGIT, LAM-ELISA, CxR	LAM-ELISA by Chemogen	≥18 years	OP
2009	Daley *et al*.[22]	India	Frozen urine	SSM (Aur), LJ, MGIT, LAM-ELISA	LAM-ELISA by Chemogen	≥18 years	OP
2009	Mutetwa *et al*.[23]	Zimbabwe	Frozen urine	SSM (Aur), LJ, LAM-ELISA	LAM-ELISA by Chemogen	≥18 years	OP
2009	Shah *et al*.[24]	South Africa	Frozen urine	SSM (Aur), MGIT, TB-ELISA	Clearview™ TB ELISA	≥18 years	IP
2010	Dheda *et al*.[25]	South Africa	Fresh urine	SSM (Aur), MGIT, TB-ELISA	Clearview™ TB ELISA	≥18 years	OP
2012	Lawn *et al*.[15]	South Africa	Frozen urine	SSM (Aur), MGIT, Xpert, TB LAM	Clearview™ TB ELISA and Determine™ TB LAM	≥18 years	OP
2012	Talbot *et al*.[26]	Tanzania	Both fresh and frozen urine	SSM (ZN), LJ, Blood Culture (Agar and BACTEC), TB ELISA	Clearview™ TB ELISA	≥18 years	IP
2012	Peter *et al*.[27]	South Africa	Frozen urine	SSM (Aur), MGIT, Sputum Xpert, Urine Xpert, TB LAM	Determine™ TB LAM	≥18 years	IP
2013	Lawn *et al*.[28]	South Africa	Frozen urine	SSM (Aur), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2014	Balcha *et al*.[29]	Ethiopia	Frozen urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2014	Nakiyingi *et al*.[30]	Uganda, South Africa	Fresh urine	SSM (ZN), MGIT, Xpert, TB LAM, CxR	Determine™ TB LAM	≥18 years	OP+IP
2014	Drain *et al*.[31]	South Africa	Fresh urine	SSM (ZN and Aur), MGIT, TB LAM	Determine™ TB LAM	≥18 years	OP
2014	Shah *et al*.[32]	Uganda	Fresh urine	SSM (ZN), LJ, MGIT, Blood Culture Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP+IP
2015	Drain *et al*.[33]	South Africa	Fresh urine	SSM (ZN and Aur), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2015	Nakiyingi *et al*.[34]	Uganda	Fresh urine	SSM (ZN and Aur), LJ, MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2015	d'Elia *et al*.[35]	South Africa	Fresh urine	SSM (ZN and Aur), LJ, MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2015	Peter *et al*.[36]	Tanzania, Zimbabwe and South Africa	Frozen urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2015	Bjerrum *et al*.[37]	Ghana	Fresh urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP+IP
2016	Drain *et al*.[38]	South Africa	Fresh urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2016	Peter *et al*.[39]	Tanzania, Zimbabwe and South Africa	Fresh urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	IP
2016	Zijenah *et al*.[40]	Zimbabwe	Fresh urine	SSM (ZN), MGIT, TB LAM	Determine™ TB LAM	≥18 years	OP
2016	Hanifa *et al*.[41]	South Africa	Frozen urine	SSM (ZN), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP
2016	Drain *et al*.[42]	South Africa	Fresh urine	SSM (ZN), MGIT, TB LAM, CxR	Determine™ TB LAM	≥18 years	OP
2017	Huerga *et al*.[43]	Kenya	Fresh urine	SSM (ZN), LJ, Xpert, TB LAM	Determine™ TB LAM	≥18 years	OP+IP

Contd...

Table 1: Contd...

Year of publication	Lead author	Country	Urine sample type	Tests conducted	LAM assay used	Age group	Patient setting
2017	Suwanpimolkul G *et al*.[44]	Thailand	Frozen urine	SSM (ZN), MGIT, Xpert, TB LAM, CxR	Determine™ TB LAM	≥18 years	OP
2017	Lawn *et al*.[45]	South Africa	Frozen urine	SSM (Aur), MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	IP
2017	Thit *et al*.[46]	Myanmar	Fresh urine	SSM (ZN), LJ, Xpert, TB LAM, CxR	Determine™ TB LAM	≥18 years	OP+IP
2017	Gina *et al*.[47]	South Africa	Fresh urine	MGIT, Xpert, TB LAM	Determine™ TB LAM	≥18 years	IP
2017	Floridia *et al*.[48]	Mozambique	Fresh urine	Xpert, TB LAM	Determine™ TB LAM	>15 years	OP
2018	LaCourse *et al*.[19]	Kenya	Fresh urine	MGIT, Xpert (Sputum and Stool), TB LAM, CxR, TST	Determine™ TB LAM	children ≤12 years	IP
2018	Boyles *et al*.[49]	South Africa	Frozen urine	SSM (Aur), Xpert, MGIT, TB LAM	Determine™ TB LAM	≥18 years	IP
2019	Songkhla *et al*.[50]	Thailand	Fresh urine	SSM (Aur), Xpert, LJ, MGIT, TB LAM	Determine™ TB LAM	≥18 years	OP
2019	Huerga *et al*.[51]	Mozambique	Fresh urine	SSM (Aur), Xpert, LJ, MGIT, TB LAM, CxR	Determine™ TB LAM	≥15 years	OP
2019	Broger *et al*.[52]	Bangladesh, Peru, South Africa and Vietnam	Frozen urine	SSM (Aur and ZN), Culture (LJ and MGIT), TB LAM and ESAT-6	Determine™ TB LAM and ESAT-6	≥18 years	OP
2019	Mthiyane *et al*.[53]	South Africa	Fresh urine	SSM (Aur and ZN), Culture (Middle Brook and MGIT), Blood Culture, TB ELISA, CxR	Clearview™ TB ELISA	≥18 years	IP
2019	Kerkhoff *et al*.[54]	South Africa	Frozen urine	SSM (Auramine), MGIT, Xpert, TB LAM, FujiLAM	Determine™ TB LAM and FujiLAM	≥18 years	OP

OD at least 0.1 above negative control was considered Positive. OD was read immediately at 450 nm; SSM: Sputum Smear Microscopy; ZN: Ziehl-Neelsen staining; Aur: Auramine staining; MGIT: Liquid Culture; LJ: Solid culture using Lowenstein-Jensen medium; TB: Tuberculosis; Xpert: Xpert MTB/Rif; TST: Tuberculin Skin Test; MGIT: Mycobacteria Growth Indicator Tube; MRS: Microbiological Reference Standard; OP: Outpatient setting; IP: Hospitalized or In-patient setting, LAM-ELISA by Chemogen: LAM-ELISA (Chemogen, So. Portland, Maine, USA); Clearview™ TB ELISA: Clearview™ TB ELISA kit; Determine™ TB LAM: Determine™ TB LAM test (Alere Inc., Waltham, USA); ESAT-6: Recombinant ESAT-6 (Alpha Diagnostics, USA); FujiLAM: Fujifilm SILVAMP TB LAM, LAM: Lipoarabinomannan

TB by urine LAM ranged from 8.3% to 93% with a crude average of 44.1% of all 37 studies, while that of SSM ranged from 14% to 65% with a crude average of 38.6% from 19 studies that reported [Table 3]. Among the 12 studies that explored the aggregate sensitivity of LAM + SSM, the sensitivity ranged from 38.3% to 92.7% with a crude average of 60.4%, which clearly demonstrated the utility of combination of SSM and LAM for detecting MTb. The specificity of urine LAM ranged from 76% to 100% with a crude average of 92.7% from 30 studies, while that of SSM ranged from 93.9% to 100% with a crude average of 97.9% from 7 studies [Table 3 and Figure 3].

ASSESSMENT OF LIPOARABINOMANNAN UTILITY

When analyzed for utility of urine LAM in diagnosing TB among the HIV-infected patients, almost all the studies have demonstrated higher sensitivity or urine LAM with lesser the CD4 count, immunocompromised patients, severely ill, and debilitated patients who cannot produce self-expectorated sputum. However, observed that the sensitivity of urine LAM did not differ significantly with HIV infection or severity.[20,22] Majority of the studies observed that the sensitivity of urine LAM is higher than the SSM (ZN/Auramine), which further increased in patients whose CD4 count is <100 cells/µL. However, few studies[36,37] observed the lower overall sensitivity of urine LAM compared to SSM [Tables 3 and 4].

A study comparing the utility of urine sample in sputum-scarce patients[27] observed that the sensitivity of urine LAM ELISA was 60% (95% CI: 39–78) which was much higher compared to that of urine Xpert MTB/RIF with a sensitivity of 40% (95% CI: 22–61). Another study[32] concluded that sensitivity of combination of sputum Xpert MTB/Rif and urine LF-LAM approached sensitivity of sputum liquid culture. Lawn *et al*.[45] observed that sensitivity of sputum Xpert MTB/Rif (28.1%; 95% CI: 20.8–36.3) was much lower than that of urine LAM (39.0%; 95% CI: 30.7–47.7), though statistically not significant due to overlapping of CIs. Among those having

**Table 2: Geographic depiction of studies under review**

Country	Number of publications reviewed
Bangladesh, Peru, South Africa and Vietnam (Multi country)	1
Ethiopia	1
Ghana	1
India	1
Kenya	2
Mozambique	2
Myanmar	1
South Africa	17
Tanzania	2
Tanzania, Zimbabwe and South Africa (Multi country)	2
Thailand	2
Uganda	2
Uganda and South Africa (Multi country)	1
Zimbabwe	2
Total	37

CD4 count <100 cells/µL, urine LAM sensitivity was much higher (51.1%; 95% CI: 40.4–61.7%) compared to those with sputum Xpert MTB/Rif (23.1%) as observed by Boyles *et al.*[49] I-PCR assay based on urinary EVs for LAM detection in TB patients certainly revealed better results than the neat urine samples analyzed previously by ELISA and lateral flow immunochromatography.[55]

POTENTIALITY OF URINE LIPOARABINOMANNAN DIAGNOSTIC KIT IN FUTURE

Upon systematic review of 37 articles, which have done commendable research in this aspect, it was observed that urine LAM could be a very useful tool to diagnose MTb, especially among the HIV-infected individuals with CD4 count ≤100 cells/µL.[36,37] In addition, utility is also very high among those who cannot produce sputum for various reasons, children, immunocompromised patients, smear-negative presumptive TB cases, and debilitated and hospitalized presumptive TB cases.[18,19] Certain studies established that the urine LAM has higher overall sensitivity of detecting MTb compared to sputum smear microscopy (SSM) either by ZN staining or auramine staining which further stands out among PLHIV with CD4 count ≤100 cells/µL. Although some studies could not establish the benefit of urine LAM over SSM, many studies have demonstrated very clearly that urine LAM and SSM together can improve the sensitivity drastically compared to either of them alone.[15] This result provides insight to include the combination of these two tests in the diagnostic algorithm, especially in resource-limited settings where Xpert MTB/Rif or culture cannot be afforded.

Surprisingly, certain studies have shown that urine LAM had higher sensitivity in detecting MTb over the Xpert MTB/Rif.[45,49] In contrast, few studies have demonstrated the additive effect of both these tests with an incremental yield on the diagnosis of MTb compared to either of
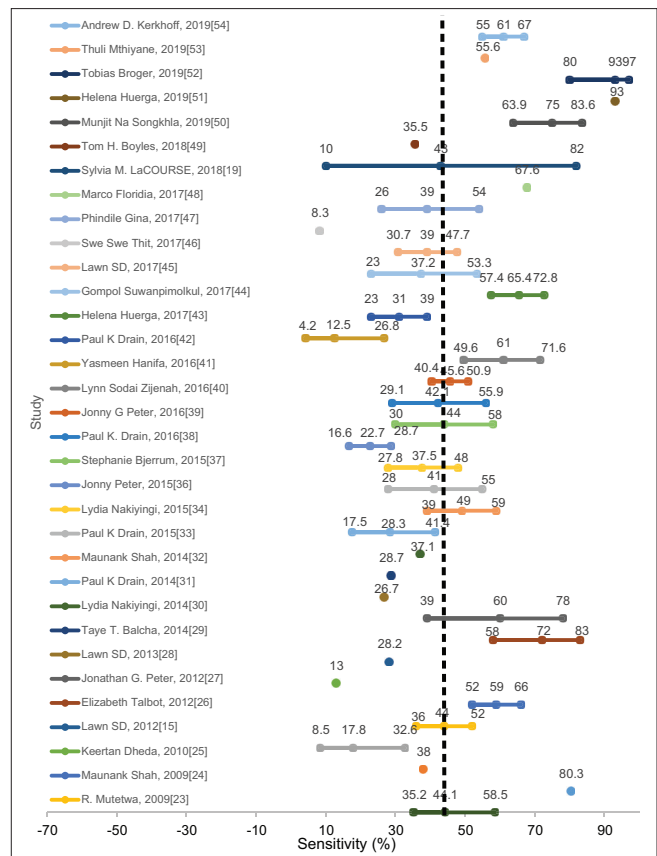
Figure 3: Comparison of urine lipoarabinomannan sensitivity against culture-confirmed tuberculosis cases

them alone.[32,42,45,48] This feature was suggested to be very useful in order not to miss any TB case, where Xpert MTB/Rif facility is available. They have also suggested that a combination of Xpert MTB/Rif along with urine LAM can reach the sensitivity of culture either by solid or liquid media, which has an added benefit of rapidness in obtaining the results compared to the culture.[33]

GEOGRAPHIC SCOPE

Our review covering the last 20 years of publications has given an insight that majority of the research on utility of urine LAM was undertaken in African countries, especially South Africa, while the research from Asia was limited to very few studies. Of the Asian studies, the Indian research was published in 2009,[22] Myanmar study in 2017,[46] and the Thailand studies were published one each in 2017[44] and 2019.[50] This might be due to the high prevalence of HIV among African countries very much earlier than Asian countries and the interest of looking for alternate methods of rapid diagnosis of MTb increased only recently in Asian countries due to recent rise in HIV cases.

RELATION TO CD4 COUNT

By analyzing for sensitivity of urine LAM among different CD4 count groups, majority of the studies concluded that

Table 3: Comparison of efficacy of urine lipoarabinomannan versus sputum smear microscopy

Study	Total sample	LAM +ve/total	95% CI				
			LAM sensitivity (%)	SSM sensitivity (%)	LAM+ SSM sensitivity (%)	LAM specificity (%)	SSM specificity (%)
Boehme *et al*., 2005[20]	231	106/132 LJ+ve	80.3	62.1	-	99	
Lawn *et al*., 2009[21]	235	22/58 culture +ve TB	38	14	45	100	100
Daley *et al*., 2009[22]	200	27/200	17.8 (8.5-32.6)	-	-	87.7 (81.3-92.3)	-
Mutetwa *et al*., 2009[23]	397	71/161 culture+ve	44 (36-52)	-	-	89 (81-94)	-
Shah *et al*., 2009[24]	499	114/193 confirmed TB; 16/89 possible TB	59 (52, 66)	42	-	96 (91-99)	-
Dheda *et al*., 2010[25]	440	17/141/ culture+ve; 3/127 probable TB	13	65	-	95	-
Lawn *et al*., 2012[15]	516	of 85 confirmed TB cases, 23+ve with TB ELISA and 24 +ve with Determine TB-LAM	28.2 with Determine; 27.1 with TB-LAM	28.20	43.5 with SSM+ Determine TB	98.6	99.8
Talbot *et al*., 2012[26]	212	45/69 culture +ve	72 (58-83)	-	-	88	-
Peter *et al*., 2012[27]	242	58/116 confirmed TB cases	60 (39-78)	56	69	98 (95-100)	-
Lawn *et al*., 2013[28]	542	23/86 confirmed TB	26.7	29.6	-	-	-
Balcha *et al*., 2014[29]	757	33/128 confirmed TB	28.7	23.5	40	92.9	-
Nakiyingi *et al*., 2014[30]	997	136 grade 2+ve/ 367 culture +ve	37.1	34.9	53.7	97.6	-
Drain *et al*., 2014[31]	342	45/342	28.3 (17.5-41.4)	18.3	38.3 (26.0-51.8)	-	-
Shah *et al*., 2014[32]	103	50/103	49, (39-59)	30 with ZN; 42 with Aur	67 (57-76)	97	-
Drain *et al*., 2015[33]	320	22/54 culture confirmed TB cases	41 (28-55)	15 (7-27)	-	92 (88-95)	99 (97-100)
Nakiyingi *et al*., 2015[34]	418	36/96 culture confirmed TB cases	37.5 (27.8-48.0)	-	-	93.1 (89.8-95.7)	-
d'Elia *et al*., 2015[35]	274	0/14 confirmed active TB cases	-	-	-	-	-
Peter *et al*., 2015[36]	583	41/181 culture +ve cases	22.7 (16.6-28.7)	43.8 (39-89)	-	93.0 (90.5-95.6)	-
Bjerrum *et al*., 2015[37]	469	24/55 microbiologically confirmed TB cases	44 (30-58)	56	62 (48-75)	95 (92-97)	99 (97-100)
Drain *et al*., 2016[38]	90	24/57 culture +ve	42.1 (29.1-55.9)	21.1 (11.4-33.9)	52.6 (39.0-66.0)	84.9 (68.1-94.9)	93.9 (79.8-99.3)
Peter *et al*., 2016[39]	2528	156/342 TB cases	45·6 (40·4-50·9)	-	-	88·7 (86·3-90·7)	-
Zijenah *et al*., 2016[40]	457	154/457 of all cases	61 (49.6-71.6)	54.9 (43.5-65.9)	74.4 (63.6-83.4)	86.1 (82.2-89.5)	95.7 (93.2-97.5)
Hanifa *et al*., 2016[41]	424	12.5% sensitivity with grade 1+ cut-off; with grade 2+ cut-off=5.4%	12.5 (4.2-26.8)	-	-	95.7 (93.0-97.5)	-
Drain *et al*., 2016[42]	675	38/123 culture confirmed TB	31 (23-39)	-	-	92 (89-94)	-
Huerga *et al*., 2017[43]	474	102/156 confirmed TB by culture/Xpert; 59/107 culture +ve TB	65.4 (57.4-72.8)	-	-	84.0	-
Suwanpimolkul *et al*., 2017[44]	109	16/43 HIV+ve confirmed TB	37.2 (23-53.3)	-	-	85 (62.1-96.8)	-
Lawn *et al*., 2017[45]	427	53/136 confirmed TB cases	39 (30.7-47.7)	19.4 (13.2-27.0)	-	98.9 (96.9-99.8)	-
Thit *et al*., 2017[46]	517	43/517 grade≥2+ve; 201/517 grade ≥1+	8.30	-	-	-	-
Gina *et al*., 2017[47]	123	5/41 confirmed TB with grade ≥2+ve; 19/41 grade ≥1+ in confirmed TB	12 (5-24) RU; 39 (26-54) EMU	-	-	-	-
Floridia *et al*., 2017[48]	972	50/74 Xpert +ve cases	67.6	-	-	98.90	-
LaCourse *et al*., 2018[19]	165	5/9 confirmed TB cases	43 (10-82)	-	-	91 (84-95)	-

Contd...

Table 3: Contd...

Study	Total sample	LAM +ve/total	95% CI				
			LAM sensitivity (%)	SSM sensitivity (%)	LAM+ SSM sensitivity (%)	LAM specificity (%)	SSM specificity (%)
Boyles *et al.*, 2018[49]	332	60/169 confirmed TB cases	35.5	-	-	93.30	-
Songkhla *et al.*, 2019[50]	280	54/72 culture +ve pts	75.0 (63.9-83.6)	61.1; (49.6-71.5	86.1 (76.3-92.3)	76.0 (69.7-81.3)	98.1 (95.2-99.2)
Huerga *et al.*, 2019[51]	456	103/205 lab confirmed TB cases	50.2	35.7	92.7	-	-
Broger *et al.*, 2019[52]	81	37/40 (93%)	93 (80-97)	-	-	97 (85-100)	-
Mthiyane *et al.*, 2019[53]	187	53/156 (34.0%) of all with available results	55.60	-	-	-	-
Kerkhoff *et al.*, 2019[54]	1079	427/553 (77.2%) microbiologically confirmed TB cases	61 (55-67)	-	-	98.2 (95.7-99.6)	-

CI: Confidence interval, LAM: Urine lipoarabinomannan, SSM: Sputum smear microscopy, LJ: Solid culture using Lowenstein-Jensen medium, TB: Tuberculosis, ZN: Ziehl-Neelsen staining, Aur: Auramine staining, Xpert: Xpert MTB/Rif, RU: Random urine, EMU: Early morning urine, "-": Data not available

Table 4: Urine lipoarabinomannan sensitivity by CD4 count

Study	95% CI			
	LAM Sensitivity overall (%)	LAM Sensitivity (CD4<50) (%)	LAM Sensitivity (CD4<100) (%)	LAM Sensitivity (CD4<200) (%)
Lawn *et al.*, 2009[21]	38.0	67.0	41.0	-
Shah *et al.*, 2009[24]	59.0 (52-66)	59.0 (52-66)	85.0 (73-93)	-
Dheda *et al.*, 2010[25]	13.0	-	-	37.0
Lawn *et al.*, 2012[15]	28.2	66.7	51.7	39.0
Talbot *et al.*, 2012[26]	72.0 (58-83)	77.0	-	67.0
Nakiyingi *et al.*, 2014[30]	37.1	-	59.2	-
Drain *et al.*, 2014[31]	28.3 (17.5-41.4)	-	37.5 (21.1-56.3)	-
Nakiyingi *et al.*, 2015[34]	37.5 (27.8-48.0)	-	55.2	-
Peter *et al.*, 2015[36]	22.7 (16.6-28.7)	-	30.4 (17.1-43.7)	-
Peter *et al.*, 2016[39]	45·6 (40·4-50·9)	63·7 (55·6-71·1)	57·7 (51·0-64·2))	50·9 (45·0-56·9)
Zijenah *et al.*, 2016[40]	61.0 (49.6-71.6)	76.6 (62.0-87.7)	43.8 (19.8-70.1)	-
Hanifa *et al.*, 2016[41]	12.5 (4.2-26.8)	-	16.7 (4.7-37.4)	6.3 (0.2-30.2)
Drain *et al.*, 2016[42]	31.0 (23-39)	-	73.0 (61-83)	-
Huerga *et al.*, 2017[43]	65.4 (57.4-72.8)	-	-	68.2 (59.4-76.1)
Suwanpimolkul *et al.*, 2017[44]	39.0 (30.7-47.7)	56.6	20.8	-
Songkhla *et al.*, 2019[50]	75.0 (63.9-83.6)	90.5 (77.9-96.2)	-	-
Huerga *et al.*, 2019[51]	50.2	-	51.9	45.1
Drain *et al.*, 2015[33]	55.6	-	70.0	-

LAM: Urine Lipoarabinomannan, CI: Confidence Interval, SSM: Sputum Smear Microscopy, LJ: Solid culture using Lowenstein-Jensen medium, TB: Tuberculosis, ZN: Ziehl-Neelsen staining, Aur: Auramine staining, Xpert: Xpert MTB/Rif, RU: Random Urine, EMU: Early Morning Urine, -: Data Not Available

the sensitivity of urine LAM in detecting MTb increases with decrease in CD4 count. However, few studies could not demonstrate such difference among the patients of different CD4 count groups. Majority of studies established that sensitivity of urine LAM is nearly equal to SSM. The PPV and NPV were also nearly similar to SSM among those analyzed.

CONCLUSIONS

Our detailed review of 37 studies reflect the added value of incorporating urine LAM in the diagnostic algorithm for detecting MTb among those TB symptomatic HIV-infected patients, especially with immunocompromised condition, non-self-expectorants of sputum, children, debilitated patients, and in those resource poor conditions where Xpert MTB/Rif or MTb culture is not easily available. This

becomes even more significant among the patients having CD4 count of ≤100 cells/μL. However, we feel that further exploratory research on this aspect should be encouraged before establishing the diagnostic utility of urine LAM in the real public health field settings, especially among Asian countries.

Limitations

One of the major limitations of our study is that majority of the analysis is skewed toward African countries, which in a way is true to the nature of HIV epidemic during the period of our review. Second limitation is the variation in the urine LAM kits used over a period of time by different researchers and variation of cutoff mark within the studies using Determine TB-LAM lateral flow kit. Third limitation is that though majority of the studies used culture of MTb as gold standard for confirmatory

TB, there were variations within studies that some used solid culture as gold standard, some liquid culture, while few others used combination of both which has its own inherent differences between both the culture methods, time taken, and yield. At the same time, certain studies used Xpert MTB/Rif as confirmatory test without any culture method in the algorithm. The fourth limitation is that there are variations in definitions of confirmatory TB, probable TB among those studies reviewed. The fifth limitation was widely varying sample sizes across the studies reviewed. Sixth limitation of the study is that though certain studies have reported on the impact of urine LAM detection on the mortality of the patients, we limited our review away from mortality and focused on the diagnostic value of urine LAM only in this report.

Conflicts of interest
There are no conflicts of interest.

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