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 10.0 (range, 9.0–11.1) million people developed TB in 2018. There were an estimated 1.2 (1.1–1.3) million
TB deaths among HIV-positive people in 2018 and an additional 251,000 deaths (223,000–281,000) among people living with HIV/AIDS (PLHIV). 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. 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. 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.

**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). 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. 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.

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.

**SCOPE OF URINE LAM 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. Mycobacterial cell wall contains a glycolipid called lipoarabinomannan. Studies established a proof of concept for using urine sample in detecting ELISA in 2001, which later was marketed by Alere, USA, as “Determine TB-LAM.” Main advantages of the test are a point-of-care utility, cheap (<3 USD), and quick (<25 min). The WHO in 2015 policy guidelines 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.

**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 1, 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-negative 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 LIPORABINOMANNAN 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 [40] 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
### 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. | Tanzania | Fresh urine       | SSM (ZN), LJ, LAM-ELISA, CxR | LAM-ELISA by Chemogen | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2009                | Lawn et al. | South Africa | Frozen urine | SSM (Aur), MGIT, LAM-ELISA, CxR | LAM-ELISA by Chemogen | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2009                | Daley et al. | India | Frozen urine | SSM (Aur), LJ, MGIT, LAM-ELISA | LAM-ELISA by Chemogen | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2009                | Mutetwa et al. | Zimbabwe | Frozen urine | SSM (Aur), LJ, LAM-ELISA | LAM-ELISA by Chemogen | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2009                | Shah et al. | South Africa | Frozen urine | SSM (Aur), MGIT, TB-ELISA | Clearview™ TB ELISA | ≥18 years | IP             |
|                     |             |         |                   |                 |               |           |                |
| 2010                | Dheda et al. | South Africa | Fresh urine | SSM (Aur), MGIT, TB-ELISA | Clearview™ TB ELISA | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2012                | Lawn et al. | South Africa | Frozen urine | SSM (Aur), MGIT, Xpert, TB LAM | Clearview™ TB ELISA and Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2012                | Talbot et al. | Tanzania | Both fresh and frozen urine | SSM (ZN), LJ, Blood Culture (Agar and BACTEC), TB ELISA | Determine™ TB LAM | ≥18 years | IP             |
|                     |             |         |                   |                 |               |           |                |
| 2012                | Peter et al. | South Africa | Frozen urine | SSM (Aur), MGIT, Sputum Xpert, Urine Xpert, TB LAM | Determine™ TB LAM | ≥18 years | IP             |
|                     |             |         |                   |                 |               |           |                |
| 2013                | Lawn et al. | South Africa | Frozen urine | SSM (Aur), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2014                | Balcha et al. | Ethiopia | Frozen urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2014                | Nakiyingi et al. | Uganda, South Africa | Fresh urine | SSM (ZN), MGIT, Xpert, TB LAM, CxR | Determine™ TB LAM | ≥18 years | OP+IP          |
|                     |             |         |                   |                 |               |           |                |
| 2014                | Drain et al. | South Africa | Fresh urine | SSM (ZN and Aur), MGIT, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2014                | Shah et al. | Uganda | Fresh urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP+IP          |
|                     |             |         |                   |                 |               |           |                |
| 2015                | Drain et al. | South Africa | Fresh urine | SSM (ZN and Aur), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2015                | Nakiyingi et al. | Uganda | Fresh urine | SSM (ZN and Aur), LJ, MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2015                | d’Elia et al. | South Africa | Fresh urine | SSM (ZN and Aur), LJ, MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2015                | Peter et al. | Tanzania, Zimbabwe and South Africa | Frozen urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2015                | Bjerrum et al. | Ghana | Fresh urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP+IP          |
|                     |             |         |                   |                 |               |           |                |
| 2016                | Drain et al. | South Africa | Fresh urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2016                | Peter et al. | Tanzania, Zimbabwe and South Africa | Fresh urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | IP             |
|                     |             |         |                   |                 |               |           |                |
| 2016                | Zijenah et al. | Zimbabwe | Fresh urine | SSM (ZN), MGIT, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2016                | Hanifa et al. | South Africa | Frozen urine | SSM (ZN), MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2016                | Drain et al. | South Africa | Fresh urine | SSM (ZN), MGIT, TB LAM, CxR | Determine™ TB LAM | ≥18 years | OP             |
|                     |             |         |                   |                 |               |           |                |
| 2017                | Huerga et al. | Kenya | Fresh urine | SSM (ZN), LJ, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP+IP          |

Contd...
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[26,37] 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[22] concluded that sensitivity of combination of sputum Xpert MTb/Rif and urine LF-LAM approached sensitivity of sputum liquid culture. Lawn et al.[43] 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 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 | IP |
| 2017                | Gina et al.[47] | South Africa | Fresh urine | MGIT, Xpert, TB LAM | Determine™ TB LAM | ≥18 years | OP+IP |
| 2017                | Floridia et al.[48] | Mozambique | Fresh urine | Xpert, TB LAM | Determine™ TB LAM | >15 years | OP |
| 2018                | LaCourse et al.[49] | Kenya | Fresh urine | MGIT, Xpert (Sputum and Stool), TB LAM, CxR, TST | Determine™ TB LAM | children | IP |
| 2018                | Boyles et al.[50] | South Africa | Frozen urine | SSM (Aur), MGIT, TB LAM | Determine™ TB LAM | ≥18 years | IP |
| 2019                | Songkhla et al.[51] | Thailand | Fresh urine | SSM (Aur), MGIT, LJM | Determine™ TB LAM | ≥18 years | OP |
| 2019                | Huerga et al.[52] | Mozambique | Fresh urine | SSM (Aur), MGIT, TB LAM, CxR | Determine™ TB LAM | ≥15 years | OP |
| 2019                | Broger et al.[53] | 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.[54] | 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.[55] | 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.
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 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.\(^{183}\)

### 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.\(^{160}\) 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 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                              |

---

**Figure 3: Comparison of urine lipoarabinomannan sensitivity against culture-confirmed tuberculosis cases**

---

**Notes and Acknowledgments**

Lung India • Volume 38 • Issue 1 • January-February 2021
### Table 3: Comparison of efficacy of urine lipoarabinomannan versus sputum smear microscopy

| Study                        | Total sample | LAM +ve/total | LAM sensitivity (%) | SSM sensitivity (%) | LAM+ SSM sensitivity (%) | LAM specificity (%) | SSM specificity (%) |
|------------------------------|--------------|---------------|---------------------|--------------------|--------------------------|---------------------|--------------------|
| **LAM sensitivity**          | **SSM sensitivity** | **95% CI**  |
| Boehme et al., 2005[29]      | 231          | 106/132      | 80.3                | 62.1               | -                        | 99                  | 100                |
| Lawn et al., 2009[21]        | 235          | 22/58        | 38                  | 14                 | 45                       | 100                 |                    |
| Daley et al., 2009[23]       | 200          | 27/200       | 17.8 (8.5-32.6)     | -                  | -                        | 87.7 (81.3-92.3)    | -                  |
| Muitvetla et al., 2009[21]   | 397          | 71/161       | 44 (36-52)          | -                  | -                        | 89 (81-94)          | -                  |
| Shah et al., 2009[24]        | 499          | 114/193      | 59 (52, 66)         | 42                 | -                        | 96 (91-99)          | -                  |
| Dheda et al., 2010[25]       | 440          | 17/141       | 13                  | 65                 | -                        | 95                  | -                  |
| Lawn et al., 2012[53]        | 516          | 282/260      | 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        | 72 (58-83)          | -                  | -                        | 88                  | -                  |
| Peter et al., 2012[27]       | 242          | 58/116       | 60 (39-78)          | 56                 | 69                       | 98 (95-100)         | -                  |
| Lawn et al., 2013[28]        | 542          | 23/86        | 26.7                | 29.6               | -                        | -                   | -                  |
| Balcha et al., 2014[38]      | 757          | 33/128       | 28.7                | 23.5               | 40                       | 92.9                | -                  |
| Nakiyingi et al., 2014[40]   | 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[42]        | 103          | 50/103       | 49, (39-59)         | 30 with ZN; 42 with Aur | 67 (57-76) | 97 | - |
| Drain et al., 2015[53]       | 320          | 22/54        | 41 (28-55)          | 15 (7-27)          | -                        | 92 (88-95)          | 99 (97-100)        |
| Nakiyingi et al., 2015[41]   | 418          | 36/96        | 37.5 (27.8-48.0)    | -                  | -                        | 93.1 (89.8-95.7)    | -                  |
| d’Elia et al., 2015[55]      | 274          | 0/14         | -                   | -                  | -                        | -                   | -                  |
| Peter et al., 2015[56]       | 583          | 41/181       | 22.7 (16.6-28.7)    | 43.8 (39-89)       | -                        | 93.0 (90.5-95.6)    | -                  |
| Bjerrum et al., 2015[37]     | 469          | 24/55        | 44 (30-58)          | 56                 | 62 (48-75)               | 95 (92-97)          | 99 (97-100)        |
| Drain et al., 2016[38]       | 90           | 24/57        | 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      | 45.6 (40.4-50.9)    | -                  | -                        | 88.7 (86.3-90.7)    | -                  |
| Zijenah et al., 2016[49]     | 457          | 154/457      | 61 (49-67.16)       | 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 (4.2-26.8) | - | - | - | 93 (93.0-97.5) | - |
| Drain et al., 2016[42]       | 675          | 38/123       | 31 (23-39)          | -                  | 92 (89-94)               | -                   | -                  |
| Huerga et al., 2017[43]      | 474          | 102/156      | 65.4 (57.4-72.8)    | -                  | -                        | 84.0                | -                  |
| Suwanpipolkul et al., 2017[41] | 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       | 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; 2/517 grade ≥1+ | 8.30 | - | - | - | - |
| Gina et al., 2017[47]        | 123          | 5/41 confirmed TB with ≥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[41]    | 165          | 5/9 confirmed TB cases | 43 (10-82) | - | - | 91 (84-95) | - |
Chatla, et al.: Utility of urine LAM for detecting TB in PLHIV: A systematic review

**Table 3: Contd...**

| Study                       | Total sample | LAM +ve/total | 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               | -                   |
| Songkha et al., 2019[40]    | 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[31]     | 456          | 103/205 lab confirmed TB cases | 50.2               | 35.7                | 92.7                     | -                   | -                   |
| Broger et al., 2019[32]     | 81           | 37/40 (93%)   | 93 (80-97)          | -                   | -                        | 97 (85-100)        | -                   |
| Mthiyane et al., 2019[33]   | 187          | 53/156 (34.0%) of all with available results | 55.60              | -                   | -                        | -                   | -                   |
| Kerkhoff et al., 2019[34]   | 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                       | 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[4]        | 59.0 (52-66)                | 59.0 (52-66)                | 85.0 (73-93)                 | -                            |
| Dheda et al., 2010[30]      | 13.0                        | -                           | -                            | -                            |
| Lawn et al., 2012[3]        | 28.2                        | 66.7                        | 51.7                         | 39.0                         |
| Talbot et al., 2012[20]     | 72.0 (58-83)                | 77.0                        | -                            | 67.0                         |
| Nakiyangi 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)             | -                            |
| Nakiyangi et al., 2015[5]   | 37.5 (27.8-48.0)            | -                           | 55.2                         | -                            |
| Peter et al., 2015[6]       | 22.7 (16.6-28.7)            | -                           | 30.4 (17.1-43.7)             | -                            |
| Peter et al., 2016[7]       | 45.6 (40-50-9)              | 63.7 (55-67-1)              | 57.1 (51-64-2)              | 50.9 (45-56-9)               |
| 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                        | -                            |
| Songkha et al., 2019[50]    | 75.0 (63.9-83.6)            | 90.5 (77.9-96.2)            | -                           | -                            |
| Huerga et al., 2019[31]     | 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.

Acknowledgments
We acknowledge the support rendered by the District TB Cell, State TB Cell, and the staff from SSCP, Warangal, for their support in completing this review.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. World Health Organization. Global Tuberculosis Report-2019, Released on 17 October, 2019.
2. Colebunders RL, Ryder RW, Nzilambi N, Dikitu K, Willame JC, Kaboto M, et al. HIV infection in patients with tuberculosis in Kinshasa, Zaire. Am Rev Respir Dis 1989;139:1082-5.
3. Chatla C, Guggulothu KC, Suryaprakash CH, Sreenivas Rao G, Prabhakaran J, Kurada J, et al. Contribution of provider initiated testing and counselling of HIV in detecting new HIV cases revised national tuberculosis control programme in Telangana State, India. Int J Curr Res 2018;10:70212-5.
4. Swaminathan S, Narendran G. HIV and tuberculosis in India. J Biosci 2008;33:527-37.
5. El-Sadr WM, Tsiouris SJ. HIV-associated tuberculosis: Diagnostic and treatment challenges. Semin Respir Crit Care Med 2008;29:523-31.
6. Morgan MA, Hontsmeier CD, DeYoung DR, Roberts GD. Comparison of a radiometric method (BACTEC) and conventional culture media for recovery of mycobacteria from smear-negative specimens. J Clin Microbiol 1983;18:384-8.
7. Kent L, McHugh TD, Billington O, Dale JW, Gillespie SH. Demonstration of homology between B6110 of Mycobacterium tuberculosis and DNAs of other Mycobacterium spp. J Clin Microbiol 1995;33:2298-9.
8. Perkins MD, Cunningham J. Facing the crisis: Improving the diagnosis of tuberculosis in the HIV era. J Infect Dis 2007;196 Suppl 1:S15.
9. Salfinger M, Pfyffer GE. The new diagnostic mycobacteriology laboratory. Eur J Clin Microbiol Infect Dis 1994;13:961-79.
10. Arrabelli M, Adidala RR, Chatla C, Shireesha T, Suryaprakash CH, Jojula M. Pulmonary Tuberculosis in HIV-infected Patients Presenting with Normal Chest Radiograph and Negative Sputum Smear. Journal of Health Sciences 2016;4:125-30.
11. Elliot AM,Namaambok K, Allen BW, Luo N, Hayes RJ, Pobee JO, et al. Negative sputum smear results in HIV-positive patients with pulmonary tuberculosis in Lusaka, Zambia. Tuber Lung Dis 1993;74:191-4.
12. Assis NC, Lopes ML, Cardoso NC, Mesquita da Costa M, Sousa CO, Lima KVB. Molecular diagnosis of pulmonary tuberculosis. J Bras Patol Med Lab 2007;43:1-7.
13. Shah M, Martinson NA, Chaisson RE, Martin DJ, Variaeva E, Dorman SE. Quantitative analysis of a urine-based assay for detection of lipoarabinomannan in patients with tuberculosis. J Clin Microbiol 2010;48:2972-4.
14. Hamasur B, Bruchfeld J, Haile M, Pawlowski A, Bjorvatn B, Källenius G, et al. Rapid diagnosis of tuberculosis by detection of mycobacterial lipoarabinomannan in urine. J Microbiol Methods 2001;45:41-52.
15. Lawn SD, Kerkhoff AD, Vogt M, Wood R. Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: A descriptive study. Lancet Infect Dis 2012;12:201-9.
16. Peter JG, Theron G, van Zyl-Smit R, Haripersad A, Mottola I, Kraus S, et al. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. Eur Respir J 2012;40:1211-20.
17. World Health Organization. The Use of Lateral Flow Urine Lipoarabinomannan Assay (LF-LAM) for the Diagnosis and Screening of Active Tuberculosis in People Living with HIV. Policy Guidance; 2015.
18. Krodi I, Clowes P, Reither K, Mfaya B, Rojas-Ponce G, Ntinginya EN, et al. Performance of urine lipoarabinomannan assays for paediatric tuberculosis in Tanzania. Eur Respir J 2015;46:761-70.
19. LaCourse SM, Pavlinac PB, Cramner LM, Njuguna IN, Mugo C, Gatimu J, et al. Stool Xpert MTB/RIF and urine lipoarabinomannan for the diagnosis of tuberculosis in hospitalized HIV-infected children. AIDS 2018;32:69-78.
20. Boehme C, Molokova E, Minja F, Geis S, Loscher T, Maboko L, et al. Detection of mycobacterial lipoarabinomannan with an antigen-capture ELISA in unprocessed urine of Tanzanian patients with suspected tuberculosis. Trans R Soc Trop Med Hyg 2005;99:893-900.
21. Lawn SD, Edwards DJ, Kranzer K, Vogt M, Bekker LG, Wood R. Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. AIDS 2009;23:1875-80.
22. Daley P, Michael JS, Hmar P, Lahra A, Chordia P, Mathai D, et al. Blinded evaluation of commercial urinary lipoarabinomannan for active tuberculosis: A pilot study. Int J Tuberc Lung Dis 2009;13:989-95.
23. Mutetwa R, Boehme C, Dismaino M, Bandason T, Munyati SS, Mangwanya D, et al. Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African TB suspects and patients. Int J Tuberc Lung Dis 2009;13:1253-9.
24. Shah M, Variaeva E, Holmes CB, Coppin A, Golub JE, McCallum J, et al. Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a High HIV prevalence setting. J Acquir Immune Defic Syndr 2009;52:1425-51.
25. Dheda K, Davids V, Lenders L, Roberts T, Meldau R, Ding L, et al. Clinical utility of a commercial LAM-ELISA assay for TB diagnosis in HIV-infected patients using urine and sputum samples. PLoS One 2010;5:e9848.
26. Talbot E, Munseri P, Teixeira P, Matee M, Bakari M, Lawey T, et al. Test characteristics of urinary lipoarabinomannan and predictors of mortality among hospitalized HIV-infected tuberculosis suspects in Tanzania. PLoS One 2012;7:e32876.
27. Peter JG, Theron G, Muchinga TE, Govender U, Dheda K. The diagnostic accuracy of urine-based Xpert MTB/RIF in HIV-infected hospitalized patients who are smear-negative or sputum scarce. PLoS One 2012;7:e39966.
28. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: Relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Med 2013;11:231.
29. Balcha TT, Winnyit N, Sturegård E, Skogmar S, Reepalu A, Jemal ZH, et al. Detection of lipoarabinomannan in urine for identification of active tuberculosis among HIV-positive adults in Ethiopian health centres. Trop Med Int Health 2014;19:734-42.
30. Nakinyirongo L, Moodley VM, Manabe YC, Nicol MP, Holshouser M, Armstrong DT, et al. Diagnostic accuracy of a rapid urine lipoarabinomannan test for tuberculosis in HIV-infected adults. J Acquir Immune Defic Syndr 2014;66:270-9.
31. Drain PK, Losina E, Coleman SM, Giddy J, Ross D, Katz JN, et al. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: A prospective, clinic-based study. BMC Infect Dis 2014;14:110.
32. Shah M, Sengbooa W, Armstrong D, Nakinyirongo B, Holshouser M, Ellner JJ, et al. Comparative performance of urinary lipoarabinomannan assays and Xpert MTB/RIF in HIV infected individuals with suspected tuberculosis in Uganda. AIDS 2014;28:1307-14.
33. Drain PK, Losina E, Coleman SM, Giddy J, Ross D, Katz JN, et al. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis.
