

The use of Urinary Lipoarabinomannan (LAM) as a Rapid Diagnostic Test for Adult Pulmonary Tuberculosis in HIV-Positive Patients: an Evidence-based Case Report

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Abstract

Tuberculosis is a major health concerns around the world as it is causing morbidity and mortality, especially in HIV infected patients. Detection of lipoarabinomannan (LAM) on urine is a non-sputum-based diagnostic test for TB that could accelerate TB case detection in HIV-positive patients. This evidence-based case report was aimed to evaluate the diagnostic value of urinary Lipoarabinomannan (LAM) test in diagnosing pulmonary tuberculosis in HIV-positive patients as compared to sputum culture.

Structured literature searching was done on cross-sectional or systematic reviews of diagnostic studies of lipoarabinomannan versus sputum culture in adult HIV-positive patients suspected with pulmonary TB. There were 9 articles that meet the eligibility criteria; 1 systematic review and 8 cross-sectional studies. Two out of nine articles were deemed as not valid due to not using sputum on all samples and the index test and reference test were not carried out on all samples. There were contradictory results regarding the sensitivity, positive predictive values and negative predictive values, meanwhile the specificity showed good results.

We conclude that urinary LAM can be used to diagnose pulmonary TB in HIV-positive patients due to its high specificity. However, it could not be used as a stand-alone test, due to its suboptimal sensitivity.

Case report (J Int Dent Med Res 2021; 14(1): 461-466)

Keywords: Sputum culture, tuberculosis, TB-HIV, urinary lipoarabinomannan.

Received date: 02 November 2020

Accept date: 13 January 2021

Introduction

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*. It's a contagious disease transmitted by coughing, sneezing, or spitting, by people infected with tuberculosis. Tuberculosis mostly infects the lungs, but it can also infect other organs such as bones, glands, and skin.^{1,2} Tuberculosis is one of the major health problems in the world, infecting about 10.0 million people and causing the death of 1.2 million people in 2019, and about 820 thousands of which are HIV positive. Due to the

compromised state of the immune system, HIV and TB co-infection often happen and can increase mortality in HIV/AIDS patients. Indonesia ranks as the second country with most case in the world, with 845 thousand cases of tuberculosis. Among those, about 19 thousand cases were HIV-positive.³

The symptoms of tuberculosis are, among others, productive cough, mucopurulent or purulent sputum, hemoptysis, breathlessness, fever, night sweats, malaise.^{1,4} The symptoms are very wide and sometimes doctors misdiagnosed patients. Diagnosing TB is usually done by culture, using Lowenstein Jensen from direct sputum. However, it takes days or weeks to receive the result, which will delay the start of treatment. Rapid identification and diagnosis TB in HIV coinfection patient is very important for reducing TB transmission, therefore accelerate treatment initiation.⁵⁻⁸

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Recently, detection of glycolipid antigen lipoarabinomannan (LAM), which is a mycobacterial cells, has become available. By applying immune-capture assay, the antigen can be detected in urine.^{9,10} Urine LAM examination is TB diagnostic test that has several advantages, such as easy to obtain samples, safe laboratory work, does not require experts in the process, and has minimal bacterial contamination. However, there were still contradictory results in many studies upon using this marker.^{11,12} Based on the above facts, the present EBCR will be discussing about a TB rapid test by urinary Lipoarabinomannan (LAM) in HIV patients suspected with pulmonary TB.

CLINICAL SCENARIO

A 30-year-old man, comes to a clinic with persistent phlegm cough since 2 months ago, sometimes accompanied with shortness of breath. His symptoms have burdened him for a week before eventually visiting the clinic. The patient also experienced extreme weight loss and occasional cold sweat. In the past, he has been diagnosed with HIV, but he doesn't take his medications regularly. The doctor suspects that the patient is infected with tuberculosis bacteria. Lowenstein Jensen culture test, the gold standard for TB diagnosis, requires a long period of time. however, the patient lives far away from the hospital, so the doctor needs a quicker way to determine if the patient is indeed infected by TB and can start the TB medication right away. In addition, the patient is also worried that he would spread his infection to his sister and her 2 under-five children that he lives with. The doctor has read an article about the measurement of LAM (Lipoarabinomannan) in the urine as an alternative for rapid TB examination. Therefore, the doctor formulated a clinical question based on the case above: can urinary LAM (Lipoarabinomannan) be used to diagnose TB in adult HIV-positive patient.

Materials and methods

Article Search Strategy

To answer this clinical question, we searched for source articles in three databases consisting of Pubmed, Cochrane, and SCOPUS. In our literature search, we used the keywords "HIV with TB", "Lipoarabinomannan", "culture" and "diagnose" along with synonyms for each term. Keywords were arranged using the

Boolean method, where each synonym is added "OR" boolean, and then we combine it by adding the "AND" boolean (Table 1). In addition, article searching were also done by the hand-searching method.

Keywords	Database	Hits	Selected Articles
HIV AND tuberculosis AND (LAM OR Lipoarabinomannan) AND (culture OR lowenstein jensen) AND diagnosis	PubMed	95	7
HIV AND tuberculosis AND (LAM OR Lipoarabinomannan) AND (culture OR lowenstein jensen) AND diagnosis	Cochrane Library	1	1
HIV AND tuberculosis AND (LAM OR Lipoarabinomannan) AND (culture OR lowenstein jensen) AND diagnosis	SCOPUS	2	0
HIV AND tuberculosis AND (LAM OR Lipoarabinomannan) AND (culture OR lowenstein jensen) AND diagnosis	Google Scholar	1	1

Table 1. Literature Search Strategy.

Article Selection Strategy

Articles showing up in the search result then went through a selection process including the removal of duplication, filtering of titles and abstracts, and selection of articles based on full text. Screening of titles, abstracts, and full texts were carried out based on eligibility criteria. Articles fitting the eligibility criteria were included to then be appraised.

Eligibility Criteria

The studies included on this report were based on study design and PICO criteria (P=population, I=intervention / type of reference standard and index test, C=comparison and O=the study outcome). We used studies which assessed the accuracy of urinary LAM test using Determine™ TB LAM Assay for diagnosing pulmonary TB and compared it to Mycobacterium tuberculosis sputum culture. We included studies that used systematic review of clinical diagnostic study or cross-sectional study in adult HIV patients suspected with pulmonary TB.

We excluded studies which were not done in clinical settings (e.g. animals and in vitro study), full-text articles were inaccessible, and articles were not written in English or Bahasa. We also excluded studies that used urinary LAM testing as screening tool for TB and if the diagnostic values or data were not reported on the study. Literature search results (Fig 1)

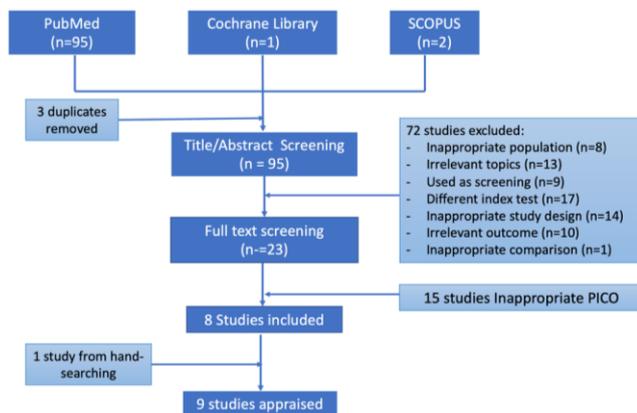


Figure 1. Literature search result.

Critical appraisal method

Critical appraisal are conducted by all authors on 9 feasible articles (8 individual studies and 1 systematic review) using Centre of the University of Oxford's Evidence-Based Medicine (CEBM) Appraisal Tools.¹³

Results

Study	Type of Study	Intervention	Comparison	Population	Sample Size	LoE*
Sahle 2017 ¹⁷	Cross sectional	Determine TM TB LAM Assay	Sputum culture in Lowenstein Jensen medium	HIV patients with suspected tuberculosis	21	2
Suwanpimokul 2017 ³⁰	Cross sectional	Determine TM TB LAM Assay	Sputum culture in BacTec MGIT medium	HIV patients with suspected tuberculosis	63	2
Boyles 2018 ³¹	Cross sectional	Determine TM TB LAM Assay	Sputum Culture (medium was not mentioned)	HIV patients with suspected tuberculosis	332	2
Zijenah 2016 ¹⁶	Cross sectional	Determine TM TB LAM Assay	Sputum culture in BacTec MGIT medium	Hospitalized HIV patients with suspected TB	457	2
Shah 2014 ¹⁴	Cross sectional	Determine TM TB LAM Assay (LF-LAM) and Clearview [®] (ELISA LAM)	Sputum culture in Lowenstein Jensen and BacTec MGIT medium and/or Blood Culture in MYCO/F LYTIC medium	HIV patients with suspected tuberculosis	208	2
Lawn 2013 ¹⁰	Cross sectional	Determine TM TB LAM Assay	Sputum culture in BacTec MGIT medium	HIV patients with suspected tuberculosis	523	2
Benjamin 2019 ³²	Cross sectional	Determine TM TB LAM Assay	Sputum culture in Lowenstein Jensen and BacTec MGIT medium	HIV patients with suspected tuberculosis and CD4 count ≤ 200 cells/mm ³	199	2
Sandjaja 2016 ¹⁸	Cross sectional	Determine TM TB LAM Assay	Sputum culture in Lowenstein Jensen medium	HIV patients with suspected tuberculosis	66	2
Bjerrum 2019 ¹⁵	Meta-analysis	Determine TM TB LAM Assay	Culture or Nucleic Acid Amplification Test	HIV patients with suspected tuberculosis	6814 (3449 HIV positive participants who are suggestive of TB)	1

Table 2. Characteristics of studies appraised.

Literature Search Result

We conduct literature search based on search strategy and eligibility criteria, 9 studies were obtained which then were critically appraised. Majority of studies were excluded because the title/abstract did not match with our PICO or study design.

Study Characteristics

There were nine studies that we appraised in our study. One of the nine is a meta-analysis study. After we carefully read full-text of each studies, none of the other eight articles were include in the meta-analysis. Characteristics of each studies are shown in Table 2.

Results of Critical Appraisal

We checked the validity of each studies that we using criteria of gold standard, blinding, appropriateness of the population as shown in Table 3.

No	Study	Validity Criteria			
		Gold Standard	Blinding	Appropriate Population	Applied to All Subjects
1	Sahle 2017 ¹⁷	Yes	Yes	Yes	Yes
2	Suwanpimokul 2017 ³⁰	Yes	Yes	Yes	Yes
3	Boyles 2018 ³¹	Yes	Yes	Yes	Yes
4	Zijenah 2016 ¹⁶	Yes	Not Mentioned	Yes	Yes
5	Shah 2014 ²⁷	No	Yes	Yes	Yes
6	Lawn 2013 ¹⁰	Yes	Yes	Yes	No
7	Benjamin 2019 ³²	Yes	Yes	Yes	Yes
8	Sandjaja 2016 ¹⁸	Yes	Not Mentioned	Yes	Yes

Table 3. Critical appraisal results for the validity of the diagnostic cross sectional study.

Study	Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR (+/-)	Pre-test prob (%)	Pre-test odds	Post-test odds (+/-)	Post-test prob (+/-)
Suwanpimokul 2017 ³⁰	40.0	85.0	80.0	48.6	$2.67 / 0.71$	60.0	1.50	6.68 / 2.14	0.87 / 0.68
Boyles 2018 ³¹	35.5	93.0	84.5	58.2	$5.29 / 0.69$	51.0	1.04	5.51 / 0.72	0.85 / 0.42
Zijenah 2016 ¹⁶	61.0	86.1	49.0	91.0	$4.38 / 0.45$	17.9	0.22	0.96 / 0.10	0.49 / 0.09
Benjamin 2019 ³²	46.9	90.7	62.2	84.0	$5.04 / 0.59$	24.6	0.32	1.61 / 0.19	0.62 / 0.16
Sandjaja 2016 ¹⁸	72.4	91.9	87.5	81.0	$8.94 / 0.30$	43.9	0.78	6.94 / 0.23	0.87 / 0.18

Table 4. Critical importance of the diagnostic study.

We concluded that two out of eight in the cross-sectional study (Shah 2014,¹⁴ Lawn 2013¹⁰) were not valid after appraisal. Hence, only six primary studies and one systematic review were included in the importance appraisal. In the six primary studies, it was shown that sensitivity of LAM test are varies around 35.2% - 72.4%, specificity was relatively high around 85% - 100%, PPV are varies around 49% - 100% and NPV are also varies around 48.6% - 91%. These importance results of the studies are shown in Table 4.

In the meta-analysis study done by Bjerrum 2019¹⁵, it was shown that pooled sensitivity was 42% (95% CI: 31% - 55%) and pooled specificity were 91% (95% CI: 85% - 95%). The meta-analysis included a plot of diagnostic accuracy in adults with signs and symptoms of tuberculosis, which explained that group of patients with low CD4 tend to have a lower specificity and higher sensitivity than group of patients with high CD4.

Discussions

In order to evaluate the diagnostic value of urinary Lipoarabinomannan (LAM) test in diagnosing pulmonary tuberculosis in HIV-positive patients as compared to sputum culture we critically appraised 9 studies according to our predetermined selection criteria. We considered 6 individual studies and 1 meta-analysis are valid. Regarding the importance, the specificity of TB LAM Assay is consistently high in all of the individual studies, ranging from 85% to 100%. This is also supported by the pooled specificity in the meta-analysis, which is as high as 91%. The high specificity of the assay shows its potential in diagnosing pulmonary tuberculosis in HIV-positive patients showing TB symptoms. Meanwhile, the sensitivity of the assay varies between studies, ranging from 35.5% to 72.4% in individual studies, with pooled sensitivity of 42% according to the meta-analysis, which is quite low. The same goes for both the positive and negative predictive value, ranging from 49.0% to 100% and 48.6% to 91.0%, respectively.

However, there are some articles that need to be highlighted. In Zijenah LS 2016, the population studies were hospitalized patients and had high specificity. This event probably occurred due to the low CD4.¹⁶ In Sahle 2017, the sample size was only 21 population and it does not

reflect the actual population.¹⁷ The blinding were not mentioned in Sahle 2017 and Sandjaja 2015.^{17,18} However, both studies is still considered valid because due to the objective measurement.^{17,18} In the systematic review-meta-analysis by Bjerrum, there are some events that were concerning. There were 75% of the individual studies assessed had high risk of bias in selecting the population. The heterogeneity also unclear due to the incomplete forest plot data.¹⁵

Currently, diagnostic laboratory methods for diagnosing active TB are based on the discovery of Mtb through acid-fast staining or conducting the culture of Mtb bacteria directly on sputum specimens. Unfortunately, acid-fast staining microscopic examination lacks of sensitivity and is practically ineffective in diagnosing TB in children, in patients with HIV co-infection, and in patients with extrapulmonary TB, whereas culture examination, which is actually the ultimate test, takes a long time of about 6-8 weeks, even more to get results.^{19,20,21} Other additional test that are also very important to establish the diagnosis of Mtb are the GeneXpert MTB/RIF and Xpert Ultra.¹⁹ In addition, to diagnose latent TB, tuberculin skin test or interferon- γ release assays (IGRAs) can be done for examination. Although both of these tests are useful in managing patients, they do not have a predictive value for progression to active TB.²² In recent studies, immune biomarkers have been suggested as additional diagnostic markers in TB/HIV patients.^{23,24} However, in clinical practice, TB patients coinfecting with HIV, it has been proven that immediate TB treatment plus ARV therapy can benefit patients, therefore rapid and accurate diagnostic tests are needed to be able to diagnose the condition.

LAM is the main surface antigen Mycobacterium tuberculosis (Mtb) and the main glycolipid surface component that makes up the Mtb cell wall. LAM is composed of the backbone of the mannan polysaccharide with oligoarabinosyl side chains.^{25,26} LAM has been demonstrated to be available in the urine of Mtb-infected patients. Previous studies have proven that LAM has a higher sensitivity for TB patients coinfecting with HIV than HIV-uninfected TB patients.^{11,12,27} In addition, Nakiyingi et al., have shown that the Determine TB-LAM test can detect well more than half of TB patients with advanced HIV, which is the group with the

highest mortality in TB patients.^{28,29} They also proved that the sensitivity of Determine TB-LAM test was associated with advanced immunosuppression and the positive Determine TB-LAM test was related with hospitalization and mycobacteremia.²⁸ Previous studies have also shown that there is a strong association between Mtb bacteremia and positive LAM urine in advanced HIV patients (CD4 cell count <100 cells/mm³).²⁸⁻³²

In Indonesia, LAM test is available, but still yet widely used in Indonesia. LAM test has relatively high specificity and however, varies in sensitivity. The TB-HIV positive in Indonesia is about 2.3% out of the total TB according to 2018 - 2019 incidence.^{3,33} LAM test is relatively easy to use because only use urine for sample. With informed consent, patients probably willing to cooperate. Because of high specificity, easy to use, and more rapid than culture test, LAM test can help out our patient.

Based on all the information above, the urinary Determine™ TB LAM (Lipoarabinomannan) Assay can be used in diagnosing TB suspected in HIV patients, especially in patients with low CD4. These findings is supported by the high specificity in all studies.

Conclusions

Urinary LAM (Lipoarabinomannan) can be used to diagnose pulmonary TB in adults-HIV patients due to its high specificity. A good diagnostic tool is supposed to have high specificity to rule in the disease. Further research is still needed on this new method especially related to the relationship of CD4 levels to the sensitivity and specificity of urine LAM test.

Declaration of Interest

The authors report no conflict of interest.

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