

Lateral flow urine  
lipoarabinomannan assay (LF-LAM)  
for the diagnosis of active tuberculosis  
in people living with HIV

Policy update (2019)

NEW DIAGNOSTIC TESTS  
EXTRA PULMONARY TB  
TUBERCULOSIS  
TUB  
PULMONARY TB  
TB/HIV  
DIAGNOSIS  
RECOMMENDATIONS  
**POLICY UPDATE**  
TB URINE TEST  
MYCOBACTERIUM  
HIV LOW CD4  
RAPID TB TEST  
TB/HIV



**Lateral flow urine lipoarabinomannan  
assay (LF-LAM) for the diagnosis  
of active tuberculosis in people  
living with HIV**

**Policy update  
2019**

Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update 2019

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**Contents**

**Abbreviations and acronyms..... v**

**Key definitions..... vi**

**Acknowledgements ..... vii**

Guideline Development Group..... vii

External Review Group ..... vii

Systematic review team..... vii

Consultants with additional technical expertise ..... vii

Observers .....viii

WHO steering committee .....viii

**Funding .....viii**

**Executive summary..... ix**

Background .....ix

Objectives .....ix

Methods used to develop these guidelines ..... x

WHO policy recommendations ..... x

Summary of changes in the evidence-based recommendations between the 2015 guidance and the 2019 update..... xii

**1. Introduction..... 1**

1.1. Background ..... 1

1.2. Scope of the document..... 1

1.3. Target audience..... 2

1.4. Objectives ..... 2

1.5 Index test ..... 2

**2. Methods ..... 4**

2.1. Preparation for evidence assessment ..... 4

2.2. Evidence retrieval, quality assessment and grading of the evidence..... 5

2.3. Findings ..... 6

2.4. Summary of the results..... 7

2.5. Economic evaluations of the LF-LAM for diagnosis of active TB in HIV-positive individuals..... 10

2.6. User perspectives on LF-LAM testing: results from qualitative research ..... 11

2.7. Formulation of the recommendations ..... 12

2.7.1. Priority of a problem..... 12

2.7.2. Test accuracy ..... 13

2.7.3. Balance between desirable and undesirable effects .....	13
2.7.4. Certainty of the evidence .....	13
2.7.5. Certainty of management.....	14
2.7.6. Confidence in values and preferences and their variability .....	14
2.7.7. Resource requirements.....	14
2.7.8. Cost–effectiveness.....	14
2.7.9. Equity .....	14
2.7.10. Acceptability .....	15
2.7.11. Feasibility.....	15
2.8. Management of conflict of interest.....	15
2.9. GDG decision-making .....	15
2.10. WHO policy recommendations.....	16
<b>3. Plan to update the guidelines.....</b>	<b>18</b>
<b>4. Research priorities .....</b>	<b>19</b>
<b>5. Publication, dissemination and implementation .....</b>	<b>20</b>
<b>6. References .....</b>	<b>21</b>
<b>Annexes.....</b>	<b>23</b>
Annex 1: Algorithm for LF-LAM use.....	23
Annex 2: List of studies included in the systematic review .....	25
Annex 3: Conflict of interest assessment for GDG members and ERG members .....	27

**Title: Web Annex A.** LF-LAM for detecting active tuberculosis in people living with HIV: an updated systematic review

<https://apps.who.int/iris/bitstream/handle/10665/329510/WHO-CDS-TB-2019.17-eng.pdf>

File size: 2.2Mb

**Title: Web Annex B.** GRADE profiles (evidence tables)

<https://apps.who.int/iris/bitstream/handle/10665/329511/WHO-CDS-TB-2019.18-eng.pdf>

File size: 89.4Kb

**Title: Web Annex C.** Economic evaluations of LF-LAM for the diagnosis of active tuberculosis in HIV-positive individuals: an updated systematic review

<https://apps.who.int/iris/bitstream/handle/10665/329512/WHO-CDS-TB-2019.19-eng.pdf>

File size: 1.1Mb

**Title: Web Annex D.** User perspectives on TB-LAM for the diagnosis of active tuberculosis: results from qualitative research

<https://apps.who.int/iris/bitstream/handle/10665/329513/WHO-CDS-TB-2019.20-eng.pdf>

File size: 1.0Mb

**Title: Web Annex E.** Evidence to decision tables

<https://apps.who.int/iris/bitstream/handle/10665/329514/WHO-CDS-TB-2019.21-eng.pdf>

File size: 1.9Mb

## Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
AlereLAM	Alere Determine™ TB LAM Ag
ART	antiretroviral therapy
COI	conflict of interest
CrI	credible interval
CV	curriculum vitae
DOI	declaration of interests
EtD	evidence-to-decision
FIND	Foundation for Innovative New Diagnostics
FujiLAM	Fujifilm SILVAMP TB LAM
GDG	Guideline Development Group
GDP	gross domestic product
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
ICER	incremental cost–effectiveness ratio
LAM	lipoarabinomannan
LF-LAM	lateral flow urine lipoarabinomannan assay
PICO	population, intervention, comparison, outcome
PLHIV	people living with HIV
QUADAS	quality assessment of diagnostic accuracy studies
TB	tuberculosis
USA	United States of America
USAID	United States Agency for International Development
WHO	World Health Organization
WTP	willingness to pay

## Key definitions

**Age groups:** the following definitions for adults, adolescents and children are used in these guidelines for the purpose of implementing recommendations (countries may have other definitions under their national regulations):

- an **adult** is a person older than 19 years of age;
- an **adolescent** is a person 10–19 years of age inclusive; and
- a **child** is a person under 10 years of age.

**Grading of Recommendations Assessment, Development and Evaluation (GRADE)** is a system for rating quality of evidence and strength of recommendations; the GRADE approach is explicit, comprehensive, transparent and pragmatic, and is increasingly being adopted by organizations worldwide.

**Inpatient health care setting** is a health care facility where patients are admitted and assigned a bed while undergoing diagnosis and receiving treatment and care, for at least one overnight stay.

**Outpatient health care setting** is a health care facility where patients are undergoing diagnosis and receiving treatment and care but are not admitted for an overnight stay (e.g. an ambulatory clinic or a dispensary).

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Technical editing was provided by **Hilary Cadman**, Cadman Editing Services, Australia.

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## Executive summary

### Background

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The World Health Organization's (WHO's) strategy for tuberculosis (TB) prevention, care and control for 2015–2035 (known as the End TB Strategy) prioritizes the early diagnosis of TB (1). This prioritization includes cases of smear-negative disease, which are often associated with coinfection with HIV and with young age. In 2017, an estimated 0.9 million (9%) of the 10.0 million people who developed TB worldwide were HIV-positive. The WHO African Region accounted for 72% of the estimated number of HIV-positive incident TB cases (2).

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for TB. The currently available urinary LAM assays have suboptimal sensitivity, and are therefore not suitable as diagnostic tests for TB in all populations. However, unlike traditional diagnostic methods, urinary LAM assays demonstrate improved sensitivity for the diagnosis of TB among individuals coinfecting with HIV. The estimated sensitivity is even greater in patients with lower CD4 cell counts. Currently, the urine lateral flow LAM assay (LF-LAM) strip-test – the Alere Determine™ TB LAM Ag, United States of America (USA), hereafter referred to as AlereLAM – is the only commercially available urinary LAM test.

The Global TB Programme convened a Guideline Development Group (GDG) meeting in 2015 to review the evidence for the use of LF-LAM (AlereLAM). The GDG concluded that LF-LAM may be used to assist in the diagnosis of TB only in HIV-positive adults and children with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/ $\mu$ L, or HIV-positive patients who are seriously ill<sup>1</sup> regardless of CD4 cell count or with unknown CD4 cell count.

Since 2015, several studies on the use of AlereLAM assay have been conducted. New evidence has emerged that might justify use of the test in a broader group of patients. In addition, a new urine-based test – the Fujifilm SILVAMP TB LAM, Tokyo, Japan (FujiLAM) – has been developed and preliminary evaluation shows promising results; however, FujiLAM is not yet commercially available.

### Objectives

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The objectives of the current policy update are to:

- assess the available data on the accuracy (sensitivity and specificity) of LF-LAM for diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB; in individuals irrespective of signs and symptoms of TB; and in individuals with advanced HIV disease;<sup>2</sup>
- assess the available data related to the impact of LF-LAM's implementation on mortality and other outcomes that are important to patients;
- collect and review *economic data* on affordability, cost and cost-effectiveness of the use of LF-LAM, to assist in the diagnosis of TB;
- collect and review *end-user data* on feasibility, acceptability and equity of the use of LF-LAM, to assist in the diagnosis of TB; and
- outline issues to be addressed by WHO in subsequent policy recommendations.

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1 "Seriously ill" is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided.

2 For adults, adolescents, and children aged 5 years or more, "advanced HIV disease" is defined as a CD4 cell count of less than 200 cells/ $\text{mm}^3$  or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV who are aged under 5 years should be considered as having advanced disease at presentation.

## Methods used to develop these guidelines

The Global TB Programme initiated an update of the current guidelines and commissioned a systematic review for the use of LF-LAM (all studies refer to AlereLAM unless otherwise specified, as the sole commercially available LF-LAM assay at the time of the review) for the diagnosis of TB in people living with HIV (PLHIV), in collaboration with the WHO Department of HIV/AIDS and Global Hepatitis Programme.

The systematic review provided a summary of current literature on the accuracy of AlereLAM as a diagnostic test, which may be used in combination with other recommended tests, for the diagnosis of TB in adults living with HIV, in line with WHO guideline development processes. The data on adolescents and children were analyzed and reported separately whenever possible.

Evidence for the use of FujiLAM assay (not yet commercially available) was generated through a study conducted by the Foundation for Innovative New Diagnostics (FIND) assessing the test's diagnostic accuracy on stored frozen urine samples from HIV-positive people from Ghana, South Africa and Viet Nam. Diagnostic accuracy was determined against microbiological and composite reference standards in comparison with AlereLAM.

The Global TB Programme convened a GDG meeting on 14–16 May 2019, in Geneva, Switzerland, to review the evidence for the use of LF-LAM. The meeting was chaired by an expert in evidence synthesis. Recommendations were developed, based on consensus among the GDG members, where possible. When it was not possible to reach consensus, then voting took place. See more details in **Online Annex 5** for details on voting.

The draft was also reviewed by the External Review Group, to identify any errors or omissions and to collect comments on clarity, setting-specific issues and implications for implementation.

The GDG also reviewed data on the use of FujiLAM. The GDG acknowledged that initial results of the assay on stored frozen urine samples from HIV-positive people are promising, with pooled sensitivity about 30% higher than AlereLAM. Prospective studies evaluating the diagnostic accuracy of FujiLAM for TB in PLHIV are underway. However, currently, FujiLAM is not commercially available; data on price, cost and cost-effectiveness are not available; and there are no studies providing evidence on the feasibility and acceptability of FujiLAM in settings of intended use. Hence, **the panel was not able to develop recommendations on FujiLAM assay.**

The WHO policy recommendations developed from the evidence synthesis process by the GDG are summarized below.

## WHO policy recommendations

**In inpatient settings**, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [1];<sup>3</sup> or
- with advanced HIV disease<sup>4</sup> or who are seriously ill<sup>5</sup> (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [1]; or

<sup>3</sup> Numbers in square brackets indicate the number of the relevant “evidence-to-decision” (EtD) table.

<sup>4</sup> For adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV aged under 5 years should be considered as having advanced disease at presentation.

<sup>5</sup> “Seriously ill” is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided.

- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm<sup>3</sup> (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [2].

**In outpatient settings,** WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (**conditional** recommendation; low certainty in the evidence about test accuracy) [3]; and
- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm<sup>3</sup> (**conditional** recommendation; very low certainty in the evidence about test accuracy) [4].

**In outpatient settings,** WHO recommends **against** using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- without assessing TB symptoms (**strong** recommendation; very low certainty in the evidence about test accuracy) [5];
- without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm<sup>3</sup> (**strong** recommendation; very low certainty in the evidence about test accuracy) [6]; and
- without TB symptoms and with a CD4 cell count of 100–200 cells/mm<sup>3</sup> (**conditional** recommendation; very low certainty in the evidence about test accuracy) [7].

### Remarks

- a. The reviewed evidence and recommendations apply to the use of AlereLAM only, because other in-house LAM-based assays have not been adequately validated or used outside limited research settings. Any new or generic LAM-based assay should be subject to adequate validation in the settings of intended use.
- b. All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have as their initial diagnostic test at least one sputum specimen submitted for Xpert<sup>®</sup> MTB/RIF (Ultra) assay. This also includes children and adolescents living with HIV who are able to provide a sputum sample.
- c. These recommendations also apply to adolescents and children living with HIV, based on generalization of data from adults, while acknowledging very limited data for these population groups.
- d. LF-LAM should be used as an add-on to clinical judgement in combination with other tests. It should not be used as a replacement or triage test. More details are given in **Annex 1. Algorithms for LF-LAM use.**

## Summary of changes in the evidence-based recommendations between the 2015 guidance and the 2019 update

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)	Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update (2019)	Changes
<p>LF-LAM may be used to assist in the diagnosis of TB in HIV positive adult <b>in-patients</b> with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/<math>\mu</math>L, or HIV positive patients who are seriously ill<sup>a</sup> regardless of CD4 cell count or with unknown CD4 cell count (<b>conditional recommendation; low quality of evidence</b>).</p>	<p><b>In inpatient settings</b>, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• with signs and symptoms of TB (pulmonary and/or extrapulmonary) (<b>strong recommendation; moderate certainty in the evidence about the intervention effects</b>); or</li> <li>• with advanced HIV disease<sup>b</sup> or who are seriously ill (<b>strong recommendation; moderate certainty in the evidence about the intervention effects</b>); or</li> <li>• irrespective of signs and symptoms of TB and with a CD4 cell count &lt; 200 (<b>strong recommendation; moderate certainty in the evidence about the intervention effects</b>).</li> </ul>	<p>Increased strength of the recommendation.</p> <p>Improved quality of evidence.</p> <p>Increased scope of the recommendation:</p> <ul style="list-style-type: none"> <li>– all symptomatic or seriously ill inpatients, irrespective of CD4 cell count;</li> <li>– all inpatients with advanced HIV disease; and</li> <li>– inpatients with or without signs and symptoms of TB who have a CD4 cell count &lt; 200.</li> </ul>
<p>This recommendation also applies to HIV positive adult out-patients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/<math>\mu</math>L, or HIV positive patients who are seriously ill regardless of CD4 cell count or with unknown CD4 cell count, based on the generalization of data from in-patients.</p>	<p><b>In outpatient settings</b>, WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (<b>conditional recommendation; low certainty in the evidence about test accuracy</b>); and</li> <li>• irrespective of signs and symptoms of TB and with a CD4 cell count &lt; 100 (<b>conditional recommendation; very low certainty in the evidence about test accuracy</b>).</li> </ul>	<p>Increased scope of the recommendation:</p> <ul style="list-style-type: none"> <li>– all outpatients with signs and symptoms of TB or seriously ill; and</li> <li>– outpatients with a CD4 cell count &lt; 100, irrespective of signs and symptoms of TB.</li> </ul>

<p>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)</p>	<p>Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update (2019)</p>	<p>Changes</p>
<p>Except as specifically described below for persons with HIV infection with low CD4 cell counts or who are seriously ill, LF-LAM should not be used for the diagnosis of TB (<b>strong recommendation, low quality of evidence</b>).</p>	<p><b>In outpatient settings</b>, WHO recommends <b>against</b> using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• without assessing TB symptoms (<b>strong recommendation; very low certainty in the evidence about test accuracy</b>);</li> <li>• without TB symptoms and unknown CD4 cell count, or without TB symptoms and CD4 cell count <math>\geq 200</math> (<b>strong recommendation; very low certainty in the evidence about test accuracy</b>); or</li> <li>• without TB symptoms and with a CD4 cell count of 100–200 (<b>conditional recommendation; very low certainty in the evidence about test accuracy</b>).</li> </ul>	<p>Better definition of patient populations for negative recommendation against use of LF-LAM.</p>
<p>LF-LAM should not be used as a screening test for TB. (<b>strong recommendation, low quality of evidence</b>).</p>	<p>See inpatient and outpatient recommendations above for situations in which LF-LAM is suggested for use among individuals, irrespective of signs and symptoms of TB.</p> <p>See outpatient recommendations above for situations in which WHO recommends <b>against</b> LF-LAM use.</p>	<p>Clarification of recommendation for usage among individuals with and without TB signs and symptoms (i.e. irrespective of signs and symptoms):</p> <ul style="list-style-type: none"> <li>– LF-LAM is strongly recommended for inpatients with advanced HIV disease, and individuals with a CD4 cell count <math>&lt; 200</math>, irrespective of symptoms; and</li> <li>– LF-LAM is suggested for outpatients with a CD4 cell count <math>&lt; 100</math>, irrespective of symptoms.</li> </ul> <p>See above for patient populations with a recommendation <b>against</b> usage.</p>

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)	Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. Policy update (2019)	Changes
<p>This recommendation also applies to HIV positive children with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults while acknowledging very limited data and concern regarding low specificity of the LF-LAM assay in children.</p>	<p>These recommendations also apply to adolescents and children living with HIV, based on generalization of data from adults, while acknowledging that data for these population groups are limited.</p>	

HIV: human immunodeficiency virus; LF-LAM: lateral flow urine lipoarabinomannan assay; TB: tuberculosis; WHO: World Health Organization.

<sup>a</sup> “Seriously ill” is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided.

<sup>b</sup> For adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV who are aged under 5 years should be considered as having advanced disease at presentation.

## 1. Introduction

### 1.1. Background

---

The World Health Organization's (WHO's) strategy for tuberculosis (TB) prevention, care and control for 2015–2035 (known as the End TB Strategy) prioritizes the early diagnosis of TB (1). This prioritization includes cases of smear-negative disease, which are often associated with coinfection with HIV and with young age. In 2017, an estimated 0.9 million (9%) of the 10.0 million people who developed TB worldwide were HIV-positive. The WHO African Region accounted for 72% of the estimated number of HIV-positive incident TB cases (2).

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests for TB. The currently available urinary LAM assays have suboptimal sensitivity, and are therefore not suitable as general diagnostic tests for TB. However, unlike traditional diagnostic methods, they demonstrate improved sensitivity for the diagnosis of TB among individuals coinfecting with HIV. The estimated sensitivity is even greater in patients with low CD4 cell counts. Currently, the urine lateral flow LAM assay (LF-LAM) strip-test – the Alere Determine™ TB LAM Ag, United States of America (USA), hereafter referred to as AlereLAM – is the only commercially available urinary LAM test, which potentially could be used as a rule-in test for TB in patients with advanced HIV-induced immunosuppression, and facilitate the early initiation of anti-TB treatment.

The Global TB Programme convened a Guideline Development Group (GDG) meeting in 2015, to review the evidence for the use of LF-LAM (AlereLAM). The GDG concluded that LF-LAM may be used to assist in the diagnosis of TB only in HIV-positive adult inpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/ $\mu$ L, or HIV-positive patients who are seriously ill,<sup>6</sup> regardless of CD4 cell count or with unknown CD4 cell count.

Since 2015, several studies on the use of the AlereLAM assay have been conducted. New evidence has emerged that might justify use of the test in a broader group of patients. In addition, a new urine-based test – the Fujifilm SILVAMP TB LAM, Tokyo, Japan (FujiLAM) – has been developed. Preliminary evaluation of the FujiLAM test showed promising results, with pooled sensitivity in HIV-positive individuals being about 30% higher than with AlereLAM.

### 1.2. Scope of the document

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The current document provides the background, justification and objectives for the revision of WHO policy on LF-LAM. It provides details on the index test (AlereLAM) being assessed. It also describes the process of evidence retrieval, quality assessment and grading; formulation of the recommendations; and GDG decision-making. Finally, the document presents policy recommendations and related remarks.

The GDG also reviewed data on the use of FujiLAM. The group acknowledged that initial results of the assay on stored frozen urine samples from HIV-positive people are promising, with pooled sensitivity about 30% higher than with AlereLAM. Prospective studies evaluating the diagnostic accuracy of FujiLAM for TB in people living with HIV (PLHIV) are underway. FujiLAM is not commercially available at present; data on price, cost and cost-effectiveness are not available; and there are no studies providing evidence on the feasibility and acceptability of FujiLAM in settings of intended use. **Hence, the panel was not able to develop recommendations on the FujiLAM**

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6 “Seriously ill” is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided.

**assay.**

The GDG can be reconvened, and recommendations developed, when the FujilAM assay becomes commercially available, and additional data on its diagnostic accuracy, and evidence on feasibility and acceptability from settings of intended use have been generated.

The WHO policy recommendations developed from the evidence synthesis process by the GDG are presented in Section 2.10.

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**1.3. Target audience**

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The target audience for this review includes policy-makers, clinicians and other health care staff, HIV and TB programme managers, technical agencies, donors and implementing partners supporting the use of TB diagnostics in resource-limited settings.

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**1.4. Objectives**

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The objectives of the current policy update are to:

- assess the available data on the accuracy (sensitivity and specificity) of LF-LAM for diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB; in individuals irrespective of signs and symptoms of TB; and in individuals with advanced HIV disease;<sup>7</sup>
- assess the available data related to the impact of LF-LAM's implementation on mortality and other outcomes that are important to patients;
- collect and review *economic data* on affordability, cost and cost-effectiveness of the use of LF-LAM, to assist in the diagnosis of TB;
- collect and review *end-user data* on feasibility, acceptability and equity of the use of LF-LAM, to assist in the diagnosis of TB; and
- outline issues to be addressed by WHO in subsequent policy recommendations.

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**1.5 Index test**

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The urine-based LF-LAM AlereLAM is a commercially available point-of-care test for active TB (Alere Determine™ TB LAM Ag). AlereLAM is an immunocapture assay that detects LAM antigen in urine, LAM being a lipopolysaccharide present in mycobacterial cell walls (3) that is released from metabolically active or degenerating bacterial cells during TB disease (4). Several hypotheses may explain the higher sensitivity of urine LAM detection in PLHIV, including higher bacillary burden and antigen load (5), greater likelihood of genitourinary tract TB involvement and greater glomerular permeability that leads to increased antigen levels in urine (6, 7).

AlereLAM is performed manually by applying 60 µL of urine to the test strip (the white pad marked by the arrow symbols in Fig. 1A) and incubating at room temperature for 25 minutes. The strip is then inspected by eye to look for visible bands. The intensity of any visible band on the test strip is graded by comparing it with the intensities of the bands on a manufacturer-supplied reference scale card (as shown in the example in Fig. 1B). Until January 2014, the reference scale card included five bands (Grade 1 representing a very low intensity band, to Grade 5 representing a

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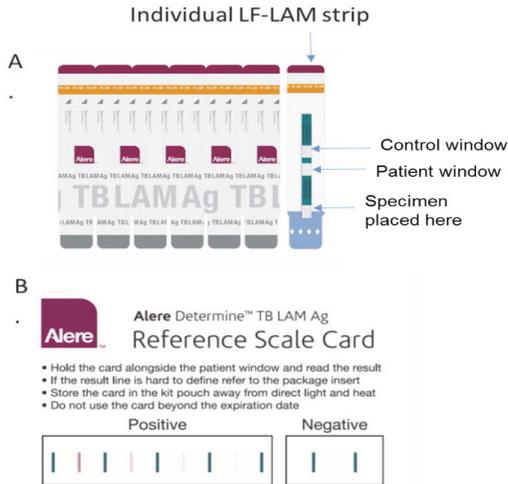
7 For adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV who are aged under 5 years should be considered as having advanced disease at presentation.

high/dark intensity band). Some studies before January 2014 used Grade 1 as the threshold for test positivity, whereas others used Grade 2 as the positivity threshold. After January 2014, the manufacturer revised the reference scale card to have four reference bands, such that the band intensity for the new Grade 1 corresponds to the band intensity for the previous Grade 2. Under the current manufacturer recommendations (using the current reference card with four bands), all bands that are Grade 1 or higher are considered positive (8).

**Fig. 1. Alere Determine™ TB LAM Ag tests (AlereLAM)**

(A) Individual test strip; (B) Reference card accompanying test strips to “grade” the test result and determine positivity.

Copyright© (2019) Abbott Inc: reproduced with permission (8).



## 2. Methods

### 2.1. Preparation for evidence assessment

The Global TB Programme has initiated an update of the current guidelines, and commissioned a systematic review of the use of LF-LAM for the diagnosis of TB in PLHIV, in collaboration with the WHO HIV/AIDS and Hepatitis Department.

The population, intervention, comparison and intervention (PICO) questions were designed to form the basis for the evidence search, retrieval and analysis. These questions are shown in Box 1.

#### Box 1: PICO questions

##### ***I. What is the diagnostic accuracy of LF-LAM for the diagnosis of TB in all HIV-positive adults and children with signs and symptoms of TB?***

- a. in inpatient settings (adults, adolescents and older children)
- b. in outpatient settings (adults, adolescents and older children)
- c. in all settings (adults, adolescents and older children)
- d. in inpatient settings (children  $\leq$  5 years)
- e. in outpatient settings (children  $\leq$  5 years)
- f. in all settings (children  $\leq$  5 years)

##### ***II. What is the diagnostic accuracy of LF-LAM for the diagnosis of TB in all HIV-positive adults and children irrespective of signs and symptoms of TB?***

- a. in inpatient settings (adults, adolescents and older children)
- b. in outpatient settings (adults, adolescents and older children)
- c. in all settings (adults, adolescents and older children)
- d. in inpatient settings (children  $\leq$  5 years)
- e. in outpatient settings (children  $\leq$  5 years)
- f. in all settings (children  $\leq$  5 years)

##### ***III. What is the diagnostic accuracy of LF-LAM for the diagnosis of TB in adults with advanced HIV disease irrespective of signs and symptoms of TB?***

- a. in inpatient settings CD4 cell count  $\leq$  200
- b. in outpatient settings CD4 cell count  $\leq$  200
- c. in all settings CD4 cell count  $\leq$  200
- d. in inpatient settings CD4 cell count  $\leq$  100
- e. in outpatient settings CD4 cell count  $\leq$  100
- f. in all settings CD4 cell count  $\leq$  100

**IV. Can the use of LF-LAM in HIV-positive adults reduce mortality associated with advanced HIV disease?**

- a. in all settings
- b. in inpatient settings
- c. in outpatient settings
- d. in individuals with CD4 cell count  $\leq 200$
- e. in inpatient settings CD4 cell count  $\leq 200$
- f. in outpatient settings CD4 cell count  $\leq 200$
- g. in individuals with CD4 cell count  $\leq 100$
- h. in inpatient settings CD4 cell count  $\leq 100$
- i. in outpatient settings CD4 cell count  $\leq 100$

**Additional questions:**

- 1. What are the comparative cost, affordability and cost-effectiveness of implementation of LF-LAM (AlerelAM versus FujiLAM)? – based on review of the published literature and estimations.
- 2. Are there possible implications for patient equity from the implementation of LF-LAM (AlerelAM versus FujiLAM)? – based on review of the published literature and estimations.
- 3. What are the human rights implications from the implementation of LF-LAM? – based on review of the published literature and comparative analysis of the two available LF-LAM (AlerelAM versus FujiLAM).

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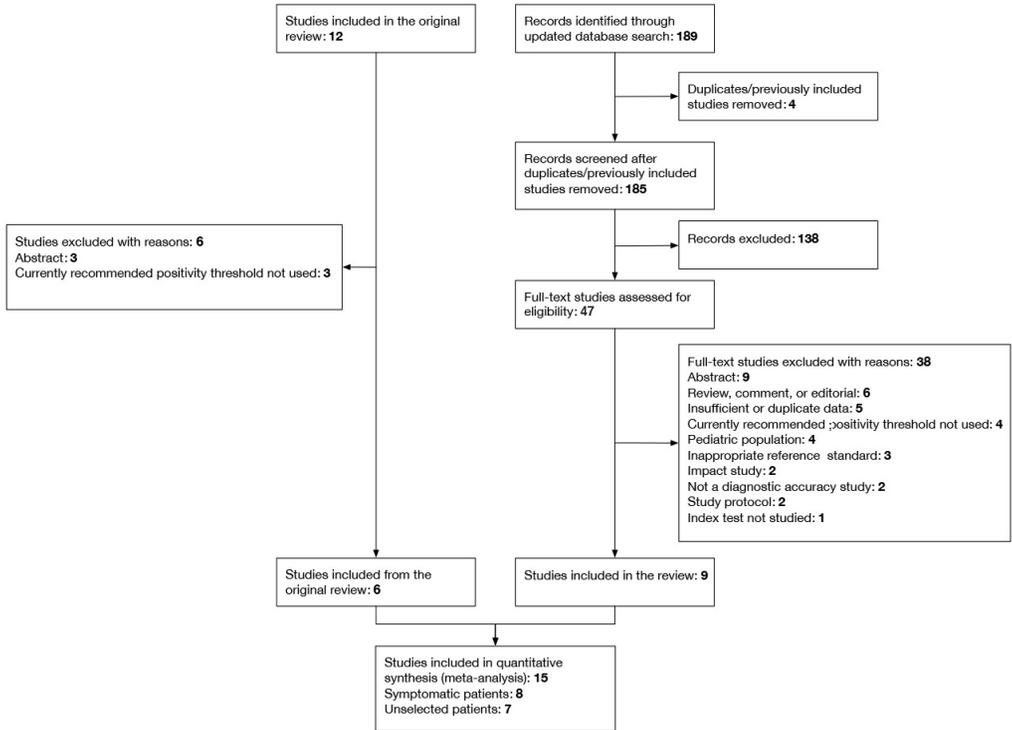
**2.2. Evidence retrieval, quality assessment and grading of the evidence**

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This systematic review summarizes the current literature on the accuracy of the AlerelAM for the diagnosis of TB in PLHIV as part of a WHO process to develop updated guidelines for use of the AlerelAM assay. AlerelAM is being considered as a diagnostic test that may be used in combination with existing tests for the diagnosis of HIV-associated TB. The data on children are reported separately from adults.

The review identified 15 unique published studies that assessed the accuracy of AlerelAM in adults, and integrated nine new studies identified since the original WHO and Cochrane reviews in 2015 and 2016, respectively (9, 10). The studies that evaluated AlerelAM in participants with signs and symptoms of TB were classified as “studies with symptomatic participants”, and studies that included both individuals with symptoms of TB and individuals without symptoms of TB (i.e. enrolled irrespective of symptoms) were classified as “studies with unselected participants”. All studies were performed in TB/HIV high burden countries. The positive AlerelAM results were reported in accordance with the manufacturer’s updated recommendations for test interpretation (graded on a scale of 1 to 4, based on band intensity). The sensitivity and specificity were evaluated at the Grade 1 cut-off for positivity on the updated reference scale card (corresponding to Grade 2 on the prior reference scale card, which had band intensities graded on a scale of 1 to 5). All analyses were performed with respect to a microbiological reference standard.

Details of studies included in the current analysis are given in **Annex 2**.

**Fig. 2. Flow chart of studies in the review**

The quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool tailored to this review was used to assess the quality of the included studies (11). The tool consists of four domains: patient selection, index test, reference standard, and flow and timing (the flow and timing domain includes differential verification of TB status for study participants). All domains were assessed for risk of bias, and the first three domains were assessed for concerns regarding applicability. Initially, guidance was developed on how to appraise the questions in each domain, after which one review author piloted the tool with two of the included studies, and finalized the QUADAS-2 tool. Two review authors independently completed the QUADAS-2 assessments. Any disagreements were resolved through discussion or consultation with a third review author.

More details on evidence quality assessment are given in **Online Annex 1. Report of the systematic review: LF-LAM assay for detecting active tuberculosis in people living with HIV: an updated systematic review**

Evidence for the use of FujilAM assay was generated through a Foundation for Innovative New Diagnostics (FIND) study assessing the test's diagnostic accuracy on stored frozen urine samples from PLHIV from Ghana, South Africa and Viet Nam. Diagnostic accuracy was determined against microbiological reference standards (MRS) and composite reference standards (CRS), including clinical diagnoses, in comparison with AlerelAM.

### 2.3. Findings

The 15 included studies involved 6814 participants, of whom 1761 (26%) had TB. Eight of the studies evaluated the accuracy of AlerelAM for TB diagnosis in participants with signs and symptoms suggestive of TB; these studies involved 3449 participants, of whom 1277 (37%) had

TB. Seven studies evaluated the accuracy of AlereLAM for diagnosis of unselected participants who may or may not have had TB signs and symptoms at enrolment; these studies involved 3365 participants, of whom 439 (13%) had TB.

All studies were performed in high TB/HIV burden countries that were classified as low-income or middle-income countries. The studies had substantial differences in the following characteristics: study population (“studies with symptomatic participants” and “studies with unselected participants”), setting (inpatients versus outpatients), median CD4 cell count, TB prevalence, inclusion and exclusion of participants based on whether or not they could produce sputa, and whether patients were evaluated for pulmonary TB, extrapulmonary TB, or both.

Most studies reported that a valid AlereLAM result was obtained on the first attempt for all tests. Uninterpretable test results (< 1%) were reported in only three studies (12-14).

### 2.4. Summary of the results

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For TB diagnosis in HIV-positive adults presenting with signs and symptoms of TB, the diagnostic accuracy of AlereLAM is as follows:

- in *inpatient* settings, sensitivity 52% (40–64%)<sup>8</sup> and specificity 87% (78–93%) (PICO 1a);
- in *outpatient* settings, sensitivity 29% (17–47%) and specificity 96% (91–99%) (PICO 1b); and
- in *all* settings, sensitivity 42% (31–55%) and specificity 91% (85–95%) (PICO 1c).

For TB diagnosis in HIV-positive adults, irrespective of signs and symptoms of TB, the diagnostic accuracy of AlereLAM is as follows:

- in *inpatient* settings, sensitivity 62% (41–83%) and specificity 84% (48–96%) (PICO 2a);
- in *outpatient* settings, sensitivity 31% (18–47%) and specificity 95% (87–99%) (PICO 2b); and
- in *all* settings, sensitivity 35% (22–50%) and specificity 95% (89–98%) (PICO 2c).

For diagnosis of TB in adults with advanced HIV disease, irrespective of signs and symptoms of TB, the diagnostic accuracy of AlereLAM (limited data available) is as follows:

- in *inpatient* settings CD4 cell count  $\leq 200$ , sensitivity of 64% (35–87%) and specificity 82% (67–93%) (one study, PICO 3a);
- in *outpatient* settings CD4 cell count  $\leq 200$ , sensitivity 21% (8–48%) and specificity 96% (89–99%) (PICO 3b);
- in *all* settings CD4 cell count  $\leq 200$ , sensitivity 26% (9–56%) and specificity 96% (87–98%) (PICO 3c);
- in *inpatient* settings CD4 cell count  $\leq 100$ , sensitivity 57% (33–79%) and specificity 90% (69–97%) (PICO 3d);
- in *outpatient* settings CD4 cell count  $\leq 100$ , sensitivity 40% (20–64%) and specificity 87% (68–94%) (PICO 3e); and
- in *all* settings CD4 cell count  $\leq 100$ , sensitivity 47% (30–64%) and specificity 90% (77–96%) (PICO 3f).

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<sup>8</sup> Numbers in brackets shown 95% credible interval (CrI).

For diagnosis of TB in HIV-positive children, the diagnostic accuracy of AlereLAM (limited data available) is as follows:

- in *all* settings, including all children, for individual studies, sensitivity and specificity were:
- 42% (15–72%) and 94% (73–100%) (one study conducted in an outpatient setting);
- 56% (21–86%) and 95% (90–98%) (one study conducted in an inpatient setting); and
- 43% (23–66%) and 80% (69–88%) (one study conducted in both inpatient and outpatient settings).

For use of AlereLAM to reduce mortality associated with advanced HIV disease (two randomized trials):

- the pooled risk ratio for mortality was 0.85 (0.76–0.94); and
- the absolute effect was 35 fewer deaths per 1000 (from 14 fewer to 55 fewer) (PICO 4).

Table 1 presents pooled sensitivity and specificity results for AlereLAM against a microbiological reference standard grouped by the study population, TB diagnosis among “symptomatic participants” and TB diagnosis among “unselected participants”.

**Table 1. AlereLAM pooled sensitivity and specificity for TB diagnosis, by study population**

Type of analysis	Symptomatic participants				Unselected participants			
	Studies (total participants)	Participants with TB (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)	Studies (total participants)	Participants with TB (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
Overall accuracy	8 studies (3449)	1277 (37%)	42% (31–55%)	91% (85–95%)	7 studies (3365)	432 (13%)	35% (22–50%)	95% (89–98%)
<b>By setting</b>								
Inpatient	6 studies (2253)	868 (39%)	52% (40–64%)	87% (78–93%)	3 studies (537)	159 (30%)	62% (41–83%)	84% (48–96%)
Outpatient	4 studies (1196)	409 (34%)	29% (17–47%)	96% (91–99%)	6 studies (2828)	273 (10%)	31% (18–47%)	95% (87–99%)
<b>By CD4 cell count</b>								
CD4 > 200	3 studies (738)	163 (22%)	16% (8–31%)	94% (81–97%)	1 study <sup>a</sup> (156)	11 (7%)	Not applicable	Not applicable
CD4 ≤ 200	4 studies (1825)	722 (40%)	45% (31–61%)	89% (77–94%)	2 studies (706)	82 (12%)	26% (9–56%)	96% (87–98%)
CD4 > 100	4 studies (1519)	425 (28%)	17% (10–27%)	95% (89–98%)	4 studies (952)	115 (12%)	20% (10–35%)	98% (95–99%)

Type of analysis	Symptomatic participants				Unselected participants			
	Studies (total participants)	Participants with TB (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)	Studies (total participants)	Participants with TB (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
CD4 ≤ 100	4 studies (1239)	512 (41%)	54% (38–69%)	88% (77–94%)	3 studies (417)	130 (31%)	47% (40–64%)	90% (77–96%)
CD4 101–200	4 studies (586)	210 (36%)	24% (14–38%)	90% (77–96%)	1 study <sup>b</sup> (103)	13 (13%)	Not applicable	Not applicable
<b>By CD4 and setting</b>								
CD4 ≤ 200 inpatients	2 studies (1009)	348 (34%)	54% (34–73%)	80% (58–91%)	1 study <sup>c</sup> (54)	14 (26%)	Not applicable	Not applicable
CD4 ≤ 100 inpatients	2 studies (734)	270 (37%)	61% (40–78%)	81% (61–91%)	2 studies (200)	84 (42%)	57% (33–79%)	90% (69–97%)
CD4 101–200 inpatients	2 studies (275)	78 (28%)	32% (16–57%)	81% (55–92%)	1 study <sup>d</sup> (9)	4 (44%)	Not applicable	Not applicable
CD4 ≤ 200 outpatients	1 study <sup>f</sup> (249)	97 (39%)	Not applicable	Not applicable	2 studies (652)	68 (10%)	21% (8–48%)	96% (89–99%)
CD4 ≤ 100 outpatients	1 study <sup>g</sup> (121)	48 (40%)	Not applicable	Not applicable	2 studies (217)	46 (21%)	40% (20–64%)	87% (68–94%)
CD4 101–200 outpatients	1 study <sup>h</sup> (128)	51 (40%)	Not applicable	Not applicable	1 study <sup>e</sup> (94)	9 (10%)	Not applicable	Not applicable

AlerLAM: Alere Determine™ TB lipoarabinomannan assay; CrI: credible interval; TB: tuberculosis.

<sup>a</sup> Bjerrum (2015) (15), sensitivity 27% (6–61%); specificity 99% (96–100%).

<sup>b</sup> Bjerrum (2015) (15), sensitivity 38% (14–68%); specificity 99% (94–100%).

<sup>c</sup> Bjerrum (2015) (15), sensitivity 64% (35–87%); specificity 82% (67–93%).

<sup>d</sup> Bjerrum (2015) (15), sensitivity 75% (19–99%); specificity 100% (48–100%).

<sup>e</sup> Bjerrum (2015) (15), sensitivity 22% (3–60%); specificity 99% (94–100%).

<sup>f</sup> Peter (2015) (12), sensitivity 24% (16–33%); specificity 94% (89–97%).

<sup>g</sup> Peter (2015) (12), sensitivity 30% (18–46%); specificity 93% (85–98%).

<sup>h</sup> Peter (2015) (12), sensitivity 18% (8–31%); specificity 95% (87–99%).

More details on the findings are given in **Online Annex 1: Report of the systematic review: Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV: an updated systematic review.**

The extracted evidence and the results of the quality assessment were structured into Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles, based on each PICO question; details are given in **Online Annex 2: GRADE profiles (Evidence tables).**

## 2.5. Economic evaluations of the LF-LAM for diagnosis of active TB in HIV-positive individuals

A systematic review of economic evaluations on the urine-based LF-LAM for the diagnosis of active TB in HIV-positive individuals was carried out. The objective of this review was to summarize current evidence and understand the costs, cost-effectiveness and affordability (in terms of budget impact) of LF-LAM implementation for the diagnosis of TB among HIV-positive populations. Six studies, all from settings in sub-Saharan Africa, were identified. Study methods and populations were heterogeneous, assessing a range of diagnostic algorithms, and only four studies assessed cost-effectiveness. The research focused exclusively on the use of AlereLAM, as the only commercially available LF-LAM.

Economic evidence for the implementation and scale-up of LF-LAM is limited. The studies that have been done show a consistent trend, suggesting that LF-LAM could be cost-effective in a population of African adults living with HIV (particularly among hospitalized patients). Willingness to pay (WTP) thresholds used across the four cost-effectiveness studies varied, with two studies in South Africa and Uganda employing per capita gross domestic product (GDP) thresholds, one study in Mozambique using three times per capita GDP, and the most recently published study using the incremental cost-effectiveness ratios (ICERs) of second-line antiretroviral therapy (ART). With only a few studies identified and differences in modelling approaches, assumptions, diagnostic algorithms assessed, analytical techniques and study settings, generalizing from these studies to other settings is difficult.

Three studies assessed cost-effectiveness among hospitalized HIV-positive adults. All of these studies suggested that LF-LAM containing algorithms could be cost-effective across the countries and models evaluated including Malawi, South Africa and Uganda.

Only one study specifically assessed cost-effectiveness in outpatient populations, and another assessed cost-effectiveness in a mixed inpatient and outpatient population. Thus, evidence for the cost-effectiveness of LF-LAM among outpatient settings is even more limited than for inpatients. However, both analyses suggested that LF-LAM containing algorithms could be cost-effective within the settings evaluated (Mozambique and Uganda) and given the studies' chosen WTP threshold (threefold GDP and GDP, respectively).

In sensitivity analyses, models found that LF-LAM remained cost-effective across most of the variables and scenarios evaluated. The inclusion of costs associated with consequential ART and HIV care led to increased ICERs because TB diagnostic costs represent only a small proportion of the overall health care costs for PLHIV. Additional key parameters that are likely to influence cost-effectiveness include TB prevalence and diagnostic yield, target population and LF-LAM specificity, cost of treating TB and HIV and life expectancy post TB survival, and time horizon. There is uncertainty around costs. The only detailed micro-costing study published in 2018 estimates the cost of a unit test for LF-LAM implementation at US\$ 23, several fold higher than the estimates used in the cost-effectiveness analyses (US\$ 2–4). These costs were driven in part by the site cost that is required to ensure quality implementation of point-of-care tests. Furthermore, this study was conducted in outpatient settings only, and detailed micro-costing concerning implementation of LF-LAM algorithms for hospitalized patients has not yet been conducted.

Current evidence is consistent in suggesting that LF-LAM is likely to be cost-effective among hospitalized people who are HIV-positive, with or without TB symptoms in sub-Saharan Africa. Nevertheless, caution should be used when extrapolating from a small number of studies, and additional local evidence and economic evaluation may be necessary as countries decide whether to roll out LF-LAM for different population groups.

More details on economic evaluations of the test are given in **Online Annex 3: Economic Evaluations of the Lateral Flow Urine Lipoarabinomannan Assay for Diagnosis of Active Tuberculosis in HIV-positive Individuals: An Updated Systematic Review.**

## 2.6. User perspectives on LF-LAM testing: results from qualitative research

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For a qualitative study on user perspectives, 15 semi-structured interviews were conducted during February and March 2019 with clinicians, nurses, programme officers, laboratory staff and patient advocates in Kenya, South Africa and Uganda. These countries were selected because they have policies in place regarding LF-LAM. Most interviews were conducted by phone; hence, it was not possible to triangulate interview data with other evidence commonly collected through ethnographic approaches (e.g. multiple interviews and informal conversations at the same facility, observations or site visits). More in-depth and on-the-ground research with face-to-face interviews (including with PLHIV and their caregivers) is required to understand all user perspectives and practices of diagnosing TB in PLHIV. The research has focused exclusively on AlereLAM use, as the only commercially available LF-LAM.

The results showed that LF-LAM clearly addresses a need and makes an important difference in a population in which TB is hard to diagnose. The characteristics of the test, specimen, turnaround time, ease of use, cost, infrastructure and maintenance requirements were viewed differently by participants. In line with the global discourse on LF-LAM, the participants in this study generally saw LF-LAM as an easy-to-use, rapid test that requires little maintenance and equipment, and crucially does not rely on sputum but on urine – a specimen that is more easily available and safer. However, the perceived benefits of specimen, turnaround time, user friendliness, cost and maintenance requirements can also pose a challenge, depending on the particular situation and the capacities in which the test is used. The urine specimen, for instance, is safer, more easily available and less stigmatized than sputum, but not everybody can collect a urine sample (e.g. in bedridden patients catheters are required), produce it (e.g. dehydrated patients with sepsis cannot urinate), adequately measure it (e.g. in some instances the dropper provided in the test kit was not accurate enough and a micropipette was required) or find a private and clean space in which to provide it (e.g. rural hospitals do not necessarily have toilets or running water available to patients). Similarly, the infrastructure requirements are minimal but there can still be challenges with stockouts, lack of urine containers and shelf life. Although the turnaround time is supposed to be just 25 minutes, in many settings, treatment is not initiated until the next day.

Another important challenge that users struggle with is the suboptimal sensitivity of the test, cross-reactions and the difficulty of reading faint results (Grade 1). The findings showed how clinicians and nurses construct confidence in test results by:

- ensuring that the test is not made to stand by itself, but is embedded in an algorithm and considerations made by the doctor rather than by the nurse who is conducting the test; and
- using test results in combination with clinical suspicion of TB or other evidence in the case of asymptomatic patients.

More research is needed to understand the implications of these practices. Despite these issues, LF-LAM provides some much-needed confidence beyond clinical suspicion in severely ill patients where pill burden, side-effects and severe complications during treatment are a real challenge.

Overall, the results from the qualitative study suggest that the benefits outweigh the challenges, especially given the absence of viable diagnostic alternatives for this particular patient group. Importantly, these results also show that it is essential to pay attention to how diagnostics are operationalized. Just because a technology is quicker, easier to conduct and cheaper than existing diagnostics, this does not mean it is necessarily more successful in being implemented.

Some users also pointed out that the restrictive eligibility criteria of the WHO 2015 guidelines (9) mean that policy-makers perceive the test as being for specific situations only, and do not prioritize it. At the same time, the test carries the implicit risk of revealing poor performance of HIV programmes; for example, the restrictive use of a CD4 cell count below 100 has the undesired

effect that countries do not like to admit that they have many patients who are so ill. Taken together, these two aspects mean that, according to some respondents, the test is not made accessible to the extent it should be. Furthermore, CD4 cell counting is not widely used to determine eligibility for LF-LAM testing. Currently, symptom screening, hospitalization and assessing whether a patient looks ill are used to decide whether a patient is eligible for LF-LAM testing, rather than CD4 cell count, which in many places is not routinely available or is not ordered to avoid time delays.

Although participants in the study indicated that they would value improved sensitivity in a new test, they also cautioned against increasing complexity and turnaround time if the test should be made to work in primary care settings.

More details on user perspectives are given in **Online Annex 4: Report user perspectives on LF-LAM testing: results from qualitative research.**

## 2.7. Formulation of the recommendations

Evidence was synthesized and presented in GRADE evidence tables. The evidence-to-decision (EtD) framework was used to facilitate consideration of the evidence and development of recommendations in a structured and transparent manner. Decisions on the direction and strength of recommendations were also made using the EtD framework, as detailed in **Online**

### **Annex 5: Evidence to decisions frameworks**

Factors that influenced the direction and the strength of a recommendation were:

- priority of a problem;
- test accuracy;
- balance between desirable and undesirable effects;
- certainty of:
  - the evidence of test accuracy;
  - the evidence on direct benefits and harms from the test;
  - the management guided by the test results;
  - the link between test results and management;
- confidence in values and preferences and their variability;
- resource requirements;
- cost-effectiveness;
- equity;
- acceptability; and
- feasibility.

These factors are discussed below.

### 2.7.1. Priority of a problem

The GDG considered that the consequences of the problem (i.e. increased morbidity and mortality) were both serious and urgent. TB remains the leading cause of hospitalization and in-hospital deaths among PLHIV, despite increased access to ART (16). TB diagnostic tests that are not sputum-based and can be performed at point of care are highly desirable, to narrow the diagnostic

gap and ensure timely treatment. Detection of mycobacterial antigen in urine is promising, because this would allow for a TB diagnosis that is not site specific. Urine is easy to collect and store, and it lacks the infection control risks associated with sputum collection. The LF-LAM was developed as a simple point-of-care test for diagnosis of active TB in PLHIV. This assay does not require access to special laboratory equipment, and it produces a result in 25 minutes, meeting many requirements of the desired target product profile.

### 2.7.2. Test accuracy

The pooled sensitivity and specificity presented in the GRADE evidence profile was assessed. The review only included studies with a microbiological reference standard (culture or Xpert); it did not assess performance against a composite reference standard that uses microbiological or clinical information to classify TB. This was done in the original WHO and Cochrane Review (9, 10), but found little difference against a microbiological reference standard. A substantial number of TB cases may not be verified by microbiological testing (i.e. may be false negative) if only sputum is tested and when patients with advanced HIV are assessed, which may lead to underestimation of sensitivity. Furthermore, as CD4 cell counts decrease, the sickest patients may not be able to produce a sputum specimen or may have extrapulmonary TB. Exclusion of these latter patient groups (i.e. individuals without sputa) may also lead to underestimation of sensitivity. The impact of nontuberculous mycobacteria and other environmental factors on test specificity remains unclear, but may possibly lead to false positive results. Only a single study was conducted outside of sub-Saharan Africa.

### 2.7.3. Balance between desirable and undesirable effects

The potential benefits and harms from the clinical use of the LF-LAM were assessed by GDG members. The considered judgement was that the desirable effects generally outweigh the undesirable effects except for the patient group “outpatients, irrespective of symptoms”; in this group, desirable effects were small and undesirable effects were moderate.

- **Desirable effects:** The test can be performed on a urine sample, which is easy to collect outside a laboratory; thus, the time to diagnosis can be reduced. The desirable effect of the test may be augmented by the fact that in low-resource settings, a certain proportion of TB patients may be diagnosed by LF-LAM and not by the WHO-recommended rapid TB diagnostic test (Xpert) owing to any of the following:
  - sputum Xpert has lower sensitivity in HIV-positive than HIV-negative people;
  - patients may not be able to produce sputum; and
  - patients may not have access to Xpert.
- **Undesirable effects:** Urine LAM does not provide information about drug resistance; thus, a positive result (both true positive and false positive) will necessitate additional testing (e.g. through Xpert or culture) to identify evidence for phenotypic or molecular drug resistance. Because urine LAM sensitivity does not allow identification of all cases of *Mycobacterium tuberculosis*, additional testing may be required following a negative result (which may be a true negative or a false negative).

### 2.7.4. Certainty of the evidence

Certainty of the evidence of test accuracy was judged to be very low to moderate. Certainty of the evidence on direct benefits and harms from the test was judged to be moderate.

### **2.7.5. Certainty of management**

For certainty of the management guided by the test results, the panel focused on whether the management would be any different, should it be guided by the test results. For this factor, the certainty was judged to be moderate.

For certainty of the link between test results and management, the panel assessed how quickly and effectively test results would transfer to management decisions. For this factor, the certainty was judged to be moderate.

### **2.7.6. Confidence in values and preferences and their variability**

The judgement was that there is no important uncertainty about or variability in how the main stakeholder groups value the diagnostic accuracy of LF-LAM. The main stakeholder groups are health workers, health managers and patients.

### **2.7.7. Resource requirements**

In relation to resource requirements, the panel answered three questions:

- How large are the resource requirements for test implementation?
- What is the certainty of the evidence about resource requirements?
- Does the cost–effectiveness of the intervention favour the intervention or the comparison?

The judgement fell between “do not know” and “moderate”. The panel had an extensive debate on the level of resources that would be required for testing, and raised several issues; for example:

- although implementation in hospitals presents a relatively low incremental cost, implementation in a weak health system would cost more;
- the cost savings of avoided transmission needs to be taken into account;
- costs will vary depending on whether the LF-LAM is being implemented alone or as part of a diagnostic cascade; and
- costs will differ by context.

### **2.7.8. Cost–effectiveness**

The question here was does the cost–effectiveness of the intervention favour the intervention or the comparison? The judgements ranged from “varies” to “do not know”. One of the concerns raised by the panel was that “Only data for cost–effectiveness for Africa are available”.

### **2.7.9. Equity**

GDG members considered whether implementation of LF-LAM will positively or negatively affect access to health care (e.g. will it be possible to implement the test in distant levels of health care or through self-administration). Equity was largely judged to fall between “increased” and “probably increased” for various patients groups, with the exception of “outpatients, irrespective of symptoms”, for whom the judgement was that equity was “probably reduced”, considering the frequency of false positive results for this patient group. Given that this is a universal test, it has the potential to reduce inequity. Patients with extrapulmonary TB are already disadvantaged and the test may be able to improve care for these patients.

### 2.7.10. Acceptability

In terms of acceptability, the panel considered whether a new test will be acceptable by all the relevant stakeholders, such as health workers, health managers and patients. The judgement was that the test will be generally acceptable.

### 2.7.11. Feasibility

In terms of feasibility, the panel considered whether the implementation of the LF-LAM test is feasible. The judgement was that implementation of the test will generally be feasible.

More details on the transition from evidence to recommendations are given in **Online Annex 5: Evidence to decision frameworks**.

## 2.8. Management of conflict of interest

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Each of the potential GDG members was asked to submit a completed declaration of interests (DOI) form and provide a curriculum vitae (CV) before being invited to be a GDG member. In addition, an abbreviated and focused Internet search was performed “to identify any obvious public controversies or interests that may lead to compromising situations for WHO and the expert concerned”. The CV, DOI and information retrieved from the Internet were evaluated by the members of the steering committee to determine whether there were or may be conflicts of interest (COI) and, if so, whether these required a management plan. The COI management was based on the WHO guidelines for DOI for experts (17), one-on-one consultation with a member of the Ethics Team from the WHO Office of Compliance, Risk Management and Ethics, and the WHO *Handbook for guideline development* (18).

Both financial and non-financial interests were considered. A “significant” COI would include:

- “intellectual bias”, when an individual may have repeatedly taken a public position on an issue under review, which may affect the individual’s objectivity and independence in the global policy development process;
- involvement in research or the publication of materials related to the issue under review; and
- financial interest above US\$ 5000.

For obvious reasons, developers of any assay are never involved in the process of policy development.

Details on outcomes of COI assessment are given in **Annex 3: Conflict of Interest assessment**.

## 2.9. GDG decision-making

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On 14–16 May 2019, the Global TB Programme convened a GDG meeting in Geneva, Switzerland, to review the evidence for the use of LF-LAM. The meeting was chaired by an expert in evidence synthesis. Recommendations were developed based on consensus among the GDG members where possible. If it was not possible to reach consensus, then voting took place. For example, **Online Annex 5** shows the result of the voting for PICO 1a, where the result for desirable effects was “Moderate” – 7 (including the chair) and “Large” – 6; and the voting on feasibility was “Probably yes” – 5, “Yes” – 6, “Varies” – 1 and “Abstained” – 1.

DOI statements were summarized by the chair at the start of the meeting. Selected individuals with intellectual or research involvement (or both) were invited as technical resource persons to provide technical input and answer technical questions. These individuals did not participate in the GRADE process and were excluded from the group discussions when recommendations were developed.

The panel also reviewed data on the use of FujiLAM. The GDG acknowledged that initial results of the use of this assay on stored frozen urine samples from PLHIV are promising, with pooled sensitivity in HIV-positive individuals about 30% higher than with Alere Determine™. However, the GDG noted that the FujiLAM assay is not currently commercially available and that there are no data on price, cost and cost-effectiveness for this assay. In addition, there are no data on diagnostic accuracy, feasibility and acceptability from settings of intended use. Thus, the panel was not able to develop recommendations on the FujiLAM assay.

Once the FujiLAM assay becomes commercially available, and additional data on diagnostic accuracy, evidence on feasibility and acceptability from settings of intended use have been generated, the GDG can be reconvened, and recommendations developed.

Based on consensus achieved in the meeting of 14–16 May 2019, the draft guidelines document was developed by the steering committee, and was then extensively corrected and commented on by the members of the GDG. The draft was also reviewed by the External Review Group, to identify any errors or omissions and to collect comments on clarity, setting-specific issues and implications for implementation.

The WHO policy recommendations developed from the evidence synthesis process by the GDG are presented below.

## 2.10. WHO policy recommendations

**In inpatient settings**, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [1];<sup>9</sup> or
- with advanced HIV disease<sup>10</sup> or who are seriously ill<sup>11</sup> (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [1]; or
- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm<sup>3</sup> (**strong** recommendation; moderate certainty in the evidence about the intervention effects) [2].

**In outpatient settings**, WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (**conditional** recommendation; low certainty in the evidence about test accuracy) [3]; and
- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm<sup>3</sup> (**conditional** recommendation; very low certainty in the evidence about test accuracy) [4].

**In outpatient settings**, WHO recommends **against** using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- without assessing TB symptoms (**strong** recommendation; very low certainty in the evidence about test accuracy) [5];

<sup>9</sup> Numbers in square brackets indicate the number of the relevant EtD table.

<sup>10</sup> For adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV aged under 5 years should be considered as having advanced disease at presentation.

<sup>11</sup> “Seriously ill” is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided.

- without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 (**strong** recommendation; very low certainty in the evidence about test accuracy) [6]; and
- without TB symptoms and with a CD4 cell count of 100–200 cells/mm<sup>3</sup> (**conditional** recommendation; very low certainty in the evidence about test accuracy) [7].

### Remarks

- a. The reviewed evidence and recommendations apply to the use of AlereLAM only, because other in-house LAM-based assays have not been adequately validated or used outside limited research settings. Any new or generic LAM-based assay should be subject to adequate validation in the settings of intended use.
- b. All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have as their initial diagnostic test at least one sputum specimen submitted for Xpert® MTB/RIF (Ultra) assay. This also includes children and adolescents living with HIV who are able to provide a sputum sample.
- c. These recommendations also apply to adolescents and children living with HIV, based on generalization of data from adults, while acknowledging very limited data for these population groups.
- d. LF-LAM should be used as an add-on to clinical judgement in combination with other tests. It should not be used as a replacement or triage test. More details are given in **Annex 1**.

### 3. Plan to update the guidelines

The current guidelines will be updated in due course, should new evidence be generated on the use of the currently available assay (AleréLAM) or new versions of the assay appear on the market. The average time frame for updating the existing guidelines is 3–5 years. In the case that the FujiLAM assay becomes commercially available earlier and there are additional data on the test's performance in clinical settings, the GDG may be reconvened earlier, to review the evidence on diagnostic accuracy, feasibility and acceptability from settings of intended use, and to develop recommendations on the use of the assay.

## 4. Research priorities

Research priorities are as follows:

- develop simple, more accurate tests based on LAM detection, with the potential to be used for HIV-negative populations;
- evaluate the use of LF-LAM in PLHIV, without signs and symptoms of TB;
- evaluate the use of LF-LAM in children and adolescents with HIV;
- evaluate the combination of parallel use of LF-LAM and rapid qualitative CD4 cell count systems;
- undertake implementation research on the acceptance, scale-up and impact of LF-LAM in routine clinical settings;
- undertake qualitative research on user perspectives of LF-LAM for feasibility, accessibility and equity issues;
- undertake implementation research on LF-LAM integrated into HIV care packages;
- evaluate the performance of LF-LAM as the HIV epidemic evolves and more people on treatment with viral load suppression are hospitalized;
- evaluate the cost-effectiveness of LF-LAM; and
- evaluate other rapid LAM-based tests such as FujilAM.

## 5. Publication, dissemination and implementation

These guidelines will be disseminated through the Global TB Programme electronic mailing lists to WHO regional offices, Member States, the Stop TB Partnership and other stakeholders (including the Global Laboratory Initiative and the WHO TB Supranational Reference Laboratory Network). They will also be published online on the websites of the WHO Global TB Programme, WHO HIV/AIDS and Hepatitis Department and Global Laboratory Initiative. The updated policy will be incorporated into the mobile application “Compendium of WHO guidelines and associated standards”, which is publicly available and is updated on an annual basis.

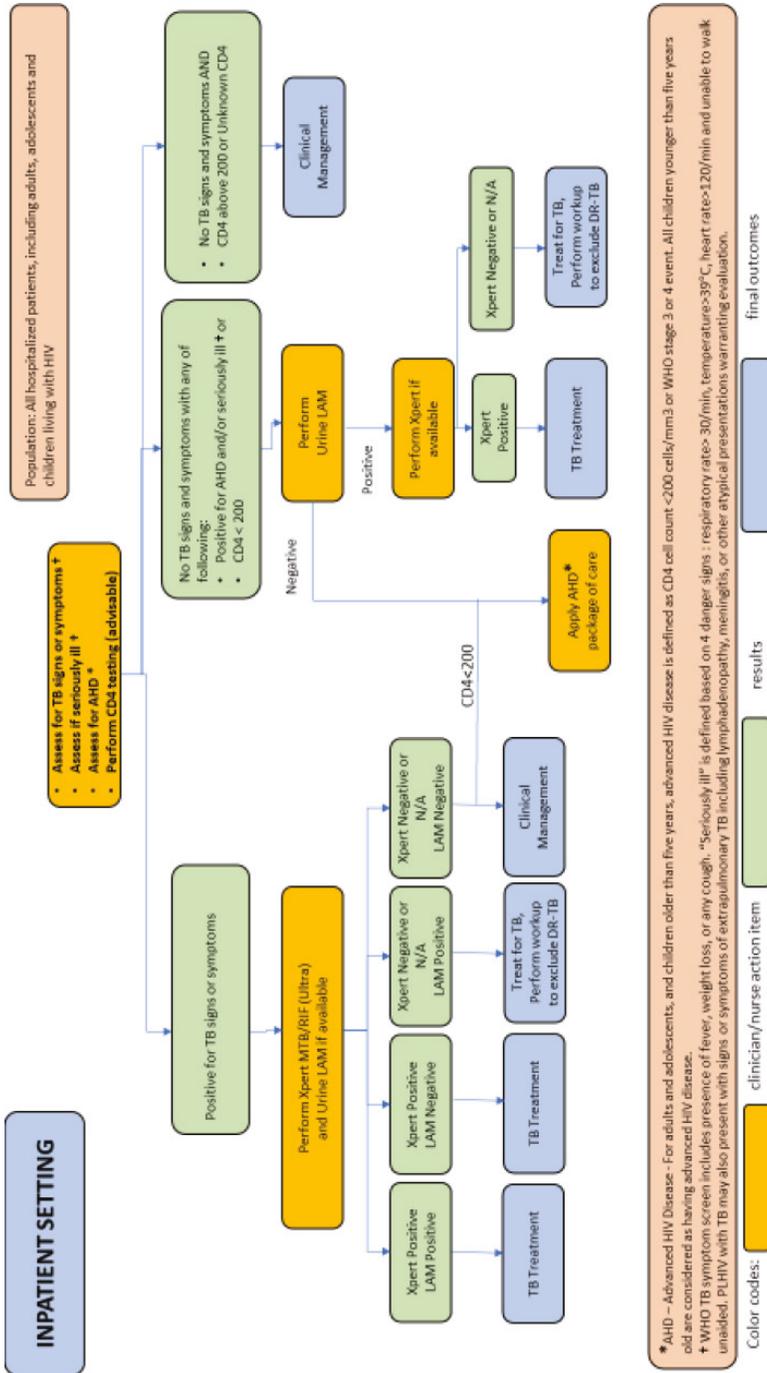
## 6. References

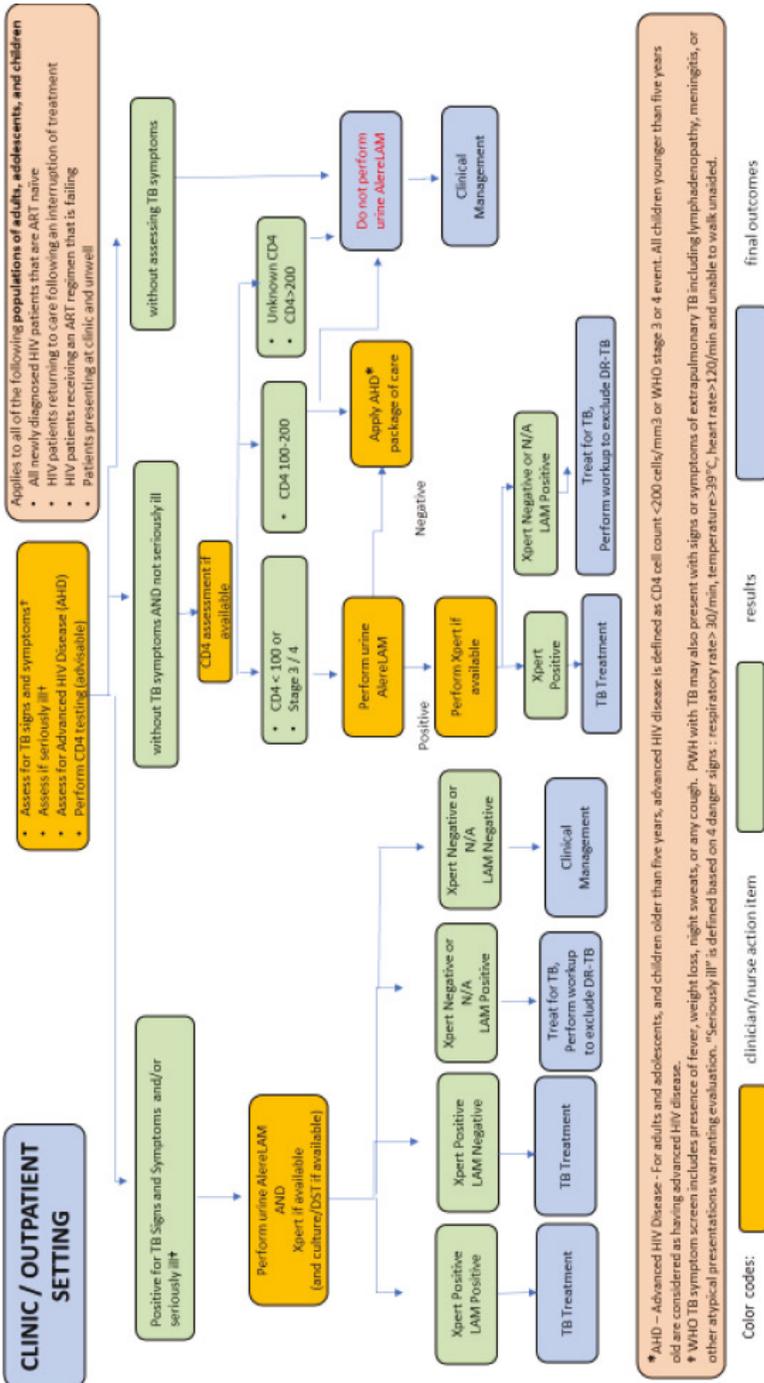
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2. Global tuberculosis report 2018. Geneva: World Health Organization; 2018 ([https://www.who.int/tb/publications/global\\_report/Main\\_text\\_21Sept2018\\_v1.1.pdf?ua=1](https://www.who.int/tb/publications/global_report/Main_text_21Sept2018_v1.1.pdf?ua=1)).
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8. Alere Determine™ TB LAM Ag: Rapid rule-in TB-HIV co-infection [website]. Abbott; 2019 (<https://www.alere.com/en/home/product-details/determine-tb-lam.html>).
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# Annexes

## Annex 1: Algorithm for LF-LAM use





AHD: advanced HIV disease; AlerLAM: Alere Determine™ TB lipoarabinomannan assay; ART: antiretroviral therapy; DR-TB: drug-resistant TB; HIV: human immunodeficiency virus; LAM: lipoarabinomannan; LF-LAM: lateral flow urine lipoarabinomannan assay; N/A: not applicable; PLWH: people living with HIV; TB: tuberculosis; WHO: World Health Organization.

**Annex 2: List of studies included in the systematic review**

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**Bjerrum 2015**

Bjerrum S, Kenu E, Lartey M, Newman MJ, Addo KK, Andersen AB, et al. Diagnostic accuracy of the rapid urine lipoarabinomannan test for pulmonary tuberculosis among HIV-infected adults in Ghana – findings from the DETECT HIV-TB study. *BMC Infect Dis* 2015;15(1) (<http://dx.doi.org/10.1186/s12879-015-1151-1>).

**Drain 2015**

Drain PK, Losina E, Coleman SM, Giddy J, Ross D, Katz JN, et al. Value of urine lipoarabinomannan grade and second test for optimising clinic-based screening for HIV-associated pulmonary tuberculosis. *JAIDS*. 2015;68(3):274–80 (<http://dx.doi.org/10.1097/qai.0000000000000436>).

**Drain 2016**

Drain PK, Gounder L, Sahid F, Moosa MY. Rapid urine LAM testing improves diagnosis of expectorated smear-negative pulmonary tuberculosis in an HIV-endemic region. *Scientific Reports* 2016;6(1) (<http://dx.doi.org/10.1038/srep19992>).

**Florida 2017**

Florida M, Ciccacci F, Andreotti M, Hassane A, Sidumo Z, Magid NA, et al. Tuberculosis case finding with combined rapid point-of-care assays (Xpert MTB/RIF and Determine TB LAM) in HIV-positive individuals starting antiretroviral therapy in Mozambique. *Clin Infect Dis*. 2017;65(11):1878–83 (<http://dx.doi.org/10.1093/cid/cix641>).

**Hanifa 2016**

Hanifa Y, Fielding KL, Chihota VN, Adonis L, Charalambous S, Karstaedt A, et al. Diagnostic accuracy of lateral flow urine LAM assay for TB screening of adults with advanced immunosuppression attending routine HIV care in South Africa. *PLoS One* 2016;11(6):e0156866 (<http://dx.doi.org/10.1371/journal.pone.0156866>).

**Huerga 2017**

Huerga H, Ferlazzo G, Bevilacqua P, Kirubi B, Ardizzoni E, Wanjala S, et al. Incremental yield of including determine-TB LAM assay in diagnostic algorithms for hospitalized and ambulatory HIV-positive patients in Kenya. *PLoS One* 2017;12(1):e0170976 (<http://dx.doi.org/10.1371/journal.pone.0170976>).

**Juma 2017**

Juma FO, Yonga G, Waweru P, Revathi G, Nelson M, Shah R. The diagnostic accuracy of Determine TB LAM antigen in detection of extra pulmonary tuberculosis (EPTB). *J Infect*. 2017;75(6):583–6 (<http://dx.doi.org/10.1016/j.jinf.2017.08.011>).

**LaCourse 2016**

LaCourse SM, Cranmer LM, Matemo D, Richardson B, Kinuthia J, John-Stewart G, et al. Active tuberculosis case finding in HIV-infected pregnant women in Kenya reveals poor performance of symptom screening and rapid diagnostic tests. *JAIDS*. 2016;71(2):219–27 (<http://dx.doi.org/10.1097/qai.0000000000000826>).

### **Lawn 2017**

Lawn SD, Kerkhoff AD, Burton R, Schutz C, Boulle A, Vogt M, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. *BMC Med.* 2017;15(1) (<http://dx.doi.org/10.1186/s12916-017-0822-8>).

### **Nakiyingi 2014**

Nakiyingi 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. *JAIDS.* 2014;66(3):270–9 (<http://dx.doi.org/10.1097/qai.0000000000000151>).

### **Pandie 2016**

Pandie S, Peter JG, Kerbelker ZS, Meldau R, Theron G, Govender U, et al. The diagnostic accuracy of pericardial and urinary lipoarabinomannan (LAM) assays in patients with suspected tuberculous pericarditis. *Sci Rep.* 2016;6(1) (<http://dx.doi.org/10.1038/srep32924>).

### **Peter 2012**

Peter JG, Theron G, van Zyl-Smit R, Haripersad A, Mottay L, 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(5):1211–20 (<http://dx.doi.org/10.1183/09031936.00201711>).

### **Peter 2015**

Peter J, Theron G, Chanda D, Clowes P, Rachow A, Lesosky M, et al. Test characteristics and potential impact of the urine LAM lateral flow assay in HIV-infected outpatients under investigation for TB and able to self-expectorate sputum for diagnostic testing. *BMC Infect Dis.* 2015;15(1) (<http://dx.doi.org/10.1186/s12879-015-0967-z>).

### **Peter 2016**

Peter JG, Zijenah LS, Chanda D, Clowes P, Lesosky M, Gina P, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *Lancet.* 2016;387(10024):1187–97 ([http://dx.doi.org/10.1016/s0140-6736\(15\)01092-2](http://dx.doi.org/10.1016/s0140-6736(15)01092-2)).

### **Thit 2017**

Thit SS, Aung NM, Htet ZW, Boyd MA, Saw HA, Anstey NM, et al. The clinical utility of the urine-based lateral flow lipoarabinomannan assay in HIV-infected adults in Myanmar: an observational study. *BMC Med.* 2017;15(1) (<http://dx.doi.org/10.1186/s12916-017-0888-3>).

### Annex 3: Conflict of interest assessment for GDG members and ERG members

GDG member	Interests declared	Conclusion
Holger Schünemann	None declared	No conflict of interest
Heather Alexander	Chair of the Global Laboratory Initiative (Working Group).  The Global Laboratory Initiative is currently developing a practical guide to support the implementation of 2015 guidelines on the use of LF-LAM for the diagnosis and screening of active tuberculosis in people living with HIV.	Non-significant
Gavin Churchyard	None declared	No conflict of interest
Kathleen England	Member of the Global Laboratory Initiative (Working Group).  The Global Laboratory Initiative is currently developing a practical guide to support the implementation of 2015 guidelines on the use of LF-LAM for the diagnosis and screening of active tuberculosis in people living with HIV.	Non-significant
Rumina Hasan	None declared	No conflict of interest
Diane Havlir	None declared	No conflict of interest
Nagalineswaran Kumarasamy	None declared	No conflict of interest
Gracia Violeta Ross Quiroga	None declared	No conflict of interest
Kenly Sikwese	None declared	No conflict of interest
Wendy Stevens	None declared	No conflict of interest
Carrie Tudor	Project funding received from Eli Lilly for organization: International Council of Nurses	Non-significant
Anna Vassall	None declared	No conflict of interest
ERG member	Interests declared	Conclusion
Maria Alice da Silva Telles	None declared	No conflict of interest
Levan Gagnidze	None declared	No conflict of interest
Alaine Nyaruhirira	None declared	No conflict of interest
Francis Varaine	None declared	No conflict of interest
Rohit Sarin	None declared	No conflict of interest
Andrei Maryandyshev	None declared	No conflict of interest
Jamilya Ismailova	None declared	No conflict of interest

ERG: External Review Group; GDG; Guideline Development Group; HIV: human immunodeficiency virus; LF-LAM: lateral flow urine lipoarabinomannan assay.

THE  
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