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MINISTRY OF HEALTH-ETHIOPIA
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Ethiopian Public Health Institute

Implementation Guidelines for Lateral Flow Urine Lipoarabinomannan Assay (Lf-lam) In The Detection of Active Tuberculosis in People Living With HIV

ADDIS ABABA, ETHIOPIA

August, 2021

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Foreword

TB/ HIV coinfection continues to be a challenge in the fight against TB and HIV. According the 2020 global TB report Ethiopia is among the 15 high TB/HIV burdened countries. This indiacates it is still very important to implement collaborative TB/HIV activities and management of comorbidities as an essential strategies to curl the impact of these two epidemics. Of these strategies rapid detection of TB among people living with HIV is very cruitial.

In the last two decades and more several strategies have been implemented to fight TB/ HIVcoinfection in Ethiopia .This measure have supported the country to reduce mortality of people living with HIV due to TB and other opportunistic infections. Of the implemented strategies one was increaseing access for early diagnosis of TB and drug resistance through expansion of sputum based rapid molecular tests and diagnostic facilities. However, there are still gaps in the early diagnosis of TB in PLHIV due to inability of such patients to expectorate sputum ,the frequency of extra-pulmonary TB and paucibacillary pulmonary TB.

Through the global guidances for early detection of TB among people living with HIV it very essential to implement WHO-recommened, rapid, point of care tests like urine based lateral flow lippoarabinamanan (LF-LAM) . In line with the 2019 World Health Organisation policy recommendations this implementation guideline aims to provide guidance on how to use urine LF-LAM to facilitate early diagnosis and treatment of TB in HIV positive patients and concurrently reduce mortality due to TB.This guideline encompasess the algorithms, strategies and laboratory diagnosis of TB in HIV patients using urine LF-LAM.

Furthermore, the Ethiopian Public Health Institute wants to expresses its organizational commitment for fight against TB and HIV. Moreover, I would also like to acknowledges all partners and experts that contributed in the development of this urine LF-LAM implementation guideline.

Sincerely,

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Disclamer

Executive Summary

The World Health Organization's (WHO's) strategy for tuberculosis (TB) prevention, care and control from 2015 to 2035 - which is better known as the End TB Strategy - prioritizes the early diagnosis of TB. This prioritization is particularly due to smear-negative TB cases, which are often associated with HIV co-infection and young age. Of the 10 million new cases of TB occurred across the world in 2019, an estimated 0.82 million (9%) incidence cases occurred among peopleliving with HIV (PLHIV). The WHO African region accounts for 72% of the estimated number of HIV-positive incident TB cases. Ethiopia is one of the 30 countries with high TB and TB/HIV countries with an estimated TB incidence cases of 140 per 100,000 population, and 5.3% TB/HIV co-infection prevalence in 2019.

Lack of an effective diagnostic test for smear-negative TB cases is a major contributor to the death of HIV positive people in countries with high burden of TB/HIV co-infection. To alleviate the problems related to diagnose smear-negative TB cases in the PLHIV, several tests have been designed and evaluated at the global level. Of these, tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care test for TB. The currently available urine LAM assays have suboptimal sensitivity hence are suitable for a specific group of TB patients such as PLHIV. Unlike traditional diagnostic methods such as smear microscopy and culture, urine LAM assays demonstrate improved sensitivity for the diagnosis of TB among individuals co-infected with HIV. The estimated sensitivity is even greater in patients with lower CD4 cell counts.

This implementation guideline is developed based on evidence obtained from national and international studies and WHO policy recommendation for the use of urine LAM for the diagnosis of TB in PLHIV in Ethiopia. It comprises the eligibility of PLHIV for the LF-LAM test, national TB diagnostic algorithm for PLHIV that incorporate LF-LAM test, and laboratory results order interpretation. It also consists case definition and registration, patient classification and relevant indicators for urine LAM test. In addition, this guideline in detail explains patient management, test principle and procedure, required laboratory infrastructure and supply issues, sample collection, quality control issues, biosafety requirements and waste disposal system. Further, it comprises monitoring and evaluation plan with its important indicators.

Abbreviations

AFB	Acid Fast Bacilli
AHD	Advanced HIV Disease
AlereLAM	Alere DetermineTM TB LAM Ag assay
ART	Anti-Retroviral Therapy
CD4	Cluster of Differentiation
CSF	Cerebro Spinal Fluid
CXR	Chest X-ray
DR-TB	Drug Resistant TB
DST	Drug Susceptibility Testing
EFDA	Ethiopian Food and Drug Administration
EMRs	Electronic Medical Records
EPHI	Ethiopian Public Health Institute
EPHI NTRL	Ethiopian Public Health Institute National Tuberculosis Reference Laboratory
EPSA	Ethiopian Pharmaceutical Supply Agency
EPTB	External pulmonary Tuberculosis
EQA	External quality Assessment
GLI	Global Laboratory Initiative
HAPCO	HIV/AIDS Prevention and Control Office
HCWs	Health Care Workers
HF	Health Facility
HIV	Human Immunodeficiency Virus
IPLS	Integrated Pharmaceutical Logistics System
IQC	Internal Quality Control
LAM	Lipoarabinomannan protein
LAMP	Loop Mediated Isothermal Amplification
LF-LAM	Lateral Flow Lipoarabinomannan assay
mWRD	WHO recommended rapid diagnostic
MDR-TB	Multidrug Resistant Tuberculosis
M & E	Monitoring and Evaluation

MOH	Ministry of Health
MTB	Mycobacterium Tuberculosis
NTP	National Tuberculosis Program
NTRL	National Tuberculosis Reference Laboratory
PT	Panel testing
PCR	Polymerase Chain Reaction
PLHIV	People Living with Human Immunodeficiency Virus
RHB	Regional Health Bureau
RRL	Regional Reference Laboratory
SOPs	Standard Operating Procedures
TB	Tuberculosis
TB/HIV GL	Tuberculosis/Human Immunodeficiency Virus Guideline
TAT	Turn Around Time
TB LAM Ag	Tuberculosis Lipoarabinomannan Antigen
TB LAMP	Tuberculosis Loop Mediated Isothermal Amplification
WHO	World Health Organization
Xpert® MTB/ RIF	GeneXpert Mycobacterium Tuberculosis/Rifampicin

1. Introduction

1.1. Epidemiology and situation analysis

Tuberculosis (TB) causes ill-health and death to millions every year across the world. An estimation indicated that more than 2 billion people are infected with *Mycobacterium tuberculosis* complex (MTB) worldwide, and 5–10% of infected individuals have a lifetime risk of progressing from TB infection to TB disease (1). A recent global TB report estimated 10 million new TB cases developed in 2019; of these, 815,000 (0.85%) were among HIV positive people (1). The World Health Organization (WHO) recent estimation indicates the risk of developing active TB disease is 18 times higher in people living with HIV (PLHIV) with 10% risk of developing TB each year than those without HIV (1). Among 10 million new TB cases developed in 2019 across the world 8.2% were in PLHIV (1) 2020), and WHO African region bears the highest burden of TB/HIV co-infection (1). Of the total of 456,426 cases of TB detected in PLHIV, 208,000 were died globally in 2019 (1). Ethiopia is among the 30 countries with high TB, TB/HIV and MDR-TB burden with an estimated incidence rate of 140 per 100,000 population (1). A recently reported systematic review study indicated that the prevalence of TB/HIV co-infection in Ethiopia is 22% (2). However, WHO estimation indicated that 5.3% of TB cases notified in PLHIV in Ethiopia in 2019 (1). Moreover, a national level data report indicated that the prevalence of TB in PLHIV is 7.3% (3).

Although there is a significant improvement in diagnosis and treatment of TB, there is still a limitation in early detection and treatment of all forms of TB cases among HIV positive individuals. A systematic review study that estimated the prevalence of TB through pooling the results of studies reported on postmortem showed 46% of TB cases remain undiagnosed (4), which made TB the most important opportunistic infection among PLHIV (4). Moreover, of the total of 815,000 estimated HIV associated TB cases worldwide in 2019, only 56% were notified (1). This indicates that TB diagnosis is still a challenge in PLHIV and it is rarely bacteriologically confirmed (5,6).

The conventional sputum microscopy is the cheapest and fastest method that is used to diagnose TB since 1882. However, the sensitivity of sputum smear microscopy for the diagnosis of TB is low in HIV infected individuals due to poor quality sputum production and low bacillary concentration (7). Particularly in severely immunocompromised HIV infected individuals, the sensitivity of sputum smear microscopy is significantly reduced (8). Other challenges that make TB diagnosis difficult include non-specific clinical presentation of TB that is attributable to high prevalence of extra-pulmonary and disseminat-

ed forms of TB in individuals with advanced HIV clinical stage disease (8).

Nowadays, rapid and more accurate molecular technologies have been developed and available to diagnose HIV related TB (9). Polymerase chain reaction (PCR), real-time PCR, and loop-mediated isothermal amplification (LAMP) are the molecular techniques that are commercially available for the diagnosis of TB(10,11). Xpert® MTB/RIF and Xpert® MTB/RIF Ultra (Cepheid, Sunnyvale, CA, United States) assays are rapid molecular technologies that are recommended by WHO as initial diagnostic tests for TB in adults, adolescent and children(10,11). TB-LAMP and TruenatTM (Molbio Diagnostics, Goa, India) are also other molecular technologies that are recommended by WHO for the diagnosis of TB(10). However, the diagnostic performance of these technologies have not been fully evaluated for the diagnosis of TB in PLHIV(10).

Although rapid and accurate molecular assays have significantly reduced the gap in TB case detection among PLHIV, their accessibility continued to be a challenge, due to the infrastructure required and the cost of procurement and maintenance. Thus, access to rapid and accurate diagnostic tests significantly restricted in resource limited settings where the burden of TB/HIV co-infection is high(10). Moreover, interruption of electricity and inadequate laboratory infrastructure and inefficient sample referral mechanisms are the challenges that limit the accessibility of rapid and accurate molecular diagnostic tests (12–14). Beside the challenges listed above, lack of quality sputum production and the paucibacillary nature of TB in HIV positive individuals are additional problems that make the use of sputum-based testing more difficult.

To minimize the challenges that are associated to sputum based diagnostic tests, urine based rapid TB diagnostic tests are recommended to detect TB in PLHIV in advanced disease condition (15–18). Alere lipoarabinomannan (LAM) assay is one of the urine based rapid diagnostic tests for TB detection in PLHIV (15). Evidence suggests the importance of LAM in the detection of TB at high TB/HIV burden settings (15,17,19,20). It is recommended for use as a simple point-of-care test to assist TB diagnosis in HIV positive adult hospital in-patients with signs and symptoms of TB and with CD4 cell counts ≤ 100 cells/mm^3 or in HIV positive people who are seriously ill regardless of their CD4 count or who have an unknown CD4 count (21). This recommendation is also applied to HIV positive adults who are outpatients and have signs and symptoms of TB and who have CD4 cell count ≤100 cells/mm^3 or who are seriously ill, regardless of their CD4 count (21). Based on the generalization of the data from adults, this recommendation is also used in children living with HIV who have signs and symptoms of TB (21). However, there is evidence limitation on the specificity of LAM test in children.

LAM test could decrease mortality through quicker diagnosis and early treatment commencement among PLHIV and severely sick (15–17,22,23).

1.2. WHO policy recommendation for the use of LF-LAM

For out patient setting use of LF-LAM

WHO suggests(21) using LF-LAM to assistin the diagnosis of active TB in HIV-positive adults, adolescents and children:

- With signs and symptoms of all forms TB or seriously ill.
- Irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm^3

WHO recommendation against(21) using LF-LAM toassist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

For outpatient settings not to use LF-LAM

- without assessing TB symptoms not recommended .
- For PLHIV Without TB symptoms and unknown CD4 cell count not recommended.
- For PLHIV without TB symptoms and CD4 cell count greater than or equal to 200 cells/ mm^3 not recommended.
- PLHIV Without TB symptoms and with a CD4 cell count of 100–200 cells/ mm^3 is **not recommended** (27, 28, 29).

Note: Strong recommendation for bullet 1&2, conditional recommendation for 3rd bullet due to very low certainty in the evidence about test accuracy.

Key WHO Remark:

- All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have at least one sputum specimen submitted for mWRD test. This also includes children and adolescents living with HIV who are able to provide a sputum sample.
- LF-LAM should be used as an add-on to clinical judgment in combination with other tests.
- LF-LAM It should not be used as a replacement or triage test.
- No recommendation for other LF -LAM Test Kit other than Alere LAM until Quality evidence is obtained.

For inpatient settings

WHO strongly recommends(21)using LF-LAM to assistin the diagnosis of active TB in HIV-positive adults, adolescents and children:

- Patient with signs and symptoms of TB (pulmonary and/or extra pulmonary).
- For persons with advanced HIV diseaseandCD4 cell count of less than 200 cells/ mm^3 or WHO clinical stage 3 or 4 event at presentation or children with HIV who are aged under 5 years at presentation,or PLHIVwho are seriously ill 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 less than 200 cells/ mm^3(27, 28, 29).

Note: Strong recommendation; moderate certainty in the evidence about the intervention effects.

Ethiopian contextual update and recommendation to use AlereLAM.

The National Guidelines for Clinical and Programmatic management of TB,DR TB and Leprosy guideline recommends (24)the use of LF-LAM in the following Key areas.

General Recommendation ForDiagnosis of TB among HIV positives in all settings

- Lateral flow lipoarabinomannan assay (LF-LAM) test is **recommended to assist** the Diagnosis of TB among selected groups of HIV-infected presumed TB patients ,in conjunction with Molecular WRDs (Xpert MTB/RIF test, Xpert Ultra, Trunat and TB-LAMP) among PLHIV with advanced HIV disease stat.
- For seriously ill patient with negative Xpert MTB/RIF and/or sputum smear results on full course anti-TB treatment using only suggestive findings on radiography. In such circumstances, the clinical response of the patient has to be monitored and if possible repeat the Xpert tests. **UrineLF-LAM test is recommended whenever available.**

For outpatient settings:

- WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV positive adults, adolescents and children who: have signs and symptoms of TB (pulmonary or extrapulmonary); are seriously ill; or have a CD4 cell count of less than 100 cells/mm3 irrespective of signs and symptoms of TB.

Not Recommended to use LF-LAM test in following condition

- Outpatient settings, it is not recommended to use LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children without TB symptoms and with an unknown CD4 cell count, or with a CD4 cell count greater than 100 cells/mm3.
- LF-LAM should be used as an add-on to clinical judgment in combination with other tests. It should not be used as a replacement or triage test.
- For hospitalized PLHIV without signs or symptoms of TB and whose CD4 is 200 cells/mm3 or above (or is unknown), do not conduct an LF-LAM test.

Remark

- For initial diagnostic test, all patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have at least one sputum specimen submitted for a molecular WRD assay. This also includes children and adolescents living with HIV who are able to provide a sputum sample. LF-LAM results (test time< 15 minutes) are likely to be available before molecular WRD test results; hence, treatment decisions should be based on the LF-LAM result while awaiting the results of other diagnostic tests (27, 28, 29).

For in patient settings LF-LAM recommended under the following conditions:

1. After evaluating hospitalized PLHIV for TB, assess the presence of danger signs for being seriously ill. In PLHIV who are not seriously ill, consider measuring CD4 cell counts, to assess eligibility for testing with the LF-LAM assay.

   A. For hospitalized HIV-positive adults, adolescents and children with signs or symptoms suggestive of all forms of TB or with a chest X-ray suggestive of TB, or hospitalized patients who have advanced HIV disease (AHD), or seriously ill or have CD4 counts of less than 200/mm3 , regardless of TB signs and symptoms is eligible for testing with the LF-LAM assay.

   B. For PLHIV who is "Seriously ill" is defined as presenting with any one of the following danger signs: **Respiratory rate >30 per minute**, **Temperature >39 °C**, **Heart rate >120 beats per minute** or **unable to walk unaided**.

   C. For adults, adolescents and children aged more than 5 years, AHD is defined as **CD4 cell count <200 cells/mm^3**or **WHO clinical stage 3 or 4** at presentation

for care. **All children aged under 5 years .**

Remark

- For PLHIV whose HIV status is unknown but who present with strong clinical evidence of HIV infection, in settings where there is a high prevalence of HIV or among members of a high risk group for HIV; recommended to Perform HIV testing in accordance with national guidelines.

1. Hospitalized PLHIV who are evaluated for TB and are positive for signs and symptoms of TB,

   A. Collect a urine specimen and conduct the LF-LAM assay and collect a Sputum specimen and conduct mWRD testing, If the mWRD test is available on site.

Remark (21,24):

A. In settings where access to mWRDs such as Xpert service on same day is not feasible, do Bacteriological test such as AFB smear microscopy on two samples on spot, and send specimen for mWRDs. If Smear results turns positive rifampicin resistance need to be ruled out.

For individuals being evaluated for pulmonary TB, the following samples may be used for the molecular WRD test: induced or expectorated sputum (preferred), Bronchoalveolar lavage, Gastric lavage or aspirate, Nasopharyngeal aspirate and stool samples can be used in line with LF-LAM. .

B. For individuals being evaluated for EPTB, theGeneXpert MTB test is recommended to diagnose TB from specimen such as CSF , lymph node aspirates and lymph node biopsies, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid , Blood may also be considered to diagnose of disseminated TB using solid TB Culture methods only.

C. The LF-LAM result (test time <15 minutes) is likely to be available before the molecular WRD test result, and should be interpreted in the context of clinical judgment, chest X-ray findings (if available) and any available bacteriological results.

D. All patients eligible for testing requirements who have a positive LF-LAM result should be initiated on TB treatment immediately, while awaiting results of the molecular WRD test .

E. TB is not ruled out if the LF-LAM test result is negative. Evaluate the results of the molecular WRD test, and follow Nation Diagnostic Algorithm (Algorithm 1 Annex) for interpretation of results and follow-up testing.

F. Treat all patients with a molecular WRD test result of "MTB detected" for TB, regardless of LF-LAM result.

G. TB is not ruled out if both the LF-LAM result and molecular WRD test results are negative (or if no molecular WRD test is performed). Re-evaluate the patient and conduct additional testing in accordance with national guidelines. Further investigations for TB may include chest X-ray, additional clinical assessments or cultur

1.3. Scope of the implementation guideline

- The Guideline is designed

  - ✓ To provide key information on Global and country specific recommendation and application to use LF–LAM for PLHIV in advanced disease conditions in Ethiopian.
  - ✓ To use for HIV care service decision-making process, particularly for all clinicians especially ART focal persons, TB focals, laboratory professionals, TB and HIV control program managers monitoring & evaluation, pharmacy and supply management staff.
  - ✓ To provide guidance to health care workers in out- and in- patient Care settings, in line with the current national Guideline for programmatic management of TB in PLHIV and the national comprehensive HIV guideline.
  - ✓ To provide role and responsibility of Health care service providers and administrators at each tire system of health care service delivery in Ethiopia.
  - ✓ To provide key Indicators for Programmatic and operational tool for Monitoring& Evaluation of appropriate utilization and performance.

1.4. Objectives of the implementation guidelines

- ✓ To review and recommend **strategic approach** for implementation and application of LF-LAM for PLHIV in advanced disease state in Ethiopian health care setting .
- ✓ To review and recommend **clinical use and application** of LF–LAM in advanced PLHIV disease conditions in Ethiopian context.
- ✓ To review and recommend **minimum laboratory operational standard** to use LF–LAM in assisting TB diagnostic strategy for PLHIV in advanced disease state .
- ✓ To assess and recommend **minimum operational standard**, implementation cost , affordability and supply chain management strategy of LF-LAM implementation

in Ethiopia .

- ✓ To review and set **key Indicators of Monitoring&Evaluation** and **impact assessment** standard.

2. Strategic approach

2.1. Eligible PLHIV for LF_LAM Test

WHO 2019 policy update on LF-LAM recommends(21)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 coinfected with HIV. The estimated sensitivity is even greater in patients with low CD4 cell counts.

Therefore, HIV-positive adults, adolescents and children with the following criteria are eligible for Urine LF_LAM test to assist in the diagnosis of active TB:

2.1.1. In outpatient settings

- With signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill
- Irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm3

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
- Without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm3
- without TB symptoms and with a CD4 cell count of 100–200 cells/mm3

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 Algorithms for LF-LAM use.

2.1.2. In inpatient settings

- With signs and symptoms of TB (pulmonary and/or extrapulmonary)
- With advanced HIV disease or who are seriously ill
- Irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm^3

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

b. 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/mm3 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.

(Further descriptionon of the strategies is available in Annex 1 and Annex 2.)

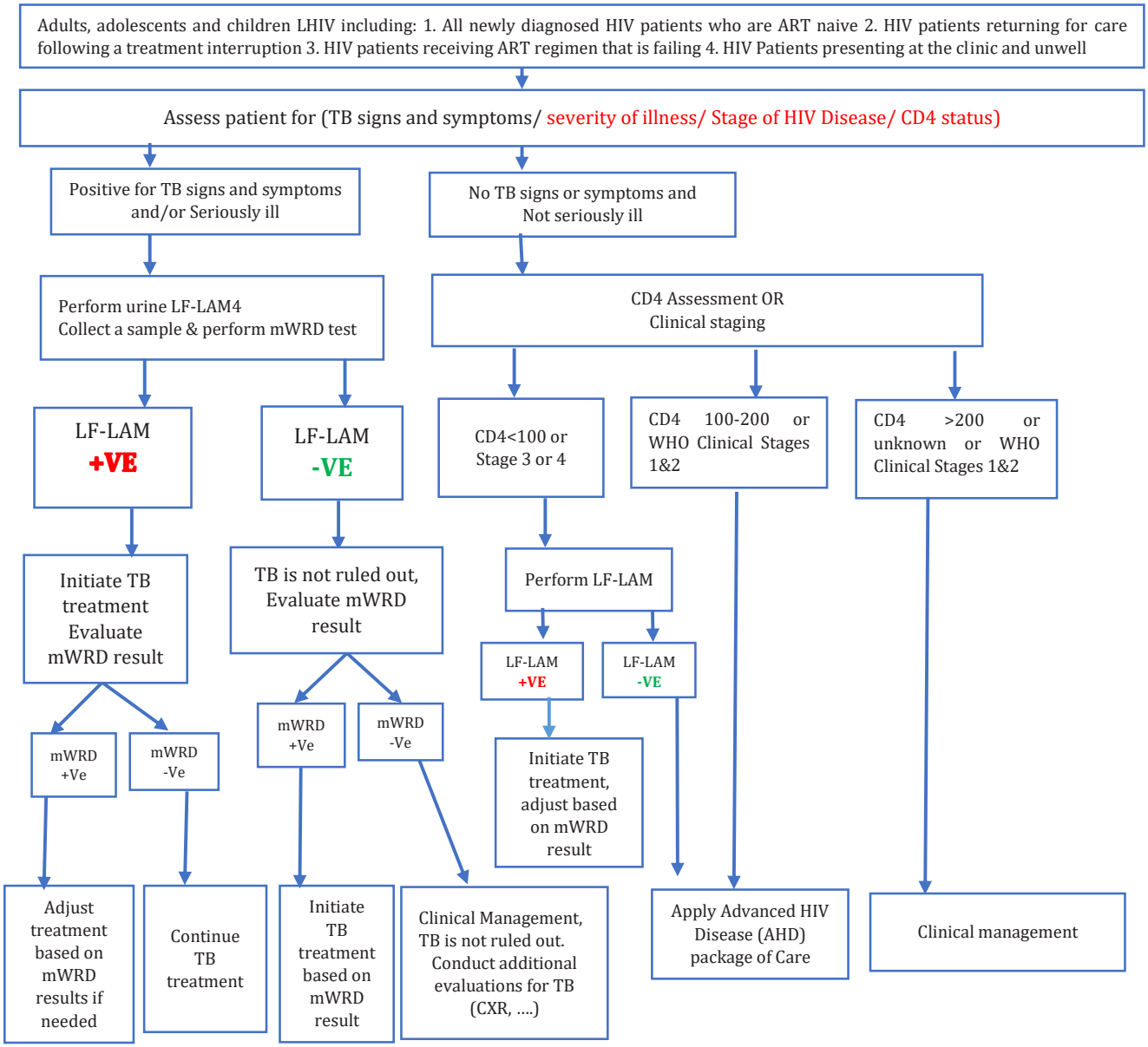
Note for using LF_LAM test for children less than 5 years:

Latest WHO guideline consider all HIV infected children age <5 years old to follow as advanced HIV disease , besides nationally we have a limited number of under 5 children on ART. Hence setting other criteria may limit the Urine LF_LAM utilization. Until further guidance given by WHO, the team suggested to conduct LF_LAM test for all HIV infected children under 5 years at least once as per below criteria:

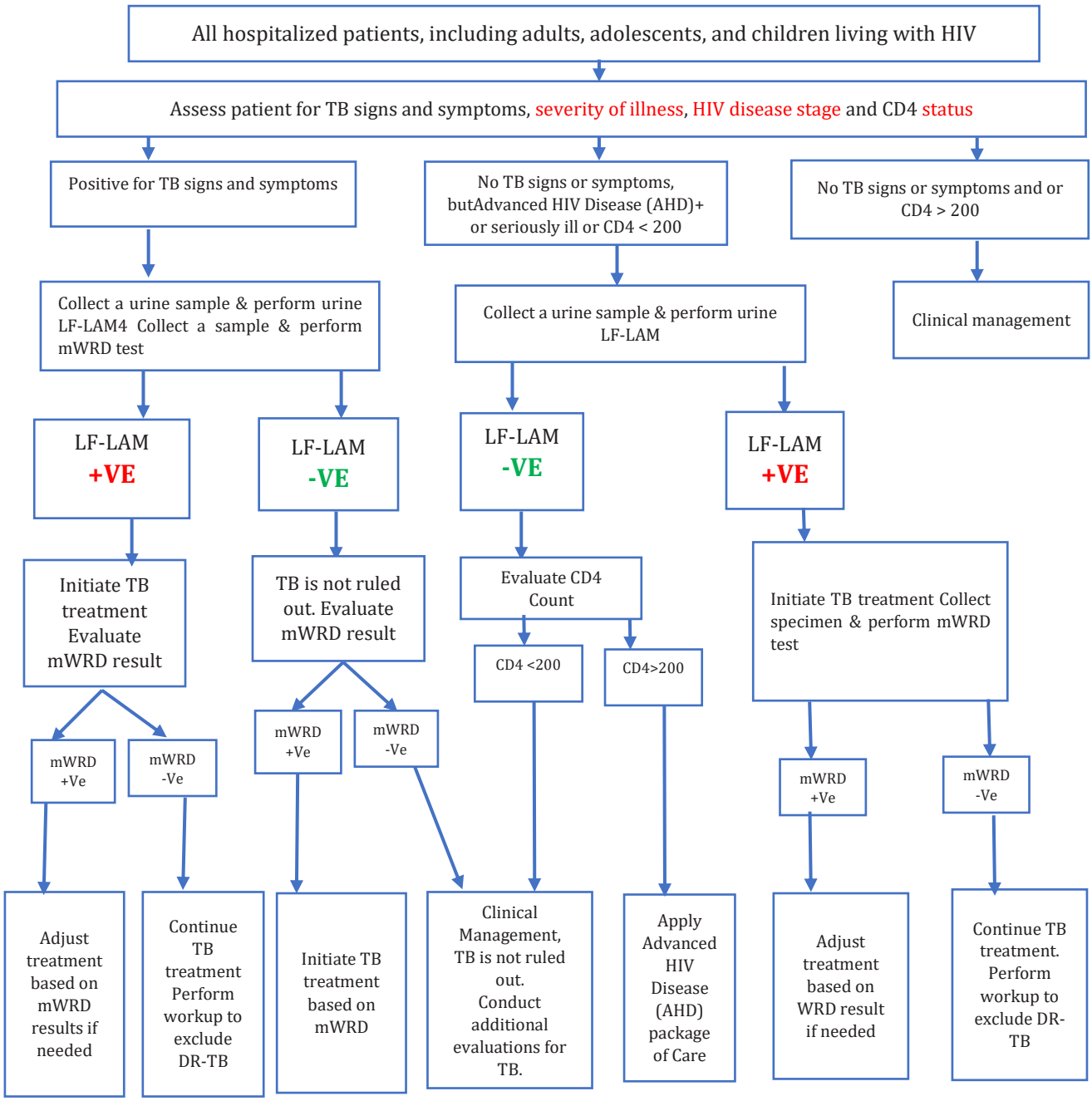
- To offer LF_LAM for all HIV infected <5 years children backlog/currently on treatment once irrespective of clinical stage or CD count/CD 4 percentage
- All newly enrolled under 5 HIV infected children (at Enrollment) irrespective of clinical stage or CD count/CD4 percentage
- Once cleared the backlog, offer LF_LAM at any time when children presented with TB symptoms, or serious illness or advanced HIV stage or CD4 percentage.

2.2. National TB Diagnostic Algorithm for PLHIV Incorporating Urine LAM test

2.2.1. Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in outpatient settings



2.2.2. Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in inpatient settings



2.3. Laboratory order and result interpretation

2.3.1. Urine LAM test workflow

The urine LF-LAM test is ordered by Health Care Workers (preferably by those received orientation on the test) using standard lab request form. The request is usually anticipated to come from ART clinics or In-Patient facilities but can also come from any department where ART clients are receiving service. Urine LAM test kits and sample collection containers should be available at the laboratory at all times (including weekends and duty hours). Urine LF-LAM test result takes only 25 minutes so the standard Turn Around Time (TAT) for result reporting should be not more than 1 hour as the result is usually required urgently for treatment decision on seriously ill patients. The lab personnel should communicate Urine LF-LAM positive results immediately by phone to the attending clinician till the result paper is ready following lab registration process.

2.3.2. Result interpretation

Urine LF_LAM positive test can aid diagnosis of TB through appropriate use of the algorithm. However, it should be well underscored that Urine TB LAM test is a rule-in test, meaning a negative test doesn't exclude TB disease. Therefore, in addition to clinical parameters, the clinicians should make every effort to use other bacteriologic, histo-pathologic, imaging, etc. tests to establish the diagnosis of TB. The following results are expected for urine LF test and recommended measures to be taken by the clinician:

- **Positive:** Manage as TB case in line with the LF-LAM algorithm recommendation
- **Negative**: The clinician should use other clinical and diagnostic test result findings to decide further management. Test may be repeated as required if the
- **Equivocal/indefinite/Indeterminate:** Means unclear to confidently say positive or negative. For better clinical decision, the test should be repeated on a fresh sample; early morning urine sample is best.
- **Invalid:** This result is normally not reported to the clinician but this may prompt the lab technician to do some quality assurance measures and repeat the test on the same or other fresh sample.

2.4. Case definition, classification,treatment follow up, case registration and relevant indicators

Monitoring the implementation of newer WHO-approved diagnostic tools, such as Xpert MTB/RIF and urine LAM (lipoarabinomannan assay), is important, as they offer advantages over other diagnostic modalities. Understanding of TB burden among people living with HIV should inform program management and planning. The WHO policy update (21) on LF-LAM test and other WHO documents didn't provide guidance on case definition and classification of TB cases diagnosed by Urine LF-LAM test. The 2020 WHO consolidated Strategic Information guidelinehowever provided some guidance regarding indicator definition for measuring performance for use of newer molecular TB diagnostic tests in different indications and diagnostic yield. Therefore the guideline development task team has made the following recommendations in relation to case definition, classification and indicators for recording and reporting of Urine LAM test use at the health facilities till further guidance is available for standardized M&E at global level:

2.4.1. Case definition:

The national TB guideline defines bacteriologically confirmed TB as follows:

A bacteriologically confirmed TB case: *Refers to a patient from whom at least one biological specimen is positive for mycobacterium TB by either smear microscopy, Xpert MTB/RIF, culture or other WHO approved bacteriologic detection tests.*

(For full detail of TB case classification(25).

Urine LF-LAM test is a WHO approved 'bacteriologic detection' diagnostic test based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine. Therefore, based on the national TB case definition, the national guideline development task team recommends that TB patients diagnosed using solely on the basis of positive urine LF-LAM test following the national algorithm are '**bacteriologically confirmed TB cases**' till further guidance from WHO is available for standardized case definition.

2.4.2. Classification

- Classification based on **previous treatment history** follows same principle also for urine LAM diagnosed cases(25).
- For practical purpose, classification based on anatomic site of involvement will be decided as follows:
  - ✓ **Pulmonary:** TB cases diagnosed based on positive Urine LAM test with any of the following evidence of pulmonary involvement are classified as pulmo-

nary TB cases:

- ✓ Signs and symptoms of pulmonary TB (cough, hemoptysis, chest findings, etc.)
- ✓ CXR Abnormal**ity on the lungs (other imaging tests)**
- ✓ Bacterial confirmation of MTB from sputum sample (or other similar e.g. bronchio-alveolar lavage) by smear microscopy, mWRDs or Culture

NB: when result of positive sputum test is received at a later time, the case classification should be updated as 'Pulmonary' on the registers accordingly; similarly if DST result shows Rif resistance, we should refer classification for DR-TB cases (25) for appropriate case classification amendment and subsequent action. Treatment regimen should also be modified as necessary based on DST result.

- Extra-Pulmonary:Patients diagnosed as TB case, solely by Urine LAM positive result but not fulfilling the criteria for 'pulmonary TB' cases as above are classified as extra-pulmonary TB cases.

2.4.3. Treatment follow up of Patients diagnosed using Urine LF-LAM test algorithm

The guideline development task team recommended the following treatment monitoring and documentation of treatment outcome till monitoring guidance is available from WHO for standardized approach.

- **Urine LAM test Negative and mWRDs test Negative:** treatment decision can still be made based on other tests e.g. imaging, histopathologic test, etc. If the clinician decides to initiate treatment in such instances, treatment follow up can be made clinically and successful treatment will be documented as 'Treatment Completed'
- **Urine LAM test Positive but mWRDs test Negative**: For both pulmonary and EPTB, monitor patients clinically and report successful treatment outcome as 'Treatment Completed'
- **Urine LAM test Negative but mWRDs test Positive from sputum sample:** Treatment follow up will be by sputum smear test and treatment outcome will be determined in the same way as other bacteriologically confirmed pulmonary TB patients (see national guideline).

NB: If patient diagnosed using the Urine LF-LAM test algorithm and solely based on positive Urine LAM test show worsening of TB symptoms while on TB treatment the patient should be investigated for superimposed infections/illnesses and anti TB drug resistance. In such instances, genotypic DST should be done for identifying Rifampicin

resistance. Patient's TB case classification and anti-TB regimen should be modified in case the mWRD test result turns out to be positive and Rifampicin resistance is detected.

2.4.4. Indicators and definitions for PLHIV evaluated with Urine LAM test

The following indicators adopted to the country program context will be used for monitoring appropriate use of Urine LAM as part of the PLHIV TB screening clinical cascade:

Indicator: TB testing among those symptom-screened positive

Indicator definition:

Percentage of people living with HIV newly initiated on ART and screened positive for TB symptoms who then are tested for TB.

Numerator

Number of people living with HIV on ART who are investigated for active TB disease with appropriate diagnostic testing

Denominator

Number of people living with HIV on ART and screened positive for TB symptoms during the reporting period

What it measures

This indicator measures the percentage of people living with HIV newly initiated on ART and screened positive for TB symptoms who then had clinical evaluation and/or appropriate TB diagnostic testing.

Rationale

Appropriate TB diagnostic testing is essential for people living with HIV who symptom-screen positive for TB. It is important to understand the cascade from ART enrolment to treatment of active TB disease; this indicator will shed light on any obstacles between positive screening for TB symptoms and proper diagnostic testing, based on national clinical guidelines.

Method of measurement

For the numerator. Program records (ART register, EMRs). "Appropriate" diagnostic testing refers to WHO & Nationally recommended testing modalities.

For the denominator. Program records (ART registers, EMRs)

Disaggregation

- ART status (New, & already on ART)
- Gender (male, female)
- Age (<15, 15+).
- Type of diagnostic test (Xpert MTB/Rif (including Ultra), Urine LF-LAM, Other.

2.5. Patient Management

Patients diagnosed as TB cases as per the national Urine LAM algorithm shall follow the management and follow up protocol described in the national comprehensive ART guideline - Advanced care package and the national TB/HIV guideline(25).

Treatment outcome will also be determined using similar parameters like in the other TB cases.

3. Laboratory testing of LF-LAM for PLHIV

3.1. The LF-LAM Assay

Lipoarabinomannan (LAM) is a major lipopolysaccharide component of the outer cell wall of mycobacteria has a 17.5 kDa glycoprotein found on the surface of the cell(21,26). It is an immunogenic virulence factor that is released from metabolically active or those that are being degraded and is specific for mycobacteria species(21,26). It has characterized as a potential marker of active TB, and it is the most-studied TB biomarker to date. Factors that make LAM an attractive biomarker for TB include that it is derived from and specific to mycobacteria species; it is abundant in the cell wall of MTB; it is heat and protease stable; and it has structural epitopes that are unique to MTB(21,26).

In people living with HIV who are seriously ill, TB can disseminate into various organs. Since LAM is filtered by the kidneys, it is detectable in urine, particularly in patients with advanced HIV disease and disseminated TB. Finding LAM in urine typically indicates severe disease that requires immediate treatment. In addition, in patients with TB who are immunocompromised, the bacilli are not contained by typical immune responses due to the patient's low CD4 cell count and impaired response; thus, TB bacilli can be degraded and excreted by normal body processes. In both scenarios, the MTB LAM antigen can be present in urine, making detection viable for diagnosis.

Test principle

LF-LAM consists of an immunochromatographic assay for the qualitative detection of LAM antigen of mycobacteria in human urine specimens. The test uses highly purified polyclonal antibodies to capture LAM molecules (the target antigen) with a lateral flow, sandwich-based enzyme-linked immunosorbent assay (Figure. A below). The specimen is added to the test strip and capillary flow moves the LAM antigen across the strip so that (A) it binds to a colloidal gold conjugate antibody to form an immunocomplex; (B) capillary flow moves the immunocomplex past the control and patient windows where it is captured by an anti-LAM antibody fixed to the nitrocellulose membrane; and (C) the presence of LAM is confirmed by the colloidal gold label. A purple–grey band in the patient window indicates a positive result, showing that LAM antigen from mycobacteria is present in the sample at or above the detection limit of the test. If no band is visible, then LAM either is not present or possibly present below the detection limit, and thus the result is presumed to be negative. A control window has been added to ensure the validity of the test; a line should be visible in the control window for every test. The control band uses an antibody with specificity to the colloidal gold(27).

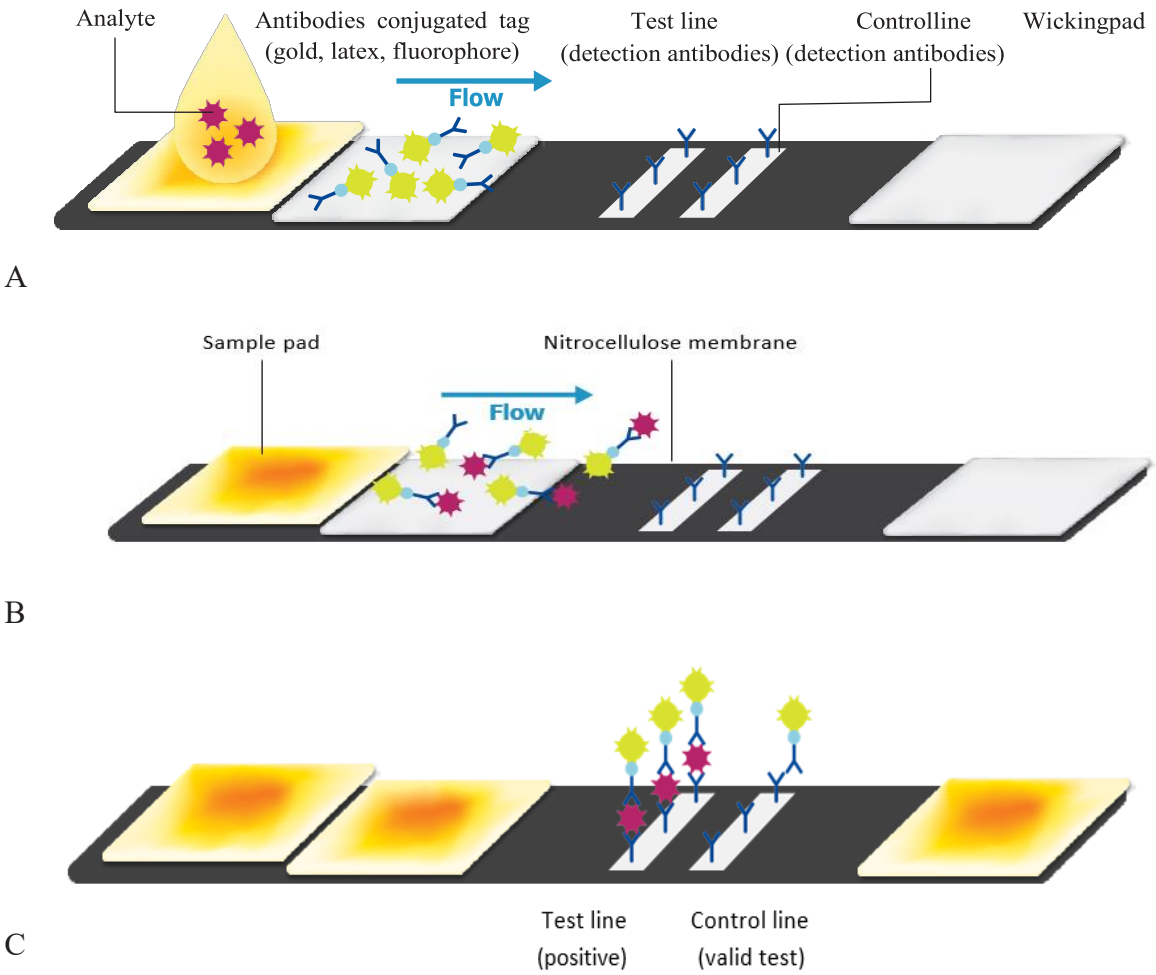


Figure A: General principles for detecting the lipoarabinomannan (LAM) antigen(27).

Performance and operational characteristics:- According to the WHO review of 2019, there were 15 included studies involving 6814 participants, of whom 1761 (26%) had TB(21). 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(21).

The study further summarized the sensitivity and specificity of AlereLAM for the diagnosis of TB among PLHIV based on inpatient and outpatient settings, sign and symptoms of TB, CD4 count and adult and children categories as presented in tables below(21).

Table 1: Performance characteristics of LF LAM for the diagnosis of TB among adult PLHIV

Setting	**Performance characteristics**							
	Sensitivity				**Specificity**			
	with sign and symptom of TB	Irrespective of TB sign and symptom	Advanced disease irrespective of sign and symptom (based on CD4 count)		with sign and symptom of TB	Irrespective of TB sign and symptom	Advanced disease irrespective of sign and symptom (based on CD4 count)	
			≤ 200 cells/ul	≤ 100 cells/ul			≤ 200 cells/ul	≤ 100 cells/ul
Outpatient	29% (17-47%)	31% (18-47%)	21% (8–48%)	40% (40-64%)	96% (91-99%)	95% (87-99%)	96% (89-99%	87% (68-94%)
Inpatient	52% (40-64%)	62% (41-83%)	64% (35-87%)	57% (33-79%)	87% (78-93%)	84% (48-96%)	82% (67-93%)	90% (69-97%)
All	42% (31-55%)	35% (22-50%)	26% (9-56%)	47% 30-64%)	91% (85-95%)	95% (89-98%)	96% (87-98%)	90% (77-96%)

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

Table 2: Performance characteristics of LF LAM for the diagnosis of TB among children living with HIV

Setting	Sensitivity	Specificity
Outpatient	42% (15-72%)	94% (73-100%)
Inpatient	56% (21-86%)	95% (90-98%)
All	43% (23-66%)	80% (69-88%)

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

3.2. Laboratory infrastructure and Supplies needed for testing

Urine LF-LAM test Minimum Requirements	
Human Resource	• Laboratory professional and/or HCWs received onsite/offsite orientation
National Guidelines, SOP, and PSTs	• National TB guideline • Urine LF-LAM job aid • LF-LAM implementation guideline • Urine LF-LAM SOPs
Equipment and supplies	• LF-LAM test kit • Urine cup • Timer • Pipette or other device capable of accurately delivering 60 µL of urine (this could be a calibrated 100 µL micropipette with filter tips or a dual-bulb 60 µL micropipette • Glove
Register and Forms	• TB Laboratory registration logbook • TB laboratory requisition and reporting format

In addition, workstation with adequate light and waste disposal system for both sold and liquid waste should be readily available.

3.3. Sample collection, testing and interpretation for LF-LAM

Sample collection and storage

The required sample for LF-LAM testing is urine(freshly colleted, catheterized and urine bag). Before collecting the urine sample, it is highly recommended that the urogenital areas are cleaned with a cleansing wipe.Midstream urine should be collected in a standard urine specimen cup.It is recommends using early morning urine to ensure optimal test performance(26,27).

Whenever feasible, fresh samples should be tested, ideally immediately after collection. If immediate testing is not possible, urine can be stored at room temperature for a maximum of 8 hours or at 2–8 °C for a maximum of 3 days. If testing is delayed more than 3 days, the samples should be frozen (-20°C or colder). For frozen or refrigerated urine bring all samples to room temperature one hour prior to testing. Frozen samples may contain aggregates. For internal quality control and research purposes, samples can be frozen at –20°C.

However, freezing can cause the formation of uncharacterized precipitates. Thus, unthawed samples require centrifugation at 10,000 g for 5 minutes at room temperature and then a 60 µL aliquot can be drawn from the clear supernatant for testing. Avoid multiple freeze–thaw cycles (i.e. allow only a maximum of three) as the LAM antigen can deteriorate. Specimens that have been frozen and thawed more than 3 times cannot be used. Note that some studies have indicated that urine LAM reactivity disappears in samples stored for 3 years at –20 °C.

Supplies needed for LF-LAM testing

The following supplies are required for LF-LAM testing are

- LF-LAM kit
- Clean urine collection cup;
- Pipette or other device capable of accurately delivering 60 µL of urine (this could be a calibrated 100 µL micropipette with filter tips or a dual-bulb 60 µL micropipette
- Timer
- Reference Scale Card
- Package insert with instructions

Figure B .The items required for the Alere Determine TB LAM Ag assay include the test card, the reference Scale Card, a sterile urine collection cup, a pipette and a timer(10).

Procedure

The basic procedure is indicated in Figure C, and the standard operating procedure is outlined in Annex 9. The test strip should be used within 2 hours after removing it from the protective foil cover. If more than one sample will be tested, be sure to properly label each test strip so that it can be linked correctly to each patient's sample. The workbench should be cleared of materials not used for testing and cleaned with disinfectant. It is important to follow an organized workflow for testing and timing to ensure the accuracy of the test.

The basic steps are:

(1) Remove the protective foil cover for each test strip needed and ensure they are properly labelled for each patient's sample;

(2) Add 60 µL of urine to the sample pad using a precision pipette or alternative device;

(3) Wait 25 minutes and then read the results. Results are stable for a total of 35 minutes. Do not read after 35 minutes;

(4) Check the results against the Reference Scale card included in the test kit.

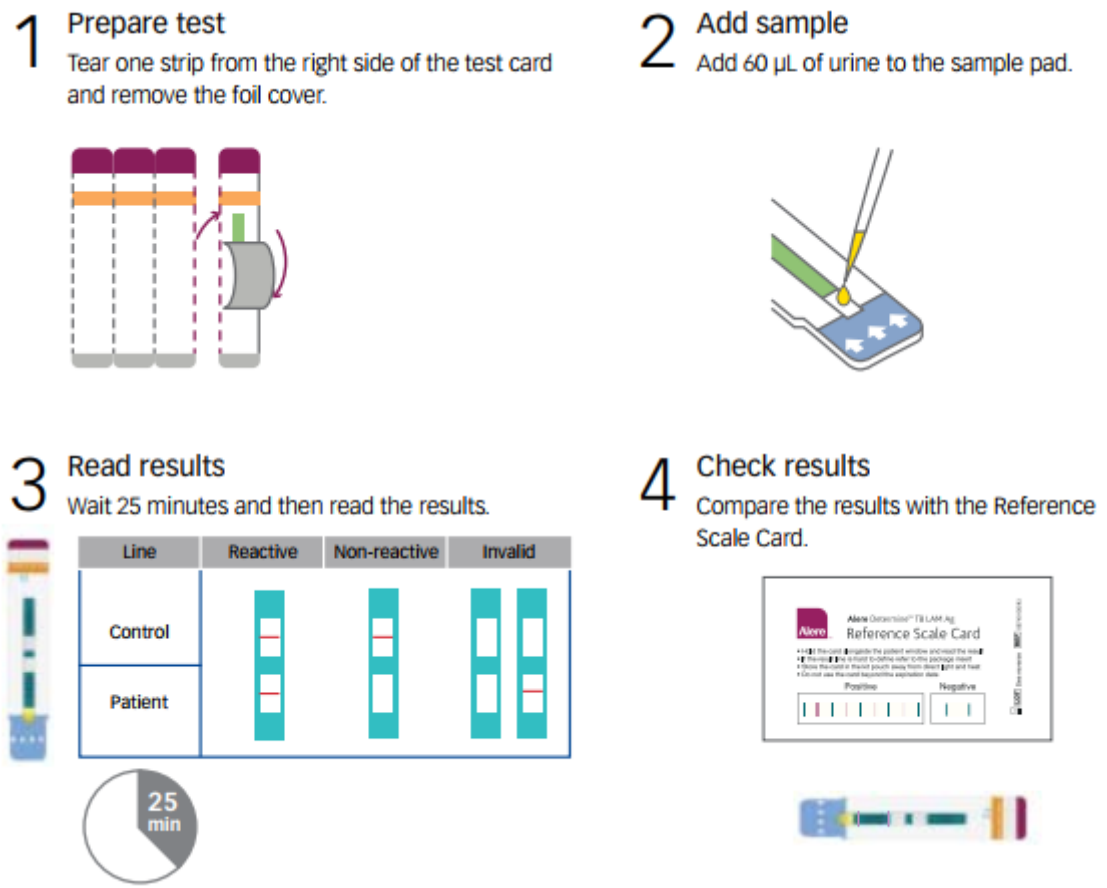


Figure C. Testing procedure for the Alere Determine TB LAM Ag assay

Result Reading, interpretation and Reporting

Read the strip using the naked eyes in well lit room, NOT in direct sunlight

Purple/grey bands will appear in the windows on the test strip

1. Check if there is a band visible in the control window of the test strip.

2. If there is a band visible in the control window, then check the patient window for a visible band

- If a band is visible in this window, the test is positive
- If there is no band in this window, the test is negative
- If the band in this window is incomplete or not clear, the test is indeterminate. Repeat the test on another urine specimen.

3. To assist with the reading match the intensity of the band in the patient window of the test strip against the reference scale card to determine the positivity.

- if the intensity of the band in the patient window is lower than any of the coloured bands in the section marked positive in the Reference scale card. The test is indeterminate and must be repeated on another sample of urine.

4. A log should be kept of all LAM positive results together with the patient details and folder numbers as a record for the purposes of future reference and in case results are required by another centre or during a following admission(30).

Quality control testing

Conduct quality control testing for LF-LAM when new batch/lot isopened(26,27). Record the results of the quality control testing in the IQC log (Annex 10).

The following procedure should be used to evaluate the AlereLAM quality controls.

For the AlereLAM positive control:

(1) First, label the test strip as the TB LAM positive control;

(2) Add 60ul of the TB LAM Ag positive control to the labelled test strip;

(3) Read the results after 25 minutes.

For the LF-LAM negative control:

(1) First, label the test strip as the TB LAM negative control;

(2) Add 2 drops of saline solution or distilled water;

(3) Read the results after 25 minutes.

3.4. Biosafety requirements and waste disposal

Safety precautions are essential and should be followed at all points in the testing process from specimen reception to testing, storage, and disposal of biohazard wastes so as to minimize occupational risk. Conduct testing in a clean workstation. Gowns and gloves must be worn awhile working in the laboratory. After use, removed gloves aseptically and washhands.

- All procedures must be performed in such a way as to minimize or prevent the formation of aerosols and splash.
- All contaminated materials, Pasture pipete and urine collection container must be decontaminated appropriately using 1:10 diluted 5 % hypoclorite solution before disposal or cleaning for reuse.diluted solutions should be prepared daily.
- Work stations must be decontaminated before and at the end of each work session ,after any spill of potentially infectious material.
- The Specimen or materials should effectively decontaminated or disinfected using proper procedures.

Materials that are decontaminated or disposed of outside the laboratory should be placed in a strong, leak-proof waste container

- Waste materials must be packaged in a closed container or bag for immediate onsite incineration.

4. Human Resource Development

4.1. Technical Training on LF-LAM

Before implementation LF-LAM, a one-day training and practical session should be provided for regional laboratory professionals.The training will provide information on cascading, patient eligibility, how to perform the test, test application and the visual interpretation .In addition the training will provide guidance on how to integrate LF-LAM with other TB laboratory trainings andsupervisions.

4.2. Sensitization Workshop on LF-LAM

As with any new technology being implemented, a sensitization workshop will be provided for respective stakeholders.Theone daysensitization workshopis recommendedforclinicians, regional health bureau TB and HIV focal, zone TB and HIV focal, EPSA, HAPCO and EFDA so that the specifics of each setting can be understood and to ensure user capability and understanding.

5. Supply chain management for LF-LAM

In order to achieve sustainable LF-LAM implementation, it is very important to ensure the availability of the supplies. The current procurement, storing and distribution system for TB diagnostic supplies in most cases is done by EPSA. Therefore, it would be better to address and include the supply system for LF-LAM into the existing IPLS. To improve the role and active engagement of EPSA hubs and health facilities, the distribution will be based on the requesting and reporting form (RRF) provided from the facilities.

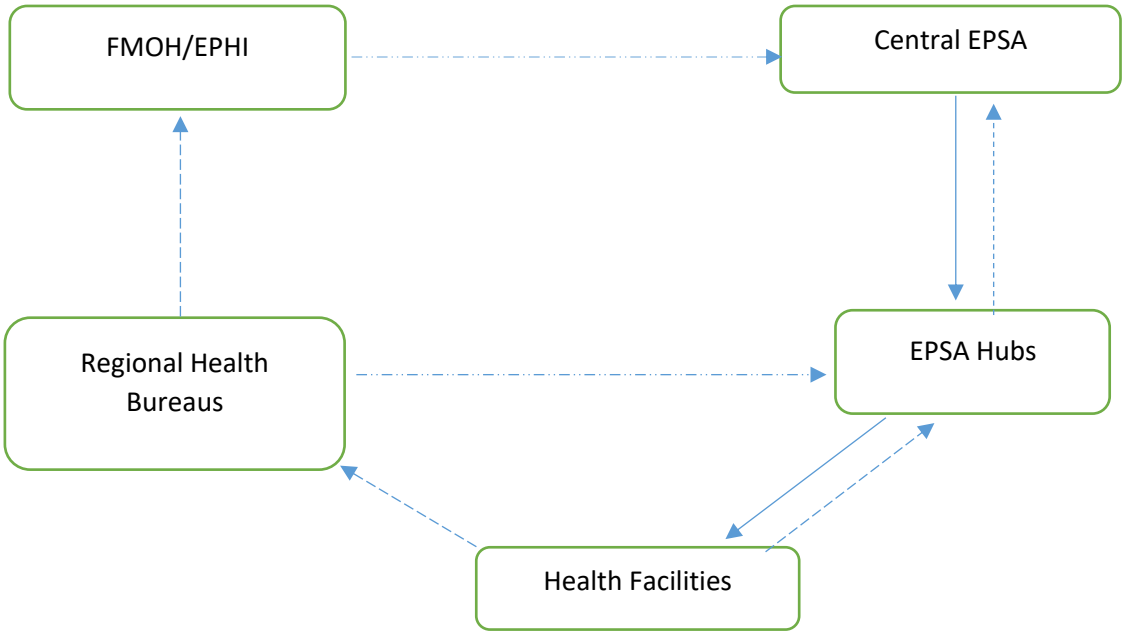
To initiate the LF-LAM testing for the first time during the implementation period, the estimated stock will be distributed to the region based on the request received from each RHBs. The regional estimation and the distribution plan for the first time to initiate the test at selected heath facilities till IPLS take place, MOH, EPHI and partners will prepare the regional quota based on the patient enrollment and stock status. The Disease Prevention and Control Program issue the letter to the central EPSA for the distribution of LF-LAM supplies. The central EPSA in turn will issue the quantity to respective EPSA hubs and they will deliver the health facilities every two- months. Sometimes, the health facilities can collect the supplies from the Hubs to avoid any delay.

As it is expected to do the test in the laboratory, the Head of health facility laboratory or any appointed personnel will fill the Internal Facility Reporting and Resupply Form (IFRR) and send the request to the pharmaceutical main store based on the stock on hand at laboratory.

In order to timely deliver and refill of the supplies, either electronically or manual reports can be employed. Therefore, each health facility can fill excel based format and send it to RHBs through email or the hard copy every two months and as the same time RRF to respective Hubs for the resupply. The RHBs will aggregate the report in both soft and hard copy and share it to FMOH for monitoring purpose. All health facilities will align the requesting and reporting of the products with the existing IPLS schedule to ensure the sustainable LF-LAM supplies.For the next refill period, each health facility will be responsible to correct the report based on the feedbacks from RHB.

In case of an emergency order, if needed, the report format to place an order will be the same as with the routine reporting RRF and excel based format.

Figure D: LF-LAM Supply Distribution flow from the National to Health Facilities



Keys:

- Flow of LF-LAM kit :
- Report and Request:
- Approval of Request:

6. Quality Assurance

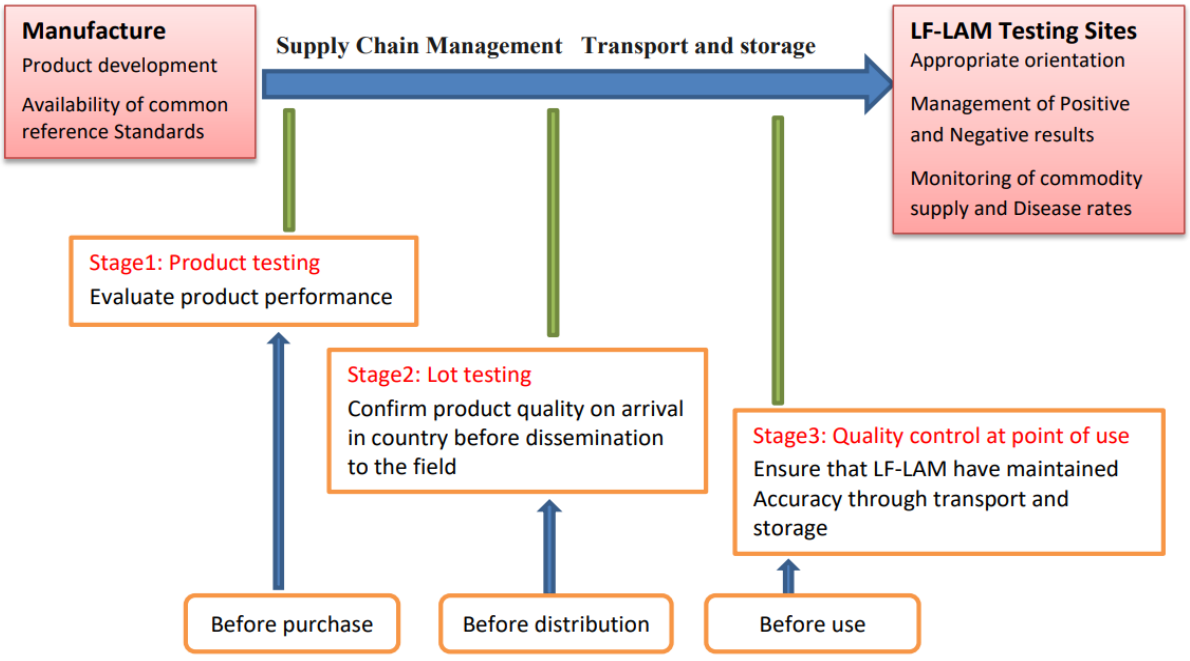
LF-LAM quality assurance aim to ensure high accuracy of tests in the hands of end-users. This will include both monitoring of the technical standard of the processes, monitoring of preparation and interpretation at all LF-LAM implementation sites describes all the activities taken by a laboratory to monitor each stage of a test procedure to ensure that tests are performed correctly and are accurate and precise maintain a quality service and provide for continuing improvement to provide reliable, relevant, timely test results(27,28).

The two quality assurance methods are implemented for LF-LAM test

- Internal Quality Control (IQC)
- External quality Assessment (EQA)
  - Panel testing (PT)
  - On-site Supervision & Evaluation

6.1. Internal quality control

IQC is used to demonstrate that a test is functioning properly and can produce a valid result. Each LF-LAM test strip includes in built internal quality control and result bar that should be evaluated for each test, as described in the interpretation section. When a new batch opened lot testing conducted by using known LAM positive and LAM negative urine samples(27,30).



6.2. External quality control

External Quality assurance performed to evaluate testing site's performance and identify any site-level needs not captured via routine reporting practices. EQA will be conducted by using on site evaluation and Proficiency testing.

6.2.1. On-site supervisory and evaluaton visits

On site supervision and evaluation conducted by EPHI and RRL biannually as per the schedule of National EQA Programme using modified existing supervisory checklists to ensure a standardized tool is used during supervisory visits across the network so that findings can be compared over time and between testing sites. The use of LF-LAM can be evaluated and reports incorporated into the existing schedule for supervisory visits(31).

6.2.2. Proficiency testing

EPHI NTRL prepares and distruibutesprofieciency testing samples on annual basis. Proficiency testing evaluates the accuracy and timeliness diagnostic serves as an efficient tool for monitoring and evaluation of testing networks. Profieciency testing results from testing facilitis will be sent back to NTRL.

6.3. Quality indicators

To monitor LF-LAM testing service quality each facility should select and monitor laboratory quality indcators. The following quality indicators shoud be monitored on reguarbaseis this are turnaround time, customer satisfaction, test interruption, internal and external quality control.

7. Monitoring and Evaluation (M&E) Plan for LF-LAM Implementation

Performance of LF-LAM at the site and network levels should be regularly evaluated using routinely collected and reported data obtained from supervisory visits, quarterly reports and proficiency testing and other reports received from existing channels of documentation. Unexpected changes in performance or performance that is below targets for quality should be promptly investigated for remediation.

Monitoring and Evaluation

Strong monitoring and evaluation system needs to be put in place which is important to monitor the effect of LF-LAM

Urine TB LAM test quarterly reporting tool					
TB-LAM indicators	**Total eligible for LF-LAM testing (A)**	**Both LF-LAM and GeneXpert tested (B)**	**Only LF-LAM tested (C)**	**Both LF-LAM and GeneXpert positive (D)**	**Positive only by LF-LAM (E)**
Outpatient TB symptomatic HIV positive (New/treatment interrupted /treatment failing / clinically unwell) clients in the quarter					
Outpatient HIV positive clients with CD4 < 100 and or stage 3/4 in the quarter					
TB symptomatic inpatient HIV positive clients in the quarter					
Inpatient HIV positive clients with Advance HIV disease or seriously ill or CD4 < 200 in the quarter					

Supportive Supervision: Ministry of Health and EPHI in collaboration with RHB, RRL and Partners will conduct a separate specific supportive supervision at the beginning of the implementation plan whereas RHB will conduct biannually. In addition, the checklist will include the monitoring tools of LF-LAM at all levels for the proceeding supportive supervision.

Review meeting: The annual meeting will be conducted at national level. Participants will be experts from FMOH, EPHI, EPSA, RHB, RRL, FHAPCO, EFDA and Partners. The best experience will be shared during the review meeting.

Reporting: Standardized recording and reporting formats(Annex 12) will be available to implementing health facilities. Each site will compile and summit report to the existing reporting system every quarter. The facility ART focal is responsible to compile the report and send to respective region and EPHI. Since it is a new initiative, the FMOH, EPHI and the development partners will follow the implementation status, so the report probably requested when needed or during the supporting supervision.

- Indicators are selected to monitor and evaluate the impact, outcome, output and input of the LF-LAM techniques

Data Sources: ART register, TB unit register and TB laboratory registration book

8. Roles and Responsibilities

Ministry of Health

- Develops and issues policy documents and guidelines on the introduction of urine LF-LAM and ensure the integration with the existing diagnostic methods
- Prepares and coordinates the national implementation plan in collaboration with EPHI and Developing Partners
- Mobilizes resources for the expansion of the LF-LAM test
- Leads the sensitization workshop or by providing the circulars to ensure the test implementation
- Defines the national algorithms, eligibility criteria and placement strategies and oversees the rollout plan
- Develop the requesting and reporting tools

Ethiopian Public Health Institute (EPHI)

- Develops training and implementation materials on the use of LF-LAM test and leads the training of laboratory professionals and program officers in collaboration with NTP and partners
- Prepare the launching ceremony for the test implementation in collaboration with EPHI and patners
- Develops quality assurance guideline for the use of the test and oversees the quality assurance of the test and produce proficiency test (PT)
- Leads the evaluation of the impact of introduction of the LF-LAM test on TB case finding
- Develops standard operating procedures (SOP) for use of LF-LAM test
- Strengthen the specimen referral and laboratory networking, and results delivery for the test
- Conducts operational and other programmatic and non programmatic researches.
- Monitoring and evaluation of LF-LAM test implementation in the country

Ethiopian Pharmaceuticals supply Agency (EPSA)

- Organize annual forecasting and quantification of the required supplies for the LF-LAM assay
- Procures, stores and distributes the required supplies for the assay as per the national quantifications
- Regular stock status update to FMOH, EPHI, RHBs

Ethiopian Food and Drug Authority (EFDA)

- Undertakes inspections of the laboratories with the assay and ensures adherence to the national standards
- Registration and certification of the LF-LAM supplies for use in Ethiopia

Regional Health Bureaus (RHB)

- Ensure the ownership and coordination of the use of the LF-LAM implementation
- Prepare the regional launching ceremony for the test implementation in collaboration with EPHI and patners
- Ensure the enrollment of all the diagnosed TB cases to treatment
- Monitor the stock status of the required supplies at HFs in all sites and ensure timely request as per the IPLS
- Conduct regular supportive supervisions with RRL to the sites
- Monitoring and evaluation of LF-LAM test implementation in the region

Regional Reference Laboratories (RRL)

- Coordinates the regional laboratory networking specimen referral linkage
- Conduct External Quality Assurance (EQA) at testing sites
- Provides the training/sensitization workshop of laboratory professionals and program officers in collaboration with RHB and partners
- Conduct regular supportive supervisions in collaboration with RHB and partners

Testing Health Facilities

- Distribute the testing circulars to all the outlet services
- Assign staffs to conduct the tests and ensures the implementation of tests
- Identify the eligible clients for the test as per the national guidelines and algorithms
- Conduct the tests and record the results as per the national guidelines
- Monitor the stock status of the required supplies in the site and ensure timely request to EPSA through the IPLS
- Participate in quality assurance activities
- Ensure the diagnosed cases are enrolled on treatment

Development Partners

- Provides technical support for the rollout plan and development of guidelines, training materials and to develop monitoring tools
- Provides financial support for the procurement of the LF-LAM
- Provides financial support for trainings and sensitization workshops

9. LF-LAM Implementation steps

- Resource mobilization and stake holder coordination
- Procurement of the LF-LAM test kit
- Conduct site assessment for placement
- Complete the LF- LAM implementation guideline
- Develop one day training material for program staffs, lab professionals and clinicians
- Conduct national LF-LAM technology launching workshop
- Provide one day training/ Sensitization for TB program staffs, lab professionals and clinicians at regional and zonal levels and district level
- Distribute the LF-LAM test kit to eligible health facilities as per the assessment
- Distribute recording and reporting formats, registration book and job aids
- Implement Quality Assurance programs (Panel tests, On-sites Evaluation)
- Ensure the implementation of the M & E system
- Conduct Operational Research

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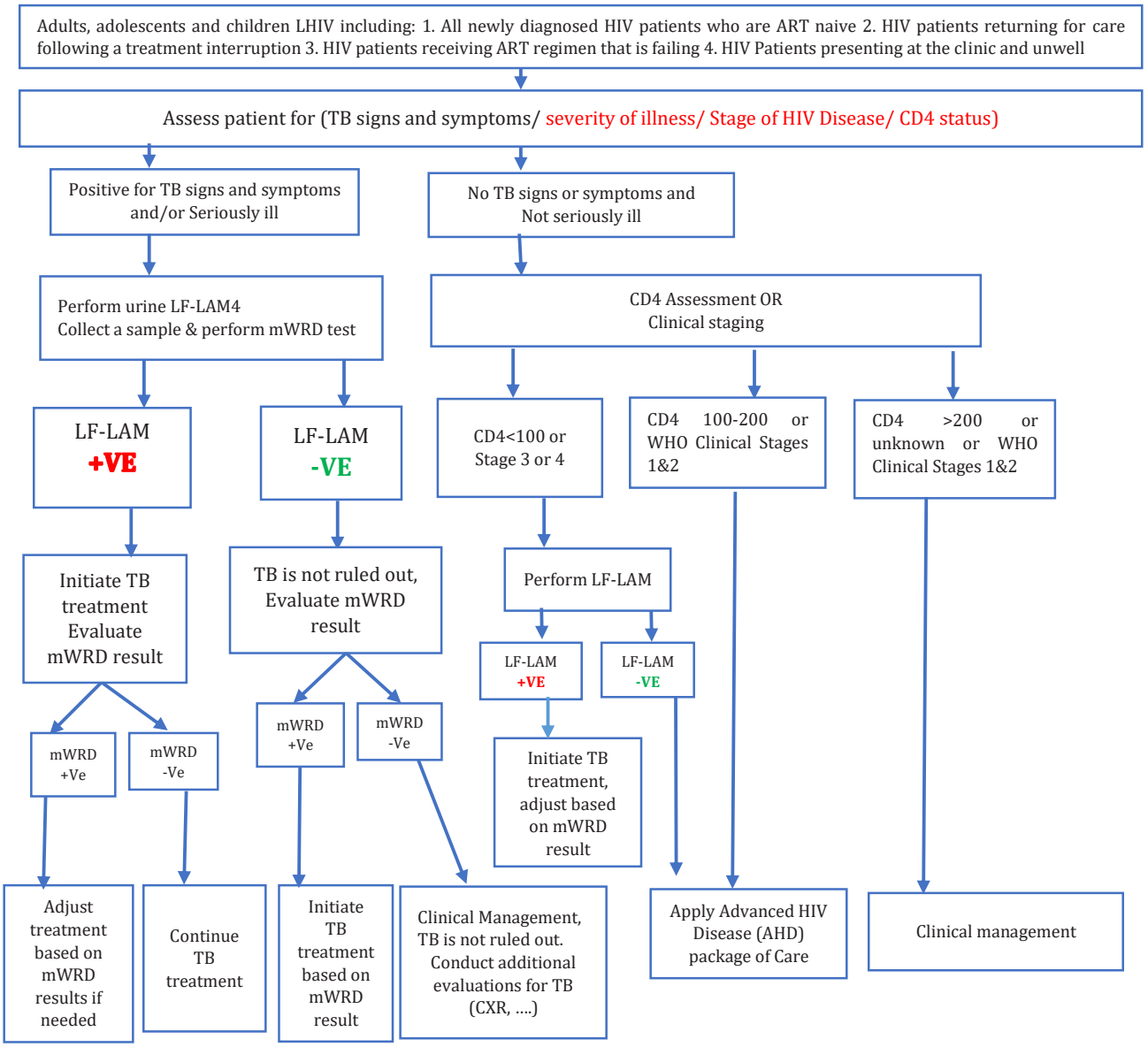
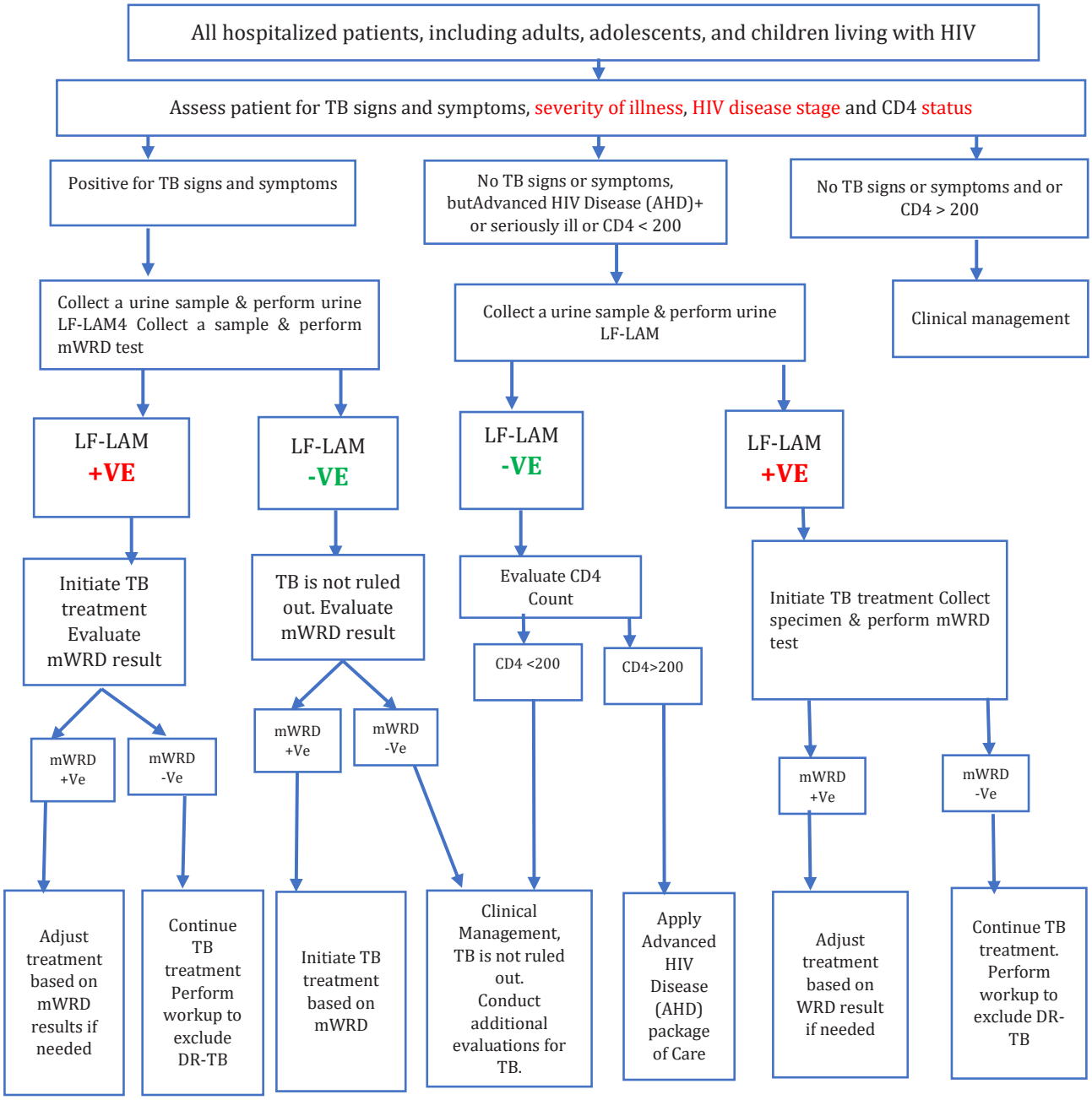
ANNEXES

Annex 1: Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in outpatient settings



Annex 2: Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in inpatient settings



Annex 3 ART register

Health Center/Clinic/Hospital

ART Register

Region	Zone/Subcity/Woreda	Health FacilityName	BeginDate	EndDate

ART Register

														TB										Fill when applic able1st				Line		2nd Line		3rd Line	
			Regist ration			Functional Status*	Weight (kg)	Height / Length(cm)	MUAC (cm)	BMI height for Age	Nutrition Screening Result write code	Food	CD4 (if child CD4 %)	Screened for TB (V) / Screening resul	GeneXpert (1)/Urine LF-LAM (2) sent (√)/Result (P/N)	TB Treatment Start date (DD/MM/YY) / Complete date (DD/MM/YY)							Fluconazole preventive therapy (FPT) ( )	Enrolled to Appointment spacing Model (DD/MM/YY)		Contraceptive (/) / Using anyModern	Date Referred to PMTCT (DD/MM/YY) / Date Returned (DD/MM/YY)	OriginalRegimen		Regimen		Regimen	

Months: 0-6											Months: 7-12									Months: 13-24																			Months: 25-36													
Month 0	1	2	3	4	5	6					7	8	9	10	11	12														24												36											
									Wt									Wt													Wt												Wt										
							Regimen	Functional status	Ht	CD4	Date VL sample collected						Regimen	Functional status	Ht	CD4	Date VL sample collected									Regimen	Functional status	Ht	CD4	Date VL sample collected									Regimen	Functional status	Ht	CD4	Date VL sample collected					
																					Detectable or Undetectable												Detectable or Undetectable												Detectable or Undetectable					
36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	(55)	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88

Annex 4 Unit TB Register

Health Centre/Clinic/Hospital

UNIT TB REGISTER

Region	Zone/Sub-city/Woreda	Health Facility Name	BeginDate	End Date

UNIT TB REGISTER

MRN	Unit TB No.	Name of the patient / Address of the patient (Woreda, Kebele, Hno.,Phone No.)	Sex (M/F) / Age	TB Most at risk group**	Name of contact person / Address contact person (Woreda, Kebele, H.No., Phone No.)	Linked to TB service by (HP, Public HF, PPM HF)	Xpert MTB/RIF(1)/Urine LF_LAM as initial diagnosis (√)	Xpert MTB/RIF(1)/Urine LF_LAM (2) result / Lab. no.	Smear result / Lab. no.	Category N.R.F.L.T.O / P/Pos, P/Neg or EPTB	Nutritional Assessment and Status: Weight (kg) / Height (cm) / BMI (kg/m2) / MUAC(cm)	Normal, MAM, SAM	Intensive phase: Drugs	Intensive phase: Dos	Treatment started (DD/MM/YY)	Write the month	Intensive phase treatment monitoring chart Days: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47

TB Most at risk category* (Key population) 1. Health care staffs including HEWs 2. Diabetes 3.Homeless 4.Refugee 5.Prisoners 6.Miners 7. Other congregated settings (University Students, Developmental mega project workers etc)

UNIT TB REGISTER

TB/HIV Co infection: HIV test offerred (√)	TB/HIV Co infection: HIV test performed (√)	TB/HIV Co infection: Targeted population category** write code	TB/HIV Co infection: HIV test result (P or N)	TB/HIV Co infection: CPT started (DD/MM/YY)	TB/HIV Co infection: Enrolled in HIV care (DD/MM/YY)	ART started (DD/MM/YY) / Unique ART No.	Presumptive DR (Y/N) / DST Result (NoRR,RR, MDR, Pre-XDR,XDR)	DR-TB Confirmed, linked to (Name of HF) / Date DRTB started (DD/MM/YY) / Unique DR TB ID	Total HH and/or Close Contacts (Number) / Total contacts Screened for TB (Number) / Total TB diagnosed among Contacts (Number)	Total under 5 Contacts (Number) / Total under 5contacts ScreenedforTB (Number) / Total under 5 contacts screened Negative (Number) / Total under 5 put on IPT (Number)	Sputum results, Lab serial No.: 2nd month	Sputum results, Lab serial No.: 5th month	Sputum results, Lab serial No.: 6th month	Nutritional Assessment and Status (End of 2nd Month): Weight (kg) / BMI (kg/m2)/ MUAC (cm)	Nutritional Assessment and Status (End of 2nd Month): Normal, MAM, SAM	Continuation phase: Drugs	Continuation phase: Dose	Continuationphasetreatmentmonitoringchart weeklyattendance: Week of the Month	Month: Ham	Month: Neh	Month: Pas	Month: Mes	Month: Tik	Month: Hid	Month: Tah	Month: Tir	Month: Yek	Month: Meg	Month: Mia	Month: Gin	Month: Sen	Treatement Outcome: Cured Completed, Failure, Died, Lost to Follow Up, Not Evaluated, Moved to DR-TB Register: Date outcome assigned in EC (DD/MM/YY):	Nutritional intervention and Outcome: Type of treatment: (RUTF) or Plumpy nut/ (RUSF) or Plumpy sup / Nutritional treatment started date in EC (DD/MM/YY):	Nutritional intervention and Outcome: Outcome of treatment: recovered, cured, No change, other outcome (specify) / Date outcome assigned in EC (DD/MM/YY):	TB Treatment Adherance support: Health Facility	TB Treatment Adherance support: Health Post	Remarks
48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
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Targeted population category** A. Female Commercial Sex workers, B. Long distance drivers, C. Mobile/Daily Laborers, D. Prisoners, E. OVC, F. Children of PLHIV, G. Partners of PLHIV, H. Other MARPS, I. General popu

Annex 5 HIV CARE/ART FOLLOW-UPFORM

HIV CARE/ART FOLLOW-UPFORM — FEDERAL MINISTRYOFHEALTH

FacilityName_____ Name: _____Age _____years(Month <5years) Sex ☐M F ☐

Address:RegionWoreda/SubcityKebele_____HouseNo._____Telephone _____PatientCardNoUnique ARTNo. _____DateconfirmedHIV+ (Retesting): //(DD/MM/YY)

TypeofHIV Test ☐RapidHIV tests ☐DNA/PCR(forchildren)Client readiness: (date client is ready)//(DD/MM/YY)Height(Adult)in cm: _____

Sr US	Follow up date dd/mm/yy	Monitoron ART	Weight (Kg) Edema+/-	MUAC (MUAC for pregnant woman or bedridden)	Pregnancy status /FP method	Functional Status W,A,B	WHO Stage (1-4 / T1- T4	TB Screen- P/N	Xpert MTB/RIF(1) LF-LAM(2) Sent (√)	Xpert MTB/RIF(1) LF-LAM(2) Result P/N	TB Treatment / TBProphylaxis	Cervical Cancer Screened (VIA)(0,1,2,3,4)	OIs/ HIVrelatedcancers	Assessed &Managed for pain	CD4 /mm^3 or % if<5 Yrs.	VL result (copies/ml)	Hgb. ALT/ AST/ Cr/ CrAg	Co-trimoxazole Preventive therapy Adherence (G,F,P)	Co-trimoxazole Preventive therapy Dispense dose	Fluconazole preventive therapy (FPT) (Dispensed Dose)	Other medications/ or nutritional supplements dispensed	Assess&counsel forARV Adherence Adherence (G,F,P)	Assess&counsel forARV Adherence Why Fair or Poor?	ARVdrugs Dispense Dose/ code	ARVdrugs Side effect	ARVdrugs Reason for change	Client sets HIV prevention plan for Disclosure Children	NextVisit Date dd/mm/yy
					If child Length/ Height/ Circumferencefor <5years	Developmental Milestone (A,D,R)																						

Version: Hamle_ 2011

Annex 6 HIV CARE/ART FOLLOW-UPFORM 2

S/US

S=Scheduled US=Unscheduled

TBSCREEN

SCREENFOR TB AT EVERYVISIT

Adult&Adolescent

1. CurrentCough?
2. Fever?
3. Nightsweats.
4. Weightloss?

P=(Positivescreen)-Yesto anyofthe above---EvaluateforTB.

N= (Negativescreen)- Noto all the questions above---- assessforIPTeligibility

Children0-14years old

1. CurrentCough?
2. Fever?
3. Weightlossor poorweightgain ?
4. ContacthistorywithTB patient?

P=(Positivescreen)-Yesto anyoneofthe four----evaluatefor TB

N=(Negativescreen)-Noto allfour---- assess foreligibilityto IPT

Xpert MTB/ RIF (GeneXpert) (1)

P= Positive
N= Negative
Urine LF-LAM (2):P,N

TB PROPHYLAXISTREATMENT

INH1-6=CurrentlyonINH prophylaxis (Numberrefers to monthson INH)
INH-C=Completedtreatment
INH- DC=discontinuedforanyreason
TB RX1-6=CurrentlyonAntiTB(numbers refertomonthsonRx)
TB RXDC=discontinuedTB Rxforany reason
TB Rx C=Completedanti TB Rx

OI/ OpportunisticCancers

NOI=NoOI or Opportunisticcancer
Z=Zoster
BP=BacterialPneumonia
PTB=PulmonaryTuberculosis
EPTB=Extra pulmonarytuberculosis
TO= Thrush oral
EC=esophagealcandidiasis
UM=ulcers-mouth
DCor DA=DiarrheaChronic/Acute
PCP=Pneumocystispneumonia
CT=CNS Toxoplasmosis
CM=CryptococcalMeningitis
NHL=NonHodgkinsLymphoma
KS=Kaposi'sSarcoma
CCa=Cervicalcancer
O=Other

Monthson ART

Durationin monthssinceinitiationofART:
0=ARTInitiationdate
1week=1 week
2weeks=2 weeks
3weeks=3 weeks
1= 1 month
2=2 months
If not started on ART (Pre-ART)leavethiscolumnblank

Pain Assessment &Management

AssessforPain&Manageas
NP= Nopain
S1= WHOStep1
S2= WHOstep2
S3= WHOstep3

Nutritional Status (adults)

BMI (wt/(ht²)) (fornon-pregnant/nonpostpartum)
1= Normal(18.5-24.99kg/m²)
2= Mild (17-18.49kg/m²)
3=Moderate malnutrition (16-16.99kg/m²)
4=Severe malnutrition (<16kg/m²)
5=Over weight (25-29.99 kg/m²)
NB: write the codes (1,2,3,4 or

MUAC (forpregnant/postpartum /bedridden)
1= Normal (>23cm)
2=Moderate malnutrition (19-23cm)3=Severe malnutrition (<19cm forpregnant and postpartum /<18cm for bedridden)

ADHERENCE

Estimatedherenceusingthe table below:

Adherence	%	# missedddoses	
G (Good)	≥95%	(of 30 doses) <2 doses	(of 60 doses) ≤3 doses
F (Fair)	85-94%	2-4 doses	4-9 doses
P (Poor)	<85%	≥5 doses	≥10 doses

IfFairorPoorsdherence,inwhycolumnnotereason:
1. Toxicity/ Sideeffects
2. Share withothers
3. Forgot
4. Felt better
5. Too ill
6. Stigma,discloser
7. Drugstockout
8. Lost/ ranoutofpills
9. Delivery/ travelproblems
10. Inabilitytopay
11. Alcohol
12. Depression
13. Other

Pregnancy Status/FamilyPlanning Method

P=Pregnant(Ifpregnant,giveestimateddue date(EDD))
PMTCT=Referredto PMTCT&indicatelinkage
WP=wanttobecomepregnant
NoFP=not pregnant& inot usinganyFP methods
FP=OnFamilyPlanning(enter code):
1=Condoms
2=Oralcontraceptivepills
3=Injectable
4= Implant
5=Intrauterinedevice
6=Vasectomy/ tuballigation
7=Abstinence(nosex)

Length / height/ HC

Measurelength/heightincm forchildren youngerthan14yearsatEVERYvisit.
Measurehead circumferenceincm forchildren younger than3yearsofageatEVERYvisit

NutritionalStatus(Children)

W/H
1=Normal/ Appropriate (> -1Z-score)
2=Mild(<-1and> -2Z-score)
3=MAM- ModerateAcuteMalnutrition (<-2and>-3 Z-score)
4=SAM-SevereAcuteMalnutrition(<-3Z-score)

SIDE EFFECTS

1. Nocide effects
2. Nausea
3. Diarrhea
4. Fatigue
5. Headache
6. Numbness/tingling/pain
7. Rash
8. Anemia
9. Abdominalpain
10. Jaundice
11. Fatchanges
12. Dizzy,anxiety,nightmare,depression
13. Other

REASONSFORREGIMENCHANGE

1. Toxicity/ Sideeffects
2. DuetoneuTB
3. Newdrugavailable
4. Drugstockout
5. Clinicalfailure
6. Immunologicfailure
7. Virologicfailure
8. Other

Functionalstatus

W=Working(able to performusualwork inor out of the house,harvest, go to schoolor,for children, normal activitiesor playing)
A=Ambulatory (ableto performactivities ofdaily Living)
B=Bedridden (not ableto performactivities of daily living)

DEVELOPMENTALMILESTONESFORCHILD

A=Appropriate:
Sittingwithout support 3 to9months
Standingwithassistance.....5to 11months:
Hands and knees crawling 6 to1 3months
Walkingwithassistance .....7 to14 months
Standingalone.....8 to17 months
Walkingalone..... 9 to18 months
Delay: Failure tomeetmilestonesforage
Regression: Loss ofwhat has beenattained for age

NutritionalStatus(Older children &adolescents)

BMIforage(5-18yrs)
1=Normal/Appropriate (>-1Zscore)
2=Mild(<-1and> -2Zscore)
3=Moderatemalnutrition(<-2and>-3Zscore)
4=Severemalnutrition(<-3Zscore)
*BMIforage forolder childrenandadolescents.

REASONSFOR STOPPINGREGIMEN

STOP=StoppedART
IfSTOP,In whycolumn,note reason:
1. Toxicity/sideeffects
2. Treatment failure
3. Poor adherence
4. Illness,hospitalization
5. Drugs out of stock
6. Patient Inclfinances
7. Otherpatient decision
8. Other

VIRAL LOAD

Mark '*' under VL column when requested specimen collected,
Write the amount and interpret as undetectable and detectable for clinical intervention

Cervical Cancer Screening

Screened with VIA (1- 4):
0. VIA Not Done
1. VIA Negative
2. VIA Positive: eligible for Crvo
3. VIA Positive: Non-Eligible for Crvo
4. Suspicious for Cervical Cancer

Client readiness

Enter the date (dd/mm/yy) client is ready for ART initiation when client is counseled, adherence barriers addressed and client is willing to start ART

Client Set HIVPreventionPlan
D =Agreedto Disclosetopartner/family/friend,
PT= Agreed to bring partner for testing
ChT=agreedtobringchildrenfor testing,
SSex=discussed&agreedto practicesafersex
SubU=Decidestoavoidor decreaseSubstanceuse
ASS=AssessedforSTI
SRX=clientmanagedforSTI

ForchildrenFill instageofHIVdisclosure
DS0 = No disclosure
DS1=Satge1, about the illness, taking medicine, keeping healthy,
DS2=Stage2, about germs, body soldiers,
DS3=Stage3, use of terms like CD4, Viral Load, HIV

DISPENSE DOSE/ REGIMEN CODE

ADULT FIRST LINE	CHILD FIRST LINE
1c = AZT-3TC-NVP	4c = AZT+ 3TC+NVP
1d = AZT - 3TC - EFV	4d = AZT+3TC+EFV
1e = TDF - 3TC - EFV	4e = TDF+3TC+EFV
1f = TDF + 3TC + NVP	4f = AZT +3TC + LPV/r
1g = ABC + 3TC + EFV	4g = ABC + 3TC + LPV/r
1h = ABC + 3TC +NVP	4i = TDF + 3TC + DTG
1j = TDF + 3TC + DTG	4j = ABC + 3TC + DTG
1K = AZT + 3TC + DTG	4K = AZT + 3TC + DTG
1i = Other specify	4L = ABC + 3TC + EFV
	4h = Other specify
ADULT SECOND LINE	**CHILD SECOND LINE**
2e= AZT +3TC +LPV/r	5e=ABC+3TC+LPV/r
2f =AZT+3TC +ATV/r	5f=AZT + 3TC + LPV/r
2g=TDF + 3TC+-LPV/r	5g=TDF + 3TC + EFV
2h= TDF + 3TC + ATV/r	5h=ABC + 3TC + EFV
2i= ABC + 3TC+ LPV/r	5i= TDF + 3TC+LPV/r
2j= Other specify	5k= RAL+AZT+3TC
	5L= RAL+ABC+3TC
	5m= ABC+3TC+DTG
	5n= AZT+3TC+DTG
	5j= Other specify
ADULT THIRD LINE	**CHILD THIRD LINE**
3a = DRV/r+DTG+AZT+3TC	6a = DRV/r + RAL + AZT +3TC
3b = DRV/r+DTG+TDF+3TC	6b = DRV/r + RAL + TDF +3TC
3d = DRV/r+ABC+EFV+3TC	6c = DRV/r + DTG + AZT +3TC
3c = Other specify	6d = DRV/r + DTG +TDF+3TC
	6F = DRV/r+DTG+ABC+3TC
	6e = Other specify

Inthefollow-up date, in2nd columnif oneof theoptionsbelowapplies, userawnext to thelast visit to enter theappropriateinformation:
TO=Transferout LOST=not seensince ≥1 month,3 months DROP= lost tofollow-upfor >3 months STOP= When the clinician stop ART for different reason and patient is on follow up DEAD

Annex 7: TB Laboratory reqeust and report form

TB Laboratory Requesting and reporting For

Ethiopian Public Health Institute
MOH- ---Tel: 251 (0) 11 551 7011 Fax: 251 (0) 11 551 9366 E-mail: moh@ethionet.et P. O. Box 1234, Addis Ababa, Ethiopia
EPHI--- Tel. +251 112 78 08 45 Email: ephi@ethionet.gov.et p.o. box:1242 , Addis Ababa, Ethiopia

TB Diagnostic Service Request and Report Form

1. **PATIENT ADDRESS:** Patient Full Name: _____ Age: _____ Sex: _____ Region: _____
   Tel: _____ Name of contact person: _____ Tel: _____ Referring HF: _____ MRN: _____
   TB registration No/DR- TB No: _____
2. **TB DISEASE TYPE & TREATMENT HISTORY**:
   - ❖ Site: i. Pulmonary _____ ii. Extra pulmonary (specify): _____ Co-infection _____ CD4 count: _____
   - ❖ Patient Registration Group: ☐ New ☐ Relapse ☐ Treatment after lost to follow-up ☐ After failure of first line treatment ☐ After failure of Second line treatment ☐ Other
   - ❖ Previous TB drug use: ☐ New, ☐ 1st line treatment, ☐ 2nd line treatment, ☐ DR-TB contact, ☐ Other, _____
3. **REQUEST FOR TESTING AT TB LABORATORY:**
   - ❖ **Reason:** I. **Diagnosis**: If Diagnosis, ☐ Presumptive TB, ☐ Presumptive DR, II. **Follow up**: If follow up, ☐ at_____ months of 1st line treatment, ☐ MDR Follow up, at _____ months after treatment, ☐ Presumptive XDR, _____
   - ❖ **Specimen Type:** ☐ Sputum ☐ Urine/LF-LAM ☐ Other, Specify: _____
   - ❖ **Requested tests:** ☐ Microscopy, ☐ GeneXpert MTB/RIF assay ☐ Culture, ☐ Phenotypic DST (First Line _____, Second Line_____) ☐ Line Probe Assay (First Line _____, Second Line_____) LF-LAM _____

   Requested Clinician: Name: _____Signature _____Tel:_____ Date of Request _____
4. **LABORATORY RESULT (for Laboratory use only) :**

   Laboratory Number: _____ ☐ Date of specimen collected (E.C): ___/____/_____ Date of sputum received (E.C): ____/___/____

4.1 Microscopic examination:

- ❖ **Specimen Quality:** bloody, saliva, purulent or semi-purulent
- ❖ **Method used:**
- ✓ Ziehl-Neelsen ☐ Direct Smear ☐ Concentrated Smear
- ✓ Fluorescence ☐ Direct Smear ☐ Concentrated Smear

Name of the Examiner: _____ Signature: _____ Date: _____

Result	Negative	Positive			
		Scanty	1 +	2 +	3+
1st Spot					
2nd Spot					

4.2 GeneXpert MTB/RIF Assay Result:

Result	Detected	Not detected	Indeterminate	Trace	Remark
M. Tuberculosis (MTB)					
Rifampicin Resistance (RR)					

Name of the Examiner: _____ Signature: _____ Date: _____

4.3 Alere LF-LAM (for PLHIV)

Indication	☐ **1-**Outpatient TB symptomatic HIV positive (New/treatment interrupted /treatment failing / clinically unwell) ☐ **2-**Outpatient HIV positive clients with CD4 < 100 and or stage 3/4 ☐ **3-** TB symptomatic inpatient HIV positive clients ☐ **4-** Inpatient HIV positive clients with Advance HIV disease or seriously ill or CD4 < 200
Result:-	☐ **Positive** ☐ **tive** **Inva** ☐

4.4 TB Culture result: Method used MGIT LJ

Result	Positive for Mycobacterium tuberculosis Complex (MTBC)					Negative	Contaminated
	1-9 colon ies Actual Count	10 – 99 colonies (1+)	≥100 colonies (2+)	Confluent growth (3+)	Non tuberculous Mycobacteria (NTM)		

4.5 TB Drug Susceptibility Testing (DST) result:

Result	1st line drugs					2nd line drugs							Other	
	INH	RMP	STM	EMB	PZA	OFL	LFX	MXF	AM	CAP	KM	EA		
Line Probe Assay														
Phenotypic DST														

Legend: INH=Isoniazid RMP= Rifampicin PZA= Pyrazinamide EMB=Ethambutol STM = Streptomycin OFL= Ofloxacin LE=Levofloxacin MO=Moxifloxacin AK=Amikacin CAP=Capreomycin KM= Kanamycin EA= Ethionamide
S=Sensitive; R = Resistant; C = Contaminated; ND = Not done.

Name of Examiner _____ Date_____ sig._____
Comment: _____Date reported: ____/____/____
GeneXpert Reviewed by: _____ Date _____Signature_____ .
LF-LAM Reviewed by: _____ Date _____Signature_____ .
Culture Reviewed by: _____ Date _____Signature_____.
LPA Reviewed by: _____ Date _____Signature_____.

Annex 8: Job aid forLF-LAM testing

JOB AID FOR ALERE DETERMINE TB LAM ANTIGEN RAPID SCREENING TEST IN ETHIOPIA
January 2021

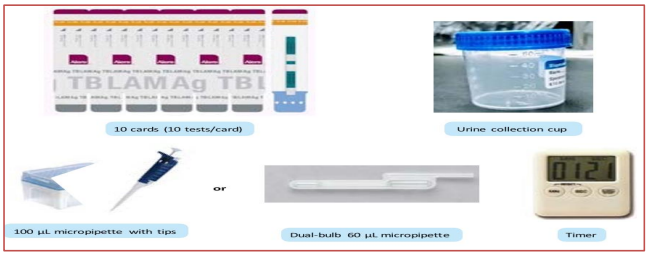
Alere Determine TB LAM Ag is a qualitative rapid test for the detection of lipoarabinomannan (LAM) antigen of Mycobacteria in human urine as an aid in the diagnosis of active mycobacterial infection in HIV positive individuals with clinical symptoms of tuberculosis

1: Who to be Tested?

PLHIV Inpatients: with signs and symptoms of TB or who are seriously ill or irrespective of whether there are TB symptoms if they have CD4 counts < 200 cells/mm3.
PLHIV Outpatients: with signs and symptoms of TB or who are seriously ill or irrespective of whether there are signs and symptoms of TB if they have a CD4 count < 100 cells/mm3

2. Materials needed:

Alere Determine TB LAM test strips, urine cap, transfer pipette or paste pipettes, timer and gloves.



3. Specimen Type and Procedure

Specimen: Use urine only

Procedure: Label test strip with patient number on urine sample container and test strip, add 60µL urine specimen to the sample pad (see the figures below).

Read results at the 25th minute.

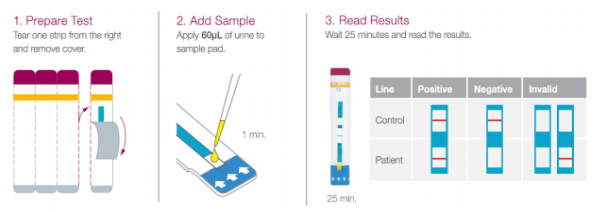


Figure 1 TB LAM Ag testing procedure

4. Test Result Interpretation

LAM Antigen POSITIVE (Two Bars - Control and Patient Bars)

Purple/gray bars appear in both the control window (labelled "Control") and the Patient window (Labelled "Patient") of the strip. Note: The test result is positive even if the patient bar appears lighter or darker than the control bar.

NEGATIVE (One Bar)

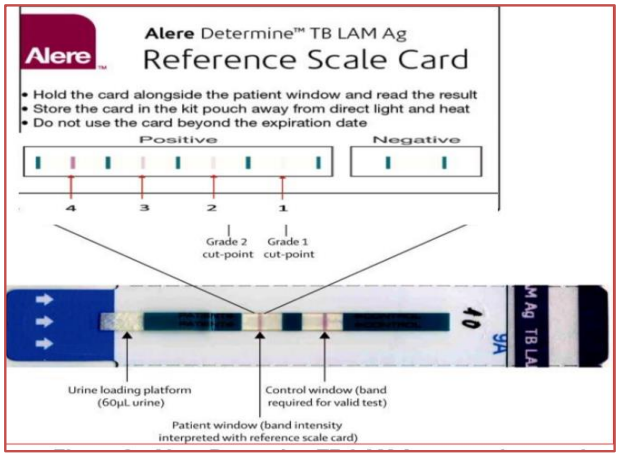
One purple/gray bar appears in the control window of the strip (labelled "Control") and no purple/gray bar appears in the Patient window of the strip (labelled "Patient").

INVALID (No Bar)

If there is no purple/gray bar in the control window of the strip, even if a purple/gray bar appears in the patient window of the strip, the result is invalid and the test should be repeated. If the problem persists, contact your local distributor or call Alere Technical Support as detailed below.

INDEFINITE:

One purple/gray bar appears in the control window of the strip (labelled "Control") with unclear or incomplete purple/gray bar in the patient window of the strip (labelled "Patient"). For a better clinical decision, the test should be repeated. Alternatively, collect a new urine sample in the following days from the patient and test. Early morning urine is recommended.



2. Quality Control:

Conduct QC for TB LAM test for new shipment and/or new lot of test kits. Follow steps in the SOP to evaluate accuracy of the test kit using +ve and –ve controls.

Annex 9: Standard operating procedure for performing the Alere determine TB LAM Ag lateral flow assay

Purpose

The purpose of this standard operating procedure[1]is to detail the steps for correctly performing, interpreting and documenting valid results for the Alere Determine™ TB LAM Ag assay (AlereLam). AlereLAM is an immunoassay used to detect the lipoarabinomannan (LAM) antigen (Ag) in human urine as an aid in diagnosing TB in persons living with HIV.

Scope

This standard operating procedure applies to all facilities performing AlereLAM to assist in diagnosing TB in HIV-positive adults who have signs and symptoms of TB (pulmonary or extrapulmonary) and who have a CD4 count < 100cells/ mm3 or who are seriously ill (WHO stage 3 or 4 disease).

Responsibility and authorization

The persons responsible for performing this test are laboratory professionals.

Materials

- LF-LAM test kit and Reference Scale Card
  - AlereLAM antigen test strips
  - AlereLAM positive TB control sample (1 mL).
- Materials required but not provided in the kit
  - Timer
  - Gloves
  - Pipette or delivery device capable of accurately delivering 60 µL of urine (this could be a calibrated micropipette with filter tips or a dual-bulb 60 µL pipette)
  - Pipette filter tips if a micropipette is used
  - Sharps disposal container
  - Pen and permanent marker
  - Biohazard disposal bags.

Safety, health and the environment

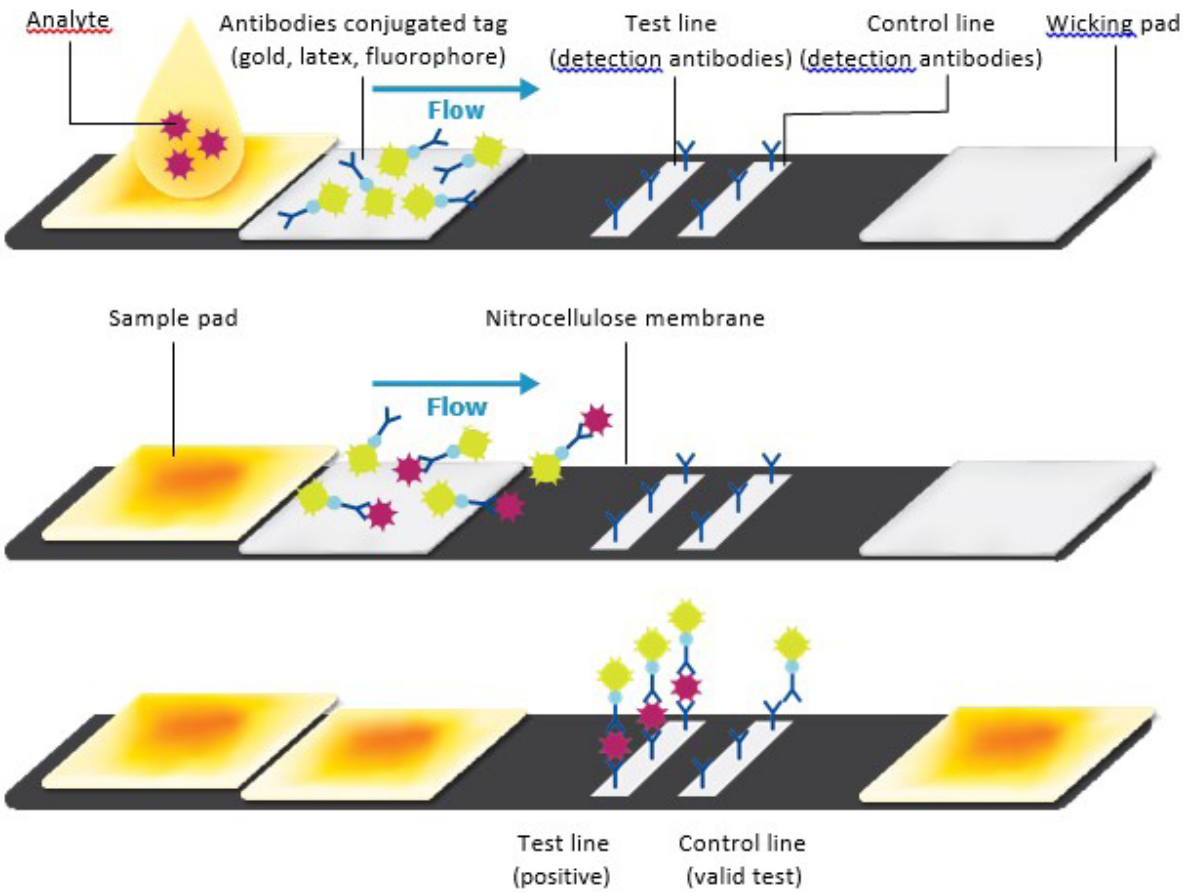
Treat all urine specimens as potentially infectious and follow basic universal precautions.

Wear protective clothing (i.e. a coat or apron and gloves) when handling the specimens.

Principles

AlereLAM is an immunochromatographic test for the qualitative detection of LAM antigen in human urine. AlereLAM employs highly purified antibodies specific to the major polysaccharide antigen of Mycobacterium: LAM. These antibodies are used for both the capture and the detection tracer. The capture antibodies are adsorbed onto the nitrocellulose membrane of the test strip. The detection antibody is labelled through conjugation to colloidal gold particles (Figure E).

After a urine specimen is added to the test strip, the colloidal gold–conjugated antibodies attach to the LAM antigen and are released by the specimen from the test strip. This immunological complex is then captured by anti-LAM antibodies immobilized on the nitrocellulose membrane and made visible due to the presence of the colloidal gold label. A positive result (a purple–grey band) indicates that LAM antigen is present in the sample at or above the detection limit of the test; a negative result (no purple–grey line) indicates it is not present or is present only below the detection limit. To ensure assay validity, a procedural control window is incorporated into the assay device.



Fgiure E. General principles for detecting the lipoarabinomannan antigen*

* Sample containing the analyte of interest moves by capillary action across an internal membrane when applied to the assay where it will bind first to capture antibodies which have a reporter molecule attached. The analyte-antibody complex then continues to migrate until reaching another set of detection antibodies fixed to the membrane which binds the complexed molecules, concentrating them in one place (test line) for detection. Any remaining unbound capture antibodies continue to migrate and complex to a second set of fixed antibodies at a control line which validates the test.

Specimen collection and storage

Collect midstream urine in a clean, standard urine collection container. Fresh urine samples can be used within 8 hours if kept at room temperature.

(1) Urine samples should be stored at 2–8 °C if the test is to be run within 3 days of collection.
(2) If testing will be delayed more than 3 days, the samples should be frozen (–20 °C or colder). For frozen or refrigerated urine, bring the sample to room temperature 1 hour prior to use. Frozen samples may contain aggregates.
(3) All thawed samples must be centrifuged at 10 000 g for 5 minutes at room temperature; the 60 µL test sample should be carefully collected from the clear supernatant. Avoid repeated freeze–thaw cycles. Specimens that have been frozen and thawed more than three times cannot be used.

Reagent storage and preparation

AlereLAM test cards must be stored at 2–30 °C until they are used. Kit components are stable until the expiration date when handled and stored as directed. Do not use kit components beyond the expiration date. Immediately reseal all unused tests in the foil pouch containing the desiccant by pressing the seal from end to end to close. Do not use strips that have become wet, and do not use strips if the packaging has become damaged.

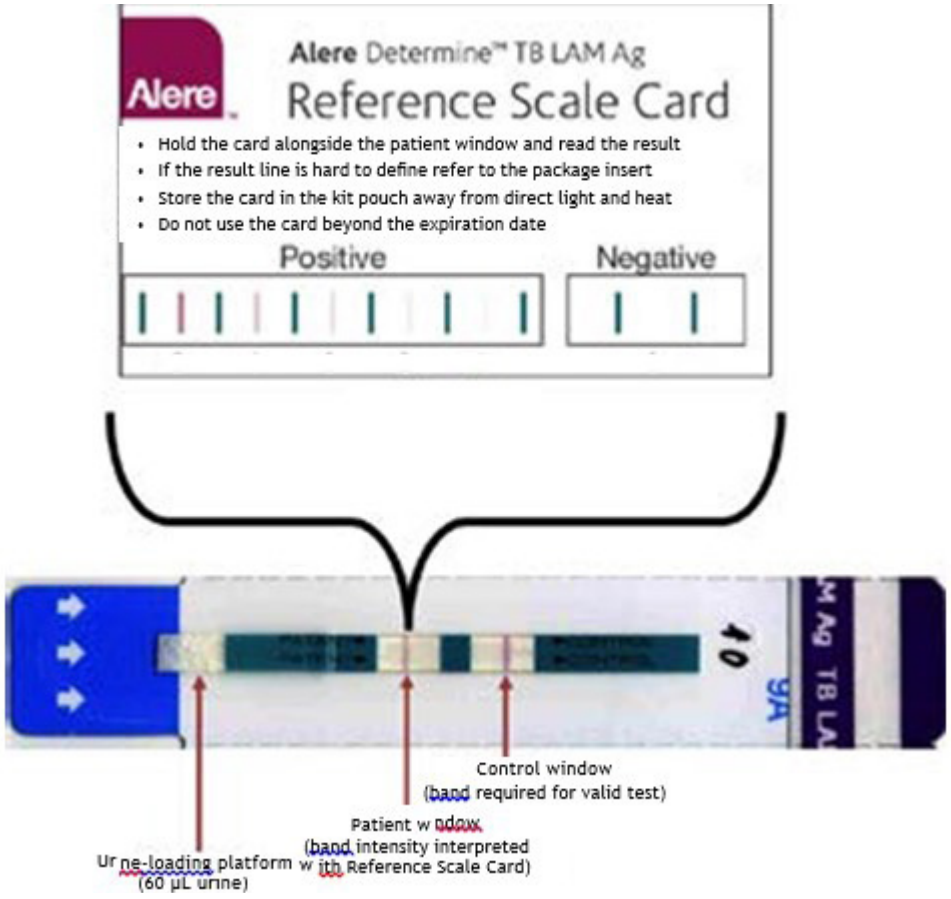
Test procedure

(1) Remove the desired number of test strips from the 10-test card by bending and tearing at the perforation. Test strips should be removed starting from the right side of the test card to preserve the lot number, which appears on the left side of the card.
(2) Remove the protective foil cover from each test strip. Label the strip with a unique patient identification number. The assay should be initiated within 2 hours of removing the protective foil cover from the strip.
(3) Add 60 µL of the sample (or 2 drops of urine) to the test strip (Figure C. ; the white pad marked with an arrow symbol).

(4) Wait a minimum of 25 minutes and a maximum of 35 minutes, and then read the result. Evaluate the strip under standard indoor lighting conditions or in the shade. Do not evaluate the strip in direct sunlight. Results are stable for up to 35 minutes after sample application. Do not read the strip after 35 minutes.

Interpreting the results

To assist with reading and interpreting the results, use the Reference Scale Card that is provided in the kit by holding it alongside the patient window (Figure. F).



Source: reproduced with permission of the publisher from EurRespir J. 2012;40;1211–20. doi:10.1183/09031936.00201711

Figure F. Using the Reference Scale Card to determine band intensity and validity of the Alere Determine TB LAM Ag assay(26).

LAM antigen positive result (showing two bands, the control and patient band)

If a test is positive, then purple–grey bands appear in both the quality control window and the patient window of the strip. Note that the test result is positive even if the patient band appears lighter or darker than the control band.

Note: The reference card must be used to correctly identify the intensity of the bands appearing in the patient window. Bands that are lighter than the bands in the positive box of the reference card must be considered as negative or indeterminate results. Only bands that are as dark as or darker than the first band in the positive box of the reference card should be considered positive.

Negative result (only one band showing)

The result is negative if a purple–grey band appears only in the quality control window of the strip and no band or only a band of Grade 1 intensity appears in the patient window.

Invalid result (no band)

The test is invalid if there is no purple–grey band in the quality control window of the strip, even if a band appears in the patient window; in this case, the test should be repeated. If the problem persists, contact your local distributor or call Alere Technical Support.

Indeterminate result

The result is indeterminate if one purple–grey band appears in the control window of the strip with an unclear or incomplete band in the patient window. To ensure that a better clinical decision is made, the test should be repeated. Alternatively, collect a new urine sample from the patient on a different day and test that sample. Early morning urine is recommended.

Quality control testing

Conduct quality control testing for AlereLAM weekly, before the first specimen is analysed for a particular week. If no specimens are to be test using the AlereLAM assay, then quality control testing need not be undertaken for that week. Record the results of the quality control testing in the TB LAM result logbook.

The following procedure should be used to evaluate the AlereLAM quality controls.

For the AlereLAM positive control:

(1) First, label the test strip as the TB LAM positive control;
(2) Add 1 drop of the TB LAM Ag positive control to the labelled test strip;
(3) Read the results after 25 minutes.

For the AlereLAM negative control:

(1) First, label the test strip as the TB LAM negative control;
(2) Add 2 drops of saline solution or distilled water;
(3) Read the results after 10 minutes.

Further information can be found on the Alere Determine LAM Ag package insert, available at https://www.alere.com/en/home/product-details/determine-tb-lam.html.

Annex 10: Internal Quality Control (IQC) log sheet for LF-LAM test

Region________________**Zone**__________ **Facility Name** ___________________________

Date tested	Analyte/ test name	QC	**Kit information**	IQC Result				Action taken for Failed IQC	Test done by	Initial s
				Positive	Negative	Invalid	Indeterm inate			
		Positive	Lot#/batch#______							
		Negative	Ex. date_________							
		Positive	Lot#/batch#______							
		Negative	Ex. date_________							
		Positive	Lot#/batch#______							
		Negative	Ex. date_________							
		Positive	Lot#/batch#______							
		Negative	Ex. date_________							
		Positive	Lot#/batch#______							
		Negative	Ex. date_________							

Annex 11: Laboratory Register for Smear Microscopy, LF-LAM and GeneXpert MTB/RIF

Name of Health facility_____ **Year (EC)** _____

Lab S. No	Date Specimen Received[a]	Patient Name / Address of the Patient	Age / Sex	Name of Contact Person / Address of the Contact	Name of referring unit (IPD/OPD) /facility	MRN	HIV Status (Pos/Neg/ Unknown)	If pos for HIV, CD4 count (Cells/µ)	If pos for HIV, Indication for LF-LAM testing) (1-4)b	TB sign and symptom (Yes/No)	Patient Registration Group (N, R, D, F)[g]	Reason for examination: Diagnosis	Reason for examination: Follow Up [c]Month	Examination Result: [d]Xpert	Examination Result: [e]LF LAM (P/N)	Examination Result: [f]Smear Microscopy 1	Examination Result: [f]Smear Microscopy 2	Test done by (Initial)	Remark Address of the Patient

[a]For diagnostic testing employing serial sputa or other specimens this is the date of receipt of the first set of specimens.

[b]If positive for HIV, Indication for LF-LAM testing

1-Outpatient TB symptomatic HIV positive (New/treatment interrupted /treatment failing / clinically unwell)

2-Outpatient HIV positive clients with CD4 < 100 and or stage 3/4

3- TB symptomatic inpatient HIV positive clients

4- Inpatient HIV positive clients with Advance HIV disease or seriously ill or CD4 < 200

[c]Patient of TB treatment ; indicate month of treatment at which follow-up examination is performed.

[d] XPERT MTB/RIF test result reported as follows: T=MTB detected, rifampicin resistance not detected, RR= MTB detected, rifampicin resistance detected, TI= MTB detected, rifampicin resistance indeterminate, N= MTB not detected, I= invalid/no result/error-specify error code

[e] LF-LAM test result reported as follow p=positive for LAM antigen, N= Negative for LAM antigen

[f] Smear results reported as follows: 0= No AFB (1-9)= exact number if 1-9/100HPF(scanty), +=10-99AFB/100HPF, ++=1-10AFB/HPF, +++= >10AFB/HPF

[g] Patient/Registration Group: ***N***-New case, ***R***-Relapse, ***D***-Treatment after loss to follow-up, ***F***-Treatment after failure (***F2***-for retreatment failure

Annex 12: LF-LAM monthly reporting form

Name of facility :_____ **Region:-**_____ **Zone:**_____

Woreda:_____ **Reporting quarter :**_____

Date from _____ **to** _____

TB-LAM indicators	Total eligible for LF-LAM testing (A)	Both LF-LAM and GeneXpert tested (B)	Only LF-LAM tested (C)	Both LF-LAM and GeneXpert positive (D)	Positive only by LF-LAM (E)
Outpatient TB symptomatic HIV positive (New/treatment interrupted /treatment failing / clinically unwell) clients in the quarter					
Outpatient HIV positive clients with CD4 < 100 and or stage 3/4 in the quarter					
TB symptomatic inpatient HIV positive clients in the quarter					
Inpatient HIV positive clients with Advance HIV disease or seriously ill or CD4 < 200 in the quarter					

Report compile by:-

Name:_____ Date:-_____ signature;_____