GLI model TB diagnostic algorithms

global laboratory initiative
advancing TB diagnosis

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diagnostic algorithms

March 2017

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Acknowledgements

Abbreviations

CSF	cerebrospinal fluid
DST	drug-susceptibility testing
FL-LPA	line probe assay for first-line drugs
FQ	fluoroquinolone
GLI	Global Laboratory Initiative
HIV	human immunodeficiency virus
LF-LAM	lateral flow lipoarabinomannan assay
LPA	line probe assay
MDR-TB	multidrug-resistant TB
MIC	minimum inhibitory concentration
MTB	*Mycobacterium tuberculosis* complex bacteria
NTP	National TB Programme
PLHIV	People living with HIV/AIDS
RR-TB	rifampicin-resistant TB
SLID	second-line injectable drug
SL-LPA	line probe assay for second-line drugs
SOPs	standard operating procedures
TB	tuberculosis
TB-LAMP	loop-mediated isothermal amplification test
WHO	World Health Organization
WRD	WHO-recommended rapid diagnostic

Background

WHO's global strategy for tuberculosis (TB) prevention, care and control for 2015–2035 (known as the End TB Strategy) calls for the early diagnosis of TB and universal drug-susceptibility testing (DST), highlighting the critical role of laboratories in the strategy. In order to meet the End TB Strategy targets, WHO-recommended rapid TB diagnostics (WRDs) should be available to all persons with signs or symptoms of TB, all bacteriologically confirmed TB patients should receive DST at least for rifampicin, and all patients with rifampicin-resistant TB should receive DST at least for fluoroquinolones (FQs) and second-line injectable drugs (SLIDs). Therefore all national TB control programmes (NTP) need to prioritize the development of a network of TB laboratories that use modern diagnostics, have efficient referral systems, use standard operating procedures (SOPs) and appropriate quality assurance (QA) processes, and have adequate biosafety and sufficient human resources. These priorities should be comprehensively addressed in national strategic plans and adequately funded.

In recent years, rapid and sensitive tests based on molecular methods, including Xpert® MTB/RIF (Cepheid, Sunnyvale USA), the loop-mediated isothermal amplification (TB-LAMP) test (Eiken Chemical, Tokyo Japan), and line probe assays (LPAs), have become available to replace or complement existing conventional tests for detecting *Mycobacterium tuberculosis* complex bacteria (MTB) and for detecting drug resistance. Despite the advantages of these newer tests, conventional microscopy and culture remain necessary for monitoring the response of a patient to treatment. Conventional culture and DST are also needed to address gaps in the approved rapid test repertoire, including DST for many important TB drugs such as pyrazinamide, bedaquiline and delamanid, as well as for testing of a full-range of respiratory and non-respiratory specimens.

In 2015, WHO published the *Policy framework for Implementing Tuberculosis Diagnostics* and the Global Laboratory Initiative (GLI) published the *GLI Guide for providing technical support to TB laboratories in low- and middle-income countries* to assist with the implementation of the latest diagnostic technologies. Since the publication of these documents, WHO has approved or updated guidance on several diagnostic tests for TB — specifically the TB-LAMP test, LPAs for first-line drugs (FL-LPA), LPA for second-line drugs (SL-LPA), and the urine-based lateral flow lipoarabinomannan (LF-LAM) assay to assist with the diagnosis of TB among seriously ill people living with HIV/AIDS (PLHIV). Both the WHO Policy framework and the GLI Guide are being updated in 2017 to incorporate the latest policies and recommendations.

The purpose of this document is to illustrate testing algorithms in line with the goals of the End TB strategy and incorporate the recent WHO recommendations for tests to detect MTB (TB-LAMP, LF-LAM) and detect drug resistance (first- and second-line LPAs). The reader is referred to the WHO Policy Framework and the GLI Guide for sample algorithms using the WHO-recommended diagnostics that were recommended as of early 2015.

As new diagnostic tests are implemented, testing algorithms will need to be modified. Modifications to algorithms must be put in place only after a formal evaluation, review, and approval by officials within the Ministry of Health and the NTP. Often nationally appointed thematic working groups are used to evaluate new technologies and develop

implementation plans, which typically include revising current algorithms. These groups consist of local ministry officials and professionals (laboratory and medical) who will decide the most optimal utilization and placement of the new technology within the current network structure.

The following points should be considered when designing or reviewing algorithms for testing at different levels of the laboratory network:

- The specific diagnostic tests in use or being considered for use;

- Whether, and for what purposes, the tests are recommended by WHO;

- The current and planned capacity of the country's laboratories, the laboratory infrastructure, and the availability of competent personnel to conduct the tests;

- The adequacy of systems for specimen collection and transport, and the average turnaround time between sites;

- The capacity of clinical services to offer diagnosis and treatment;

- Which drugs are used for the treatment of TB; and

- Characteristics (risk groups) of the population being served, which should be derived from population-based studies (if available), including the proportion with drug-resistant TB, the proportion that is HIV-positive, the proportion with extrapulmonary TB, and the proportion that is among children.

Algorithms should be designed to use existing laboratory services so that specimens can be referred to the appropriate level for tests that are not available at the peripheral level laboratories. Such referrals are particularly important when persons are being evaluated for drug-resistant TB or HIV-associated TB, when children are being evaluated for TB, or when persons are being evaluated for extrapulmonary disease.

In this document, four model algorithms are presented that incorporate the goals of the End TB Strategy that emphasize that WHO-recommended rapid TB diagnostics should be available to all persons with signs or symptoms of TB and that all bacteriologically confirmed TB cases should receive DST. The algorithms are illustrative and must be adapted by countries to the local situation.

The landscape of TB diagnostics is rapidly changing, and new tests may be recommended by WHO in the near future. This document will therefore be updated periodically to modify or add algorithms as needed.

Suggested Reading

Policy framework for implementing new tuberculosis diagnostics. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.11).
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

GLI guide for providing technical support to TB laboratories in low- and middle-income countries. Global Laboratory Initiative. 2015.
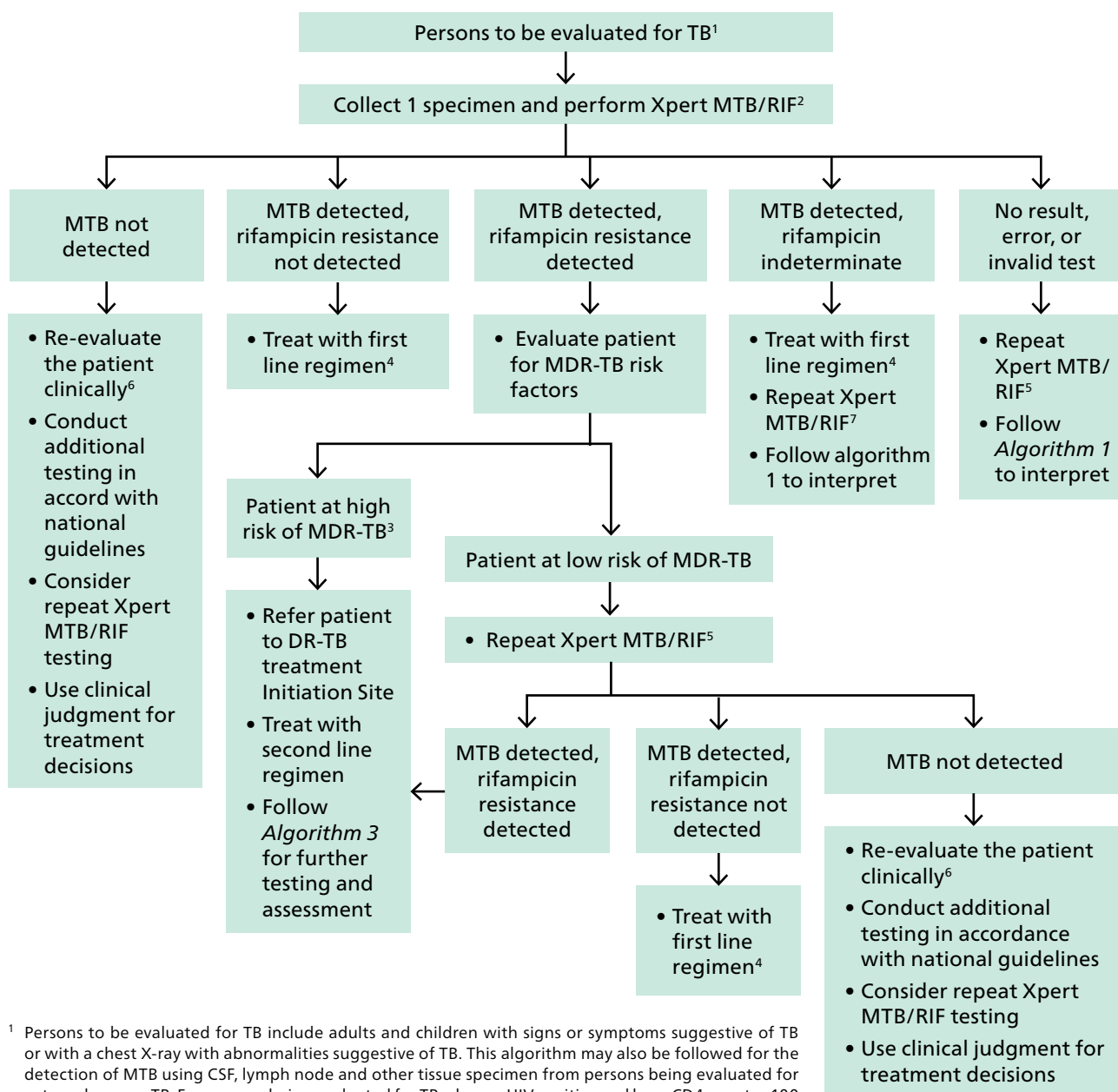http://stoptb.org/wg/gli/assets/documents/guideforprovidingtechnicalsupport_gb_web.pdf

Framework of indicators and targets for laboratory strengthening under the End TB Strategy. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.18).
http://www.who.int/tb/publications/labindicators/en/

Algorithm 1

Algorithm 1: Preferred algorithm for universal patient access to rapid testing to detect MTB and rifampicin resistance

```
                          Persons to be evaluated for TB[1]
                                        ↓
                       Collect 1 specimen and perform Xpert MTB/RIF[2]
```

MTB not detected	MTB detected, rifampicin resistance not detected	MTB detected, rifampicin resistance detected	MTB detected, rifampicin indeterminate	No result, error, or invalid test
• Re-evaluate the patient clinically[6] • Conduct additional testing in accord with national guidelines • Consider repeat Xpert MTB/RIF testing • Use clinical judgment for treatment decisions	• Treat with first line regimen[4]	• Evaluate patient for MDR-TB risk factors	• Treat with first line regimen[4] • Repeat Xpert MTB/RIF[7] • Follow algorithm 1 to interpret	• Repeat Xpert MTB/RIF[5] • Follow *Algorithm 1* to interpret

Patient at high risk of MDR-TB[3]

- Refer patient to DR-TB treatment Initiation Site
- Treat with second line regimen
- Follow *Algorithm 3* for further testing and assessment

Patient at low risk of MDR-TB

- Repeat Xpert MTB/RIF[5]

MTB detected, rifampicin resistance detected	MTB detected, rifampicin resistance not detected	MTB not detected
	• Treat with first line regimen[4]	• Re-evaluate the patient clinically[6] • Conduct additional testing in accordance with national guidelines • Consider repeat Xpert MTB/RIF testing • Use clinical judgment for treatment decisions

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[1] Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the detection of MTB using CSF, lymph node and other tissue specimen from persons being evaluated for extrapulmonary TB. For persons being evaluated for TB who are HIV positive and have CD4 counts ≤100 cells/µl or are seriously ill, see Algorithm 4.

[2] Programmes may consider collecting two specimens upfront. The first specimen should be promptly tested using the Xpert MTB/RIF test. The second specimen may be used for the additional testing described in this algorithm. For persons being evaluated for pulmonary TB, sputum is the preferred specimen.

[3] Patients at high risk for multidrug-resistant TB (MDR-TB) include previously treated patients including those who had been lost to follow-up, relapsed, and failed a treatment regimen; non-converters (smear positive at end of intensive phase); MDR-TB contacts; and any other MDR-TB risk groups identified in the country.

[4] Patients should be initiated on a first-line regimen according to national guidelines. A sample may be sent for molecular or phenotypic DST for isoniazid if the patient has been previously treated with isoniazid or if there is a high prevalence of isoniazid resistance not associated with rifampicin resistance (i.e., isoniazid mono- or poly-resistance) in this setting or for DST for rifampicin if rifampicin resistance is still suspected.

[5] Repeat Xpert MTB/RIF test at the same testing site with a fresh specimen. Interpret the result of the repeat test as shown in this algorithm. Use the result of the second Xpert MTB/RIF test for clinical decisions.

[6] Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents, repeat Xpert MTB/RIF testing, or culture.

[7] Repeat Xpert MTB/RIF test at the same testing site with a fresh specimen. Use the rifampicin result of the second Xpert MTB/RIF test in this algorithm for a decision(s) regarding choice of regimen (first line or second line regimen).

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Algorithm 1 is the preferred algorithm for testing to detect MTB in individuals being evaluated for pulmonary TB and incorporates the goals of the End TB Strategy for the use of WRDs and universal DST. This algorithm is feasible when a GeneXpert instrument is available on site or when Xpert MTB/RIF testing can be accessed through a reliable referral system with short turnaround time. This algorithm may also be used for the detection of MTB using cerebrospinal fluid (CSF), lymph nodes and other tissue types from persons being evaluated for extrapulmonary TB.

Decision Tree for Algorithm 1 in which the Xpert MTB/RIF test is used as the initial diagnostic test for all adults and children (regardless of HIV status) with signs or symptoms of pulmonary TB or with a chest X-ray with abnormalities suggestive of TB

- The Xpert MTB/RIF test is recommended as the initial diagnostic test for persons being evaluated for TB. This includes all newly presenting symptomatic persons and may also include patients who are on therapy or have been previously treated if the patient is being evaluated for possible rifampicin-resistant TB (e.g., non-converters at the end of the intensive phase of treatment) or for a new or continuing episode of TB (e.g., relapse cases or previously treated patients including those who had been lost to follow-up).

- The Xpert MTB/RIF test is also recommended for use in persons being evaluated for extrapulmonary TB, although the test is not recommended for use with all types of extrapulmonary specimens. It is recommended for use with CSF, lymph nodes and other tissue samples. However, the test has low sensitivity for pleural fluid specimens and data are limited for its sensitivity with stool, urine or blood specimens. See the WHO *Policy Update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children* for a discussion of the use of the Xpert MTB/RIF assay with extrapulmonary specimens.

- The Xpert MTB/RIF test is not recommended as a test to monitor treatment; instead microscopy and culture should be used according to national guidelines.

- The algorithm describes the collection of one initial specimen to be used for Xpert MTB/RIF testing and the collection of additional specimens as needed. Operationally, it may be easier to collect two specimens (e.g., spot and morning sputum samples or two spot specimens) from each patient routinely instead of only collecting a second specimen when additional testing is needed. The first specimen should be promptly tested using the Xpert MTB/RIF test. The second specimen may be used for the additional testing described in the algorithm (e.g., repeat Xpert MTB/RIF testing) or for smear microscopy as a baseline for treatment monitoring.

  — If more than one specimen cannot be collected (e.g., only one lymph node biopsy can be collected), the algorithm should be modified to prioritize testing using the Xpert MTB/RIF test and consider using any portions of the sample remaining after the Xpert MTB/RIF test for other testing. Clinical decisions should be made based on clinical judgement and the results of available laboratory tests.

- The GeneXpert software provides Xpert MTB/RIF assay results as 'MTB not detected'; 'MTB detected (high, medium, low, or very low), rifampicin resistance detected, not detected, or indeterminate'; 'no result'; 'error'; or 'invalid'. In this document, each of the semi-quantitative categories of MTB detected is considered as bacteriological confirmation of TB.

- For persons being evaluated for TB who are HIV positive and seriously ill with danger signs or have CD4 counts ≤100 cells/μl, a urine LF-LAM assay may also be used (see Algorithm 4).

1. Collect a good quality specimen and transport it to the testing laboratory. Conduct the Xpert MTB/RIF test. For persons being evaluated for pulmonary TB, induced or expectorated sputum (preferred), bronchoalveolar lavage, gastric lavage, and gastric aspirate specimens may be used. Data are limited for the sensitivity of the Xpert MTB/RIF with other samples such as nasopharyngeal aspirates, string test samples, or stool samples.

2. If the Xpert MTB/RIF test result is MTB detected, rifampicin resistance not detected:

   a. The patient should be initiated on an appropriate regimen using first-line TB drugs according to national guidelines.

   b. Some programmes may request additional DST in some situations:

      i. Programmes may request molecular (e.g., FL-LPA) or phenotypic DST for isoniazid if the patient has been previously treated with isoniazid or if there is a high prevalence of isoniazid resistance that is not associated with rifampicin resistance (i.e., isoniazid mono-resistance or poly-resistance, but not MDR-TB) in this setting.

         1. Note that current treatment guidelines do not recommend a specific regimen for isoniazid-resistant TB. A regimen with first-line TB drugs is currently recommended. See WHO *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.*

         2. However, a recent systematic review suggests that treatment of isoniazid-resistant TB with a first-line regimen may be suboptimal and may result in higher rates of treatment failure, relapse and acquisition of multidrug resistance.[1] Evidence will be reviewed by WHO in 2017.

      ii. Additional molecular or phenotypic DST for resistance to rifampicin may be requested if the patient is considered to be at risk of having MDR-TB despite the initial Xpert MTB/RIF result. False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1–5% of TB cases tested in various epidemiologic settings. In contrast, phenotypic DST for rifampicin, especially using liquid culture, is associated with a higher proportion of false-susceptible results.[2]

   c. If additional molecular or phenotypic testing is done:

      i. The molecular and phenotypic testing may be done in different laboratories. These tests should be initiated in parallel; do not wait for the results of one test before initiating the other test.

      ii. The molecular and phenotypic DST may be done using the specimen (direct DST) or using bacteria recovered by culture (indirect DST). While direct DST has a much shorter turnaround time, indirect phenotypic DST may be preferred because of technical issues.

      iii. A rapid molecular test is preferred. Currently, FL-LPA is the only WHO-approved rapid molecular test for isoniazid resistance. DNA sequencing has proven useful in many cases but has not yet been evaluated by WHO.

      iv. Culture-based phenotypic DST for isoniazid and rifampicin requires 3 to 8 weeks to produce a result. Phenotypic DST may be useful for the evaluation of patients with a negative FL-LPA result, particularly in populations with a high pre-test probability for resistance to isoniazid.

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[1] M. Gegia et al. 2016. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* (2016) published online Nov 16. DOI: http://dx.doi.org/10.1016/S1473-3099(16)30407-8

[2] A. Van Deun et al. Rifampin drug resistance tests for tuberculosis: Challenging the gold standard. *J Clin Microbiol*. August 2013; 51 (8): 2633-2640. DOI: http://dx.doi.org/10.1128/JCM.00553-13

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3. If the Xpert MTB/RIF test result is MTB detected, rifampicin resistance detected, an MDR-TB risk assessment is needed. Patients at high risk for MDR-TB include previously treated patients including those who had been lost to follow-up, relapsed, or failed a treatment regimen; non-converters (smear positive at end of intensive phase); contacts of MDR-TB patients; and any other MDR-TB risk groups identified in the country.

   a. If the patient is at high risk of having MDR-TB, the rifampicin-resistant test result is definitive and the patient should be initiated on a regimen for rifampicin-resistant (RR-TB) or MDR-TB according to national guidelines and follow Algorithm 3 for additional testing.

   b. If the patient is at low risk of having MDR-TB, repeat the Xpert MTB/RIF test with a second sample. If FL-LPA is available at the site and the sputum specimen is smear positive, FL-LPA can be used for confirming the rifampicin-resistant result.

      i. Initiate an MDR-TB regimen according to national guidelines if the second test also indicates rifampicin resistance and follow Algorithm 3 for additional testing.

      ii. Initiate treatment with a first-line regimen according to national guidelines if the Xpert MTB/RIF result for the second sample is MTB detected, rifampicin resistance not detected. While in most situations false-positive rifampicin-resistant results due to technical performance of the assay are rare, false-positive rifampicin-resistant results due to laboratory or clerical errors may be more likely. Therefore it may be assumed that the result of the second test is correct and the result of the first test may have been due to a laboratory or clerical error.

   c. For all patients with RR-TB or MDR-TB follow Algorithm 3.

4. If the Xpert MTB/RIF test gives a result of MTB detected, rifampicin indeterminate, the Xpert MTB/RIF test should be retested at the same testing site with a second specimen.

   a. The initial Xpert MTB/RIF result of MTB detected should be considered as bacteriological confirmation of TB. The patient should be initiated on an appropriate regimen using first-line TB drugs according to national guidelines.

   b. If the result of the second Xpert MTB/RIF test is MTB detected, rifampicin resistance not detected, follow Step 2. If it is MTB detected, rifampicin resistance detected, follow Step 3.

   c. An Xpert MTB/RIF result of MTB detected, rifampicin indeterminate often occurs when there are very few bacteria in the specimen. Testing of a second sample, which also may contain very few bacteria, may, in some cases, generate a result of MTB detected, rifampicin indeterminate or a result of MTB not detected. In this situation, additional investigations such as culture and phenotypic DST may be needed to confirm or exclude resistance to rifampicin because the indeterminate result provides no information on resistance.

5. If the Xpert MTB/RIF test result is MTB not detected, re-evaluate the patient and conduct additional testing in accordance with national guidelines.

   a. Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents (fluoroquinolones should not be used), additional Xpert MTB/RIF testing, or culture.

   b. Consider the possibility of clinically defined TB (i.e., no bacteriological confirmation). Use clinical judgement for treatment decisions.

6. If the Xpert MTB/RIF test does not give a result or gives a result of error or invalid, the Xpert MTB/RIF test should be retested at the same testing site with a second specimen. If FL-LPA is available at the site and the second specimen is smear positive, FL-LPA can be used for the repeat testing; although repeat Xpert MTB/RIF testing is preferred.

This algorithm relies on testing of a sample with the Xpert MTB/RIF test for the detection of MTB and assessment of susceptibility to rifampicin. On occasion follow-up testing is recommended to ensure that clinical decisions are well informed. However, discordant results may happen, usually when comparing culture-based results with molecular results. Each discordant result will need to be investigated, on a case-by-case basis. General considerations are:

1. Xpert MTB/RIF MTB detected, culture negative.

   a. The Xpert MTB/RIF result should be used to guide treatment decision pending additional testing.

   b. The Xpert MTB/RIF result should be considered as bacteriological confirmation of TB if the sample was collected from a person who was not recently receiving treatment with anti-TB drugs. Cultures from persons with pulmonary TB may be negative for a variety of reasons including the patient being treated for TB, transport or processing problems that inactivated the tubercle bacilli, cultures lost to contamination, or inadequate testing volume, or the discrepancy may be due to laboratory or clerical error.

   c. Follow-up actions may include re-evaluate the patient for TB, reassess possibility of prior or current treatment with anti-TB drugs (including fluoroquinolone use), evaluate the possibility of laboratory or clerical error, and repeat culture.

2. Xpert MTB/RIF MTB not detected, culture positive.

   a. Treatment decision should be based on the culture result.

   b. The culture-positive result should be considered as bacteriological confirmation of TB because culture is the current gold standard for the laboratory confirmation of TB. Using a sputum specimen, Xpert MTB/RIF has a pooled sensitivity of 89% for detecting MTB compared to culture.[3] Its sensitivity is lower in PLHIV, children, and other specimen types such as CSF.

   c. False-positive cultures can result from a variety of causes such as cross-contamination in the laboratory or from sample labelling problems. In well-function laboratories, such errors are rare.

   d. Follow-up actions may include re-evaluation of the patient for TB and response to anti-TB therapy; conduct additional testing using Xpert MTB/RIF; process and culture additional samples; and evaluate the possibility of laboratory or clerical error.

3. Xpert MTB/RIF MTB detected, rifampicin resistance detected; rifampicin susceptible by phenotypic DST.

   a. The Xpert MTB/RIF result should be used to guide treatment decisions pending additional testing.

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[3] K.R. Steingart et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2014 Jan 21;(1):CD009593. DOI: http://dx.doi.org/10.1002/14651858.CD009593.pub3

ALGORITHM 1

    b. Certain mutations are known to generate this discordant result, particularly in the BACTEC™ MGIT™ system (i.e., a false-susceptible phenotypic result). Patients infected with strains carrying these mutations often fail treatment with rifampicin-based first-line regimens.[4]

    c. In some low MDR-TB prevalence settings, silent mutations have been observed that generate a false-resistant Xpert MTB/RIF result but these tend to be very rare.

    d. Follow-up actions may include DNA sequencing, phenotypic DST using solid media, and evaluating the possibility of laboratory or clerical error.

4. Xpert MTB/RIF MTB detected, rifampicin resistance not detected; rifampicin resistant by phenotypic DST.

    a. Treatment decisions should be based on the phenotypic DST result.

    b. False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1–5% of TB cases tested in various epidemiologic settings. Mutations in the region of the *rpoB* gene sampled by the Xpert MTB/RIF tests have been shown to account for 95–99% of rifampicin resistance. The remainder of rifampicin resistance arises from mutations outside the sampled region, which produce an Xpert MTB/RIF result of rifampicin resistance not detected.

    c. Follow-up actions may include DNA sequencing, repeating the phenotypic DST, and evaluating the possibility of laboratory or clerical error.

Suggested Reading

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16).

http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.03).

http://www.who.int/tb/publications/childtb_guidelines

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).

http://www.who.int/tb/publications/molecular-test-resistance

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).

http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014 (WHO/HTM/TB/2014.11).

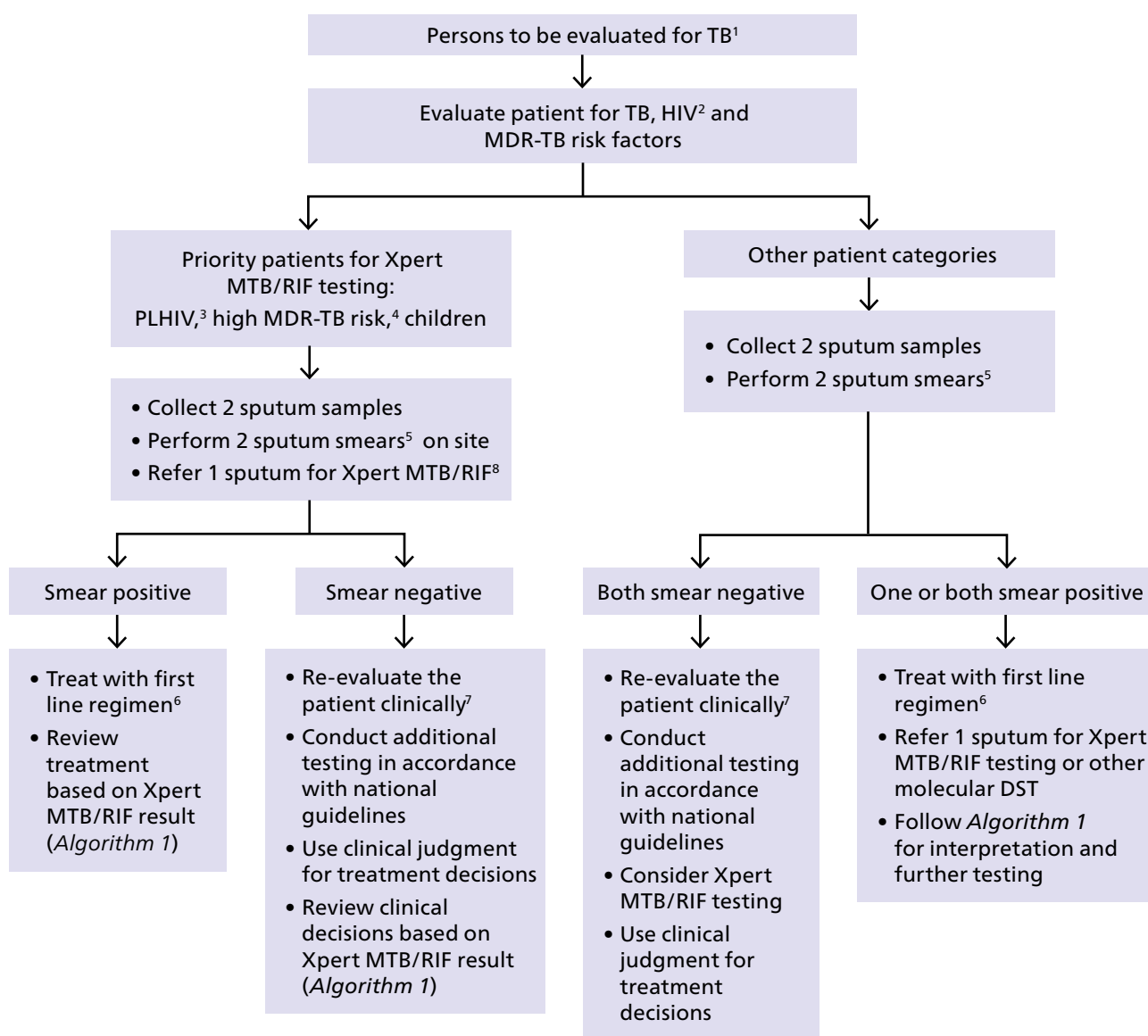http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Training package on Xpert MTB/RIF. Global Laboratory Initiative. 2014.

http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

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[4] A. Van Deun et al. Rifampin drug resistance tests for tuberculosis: Challenging the gold standard. *J Clin Microbiol*. August 2013; 51 (8): 2633-2640. DOI: http://dx.doi.org/10.1128/JCM.00553-13

Algorithm 2

Algorithm 2: Interim algorithm moving towards universal access, with rapid testing for priority populations

Persons to be evaluated for TB[1]

↓

Evaluate patient for TB, HIV[2] and MDR-TB risk factors

↓

Priority patients for Xpert MTB/RIF testing:
PLHIV,[3] high MDR-TB risk,[4] children

Other patient categories

↓

- Collect 2 sputum samples
- Perform 2 sputum smears[5] on site
- Refer 1 sputum for Xpert MTB/RIF[8]

↓

- Collect 2 sputum samples
- Perform 2 sputum smears[5]

Smear positive | **Smear negative** | **Both smear negative** | **One or both smear positive**

Smear positive
- Treat with first line regimen[6]
- Review treatment based on Xpert MTB/RIF result (*Algorithm 1*)

Smear negative
- Re-evaluate the patient clinically[7]
- Conduct additional testing in accordance with national guidelines
- Use clinical judgment for treatment decisions
- Review clinical decisions based on Xpert MTB/RIF result (*Algorithm 1*)

Both smear negative
- Re-evaluate the patient clinically[7]
- Conduct additional testing in accordance with national guidelines
- Consider Xpert MTB/RIF testing
- Use clinical judgment for treatment decisions

One or both smear positive
- Treat with first line regimen[6]
- Refer 1 sputum for Xpert MTB/RIF testing or other molecular DST
- Follow *Algorithm 1* for interpretation and further testing

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[1] Persons being evaluated for TB include all persons with signs or symptoms suggestive of TB or persons with a chest X-ray with abnormalities suggestive with TB. This algorithm may also be used for persons being evaluated for extrapulmonary TB. See footnotes to Algorithm 1.

[2] For persons being evaluated for TB who are HIV positive and have CD4 counts ≤100 cells/µl or are seriously ill, see Algorithm 4.

[3] PLHIV include persons who are HIV positive or 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 risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

[4] Patients at high risk for MDR-TB include previously treated patients including those who had been lost to follow-up, relapsed, and failed a treatment regimen; non-converters (smear positive at end of the intensive phase of treatment); MDR-TB contacts; and any other MDR-TB risk groups identified in the country.

[5] TB-LAMP may be used as a replacement test for sputum smear microscopy.

[6] Patients should be initiated on a regimen with first-line TB drugs according to national guidelines unless the patient is at very high risk of having MDR-TB. In that case, treat according to national guidelines while awaiting the Xpert MTB/RIF result.

[7] Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents, or culture if available.

[8] A third sample should be collected if neither of the original two samples collected has sufficient volume for both microscopy and Xpert MTB/RIF testing, or according to national guidelines.

ALGORITHM 2

Algorithm 2 is an interim measure towards meeting the goals of the End TB Strategy, in which Xpert MTB/RIF testing is used primarily for priority populations (adults being evaluated for HIV-associated TB or MDR-TB, and children) as described in the WHO *Policy Update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children*. This algorithm is suitable when there is no GeneXpert instrument on site and when Xpert MTB/RIF testing cannot be accessed through a reliable referral system with short turnaround time or when resources do not permit testing of all samples with the Xpert MTB/RIF test. As countries move toward the goals of access to rapid diagnostics and universal drug-susceptibility testing and as access to prompt Xpert MTB/RIF testing becomes available at a site (either through phased implementation of additional instruments or strengthening of the sample referral system), Algorithm 1 should be implemented.

Decision Tree for Algorithm 2 in which the Xpert MTB/RIF test is not available for all persons being evaluated for TB but is only available for priority populations because of resource limitations or lack of testing capacity, and smear microscopy is used for other patients being evaluated for TB

- Algorithm 1 (not Algorithm 2) should be followed in any setting where Xpert MTB/RIF testing is available on site or when Xpert MTB/RIF testing can be accessed through a reliable referral system with short turnaround time.

- Many countries have not yet built the capacity to conduct Xpert MTB/RIF testing for all persons being evaluated for TB. In such situations, Xpert MTB/RIF testing often initially focuses on testing the priority populations identified in the WHO *Policy Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children* and builds towards universal access. The priority populations are adults being evaluated for HIV-associated TB and MDR-TB, and children.

- This algorithm may also be used for persons being evaluated for extrapulmonary TB. See Decision Tree for Algorithm 1 for sample types and considerations.

- See Annexes 14 and 15 of the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition* for detailed algorithms for the management of persons being evaluated for HIV-associated TB.

- The TB-LAMP test may be used as a replacement for smear microscopy for the detection of MTB in adults and children with signs or symptoms suggestive of TB. However, TB-LAMP should not replace the use of rapid molecular tests that detect MTB and resistance to rifampicin (e.g., Xpert MTB/RIF) especially among populations at risk of MDR-TB when there are sufficient resources and infrastructure to support their use. TB-LAMP should also not replace the use of rapid molecular tests that have a higher sensitivity for detection of MTB among PLHIV.

1. Evaluate the person for TB, determine HIV status, and assess risk factors for having MDR-TB.

   a. As Xpert MTB/RIF testing becomes available, expand access to include testing of all adults and children being evaluated for TB (i.e., Algorithm 1).

   b. PLHIV include persons who are HIV positive or 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 risk group for HIV. For all persons with unknown HIV status, HIV testing should be performed according to national guidelines.

   c. For PLHIV who have CD4 counts ≤100 cells/µl or are seriously ill with one or more danger signs, a urine LF-LAM assay may also be used (See Algorithm 4).

2. For PLHIV, persons at risk of having MDR-TB, and children, collect two or three good quality sputum specimens. Conduct smear microscopy or TB-LAMP test on site and transport a sample to the testing laboratory for the Xpert MTB/RIF test.

   a. Because of a potential delay in receiving the Xpert MTB/RIF result, programmes may prefer having smear microscopy results from two specimens.

      i. If only two specimens are collected, smear microscopy may be done on both specimens if at least one of the samples has adequate volume for conducting both microscopy and Xpert MTB/RIF. The Xpert MTB/RIF test should be given priority. If not, a third sample should be collected.

      ii. In some settings, collecting three specimens (two for smear microscopy and one for Xpert MTB/RIF testing) may be preferred.

   b. If one or both samples are positive by smear microscopy or the TB-LAMP test, treat with TB drugs while awaiting the result of the Xpert MTB/RIF test.

      i. The patient should be initiated on a regimen with first-line TB drugs according to national guidelines unless the patient is at very high risk of having MDR-TB. For patients at very high risk of having MDR-TB (e.g., household contacts of MDR-TB patients), an MDR-TB regimen should be initiated according to national guidelines.

      ii. Follow Algorithm 1 for the interpretation of the Xpert MTB/RIF test results.

   c. If both samples are negative by smear microscopy or the TB-LAMP test, use clinical judgement for further evaluation or treatment while awaiting the Xpert MTB/RIF result.

      i. If Xpert MTB/RIF positive, follow the decision tree for Algorithm 1.

      ii. If Xpert MTB/RIF negative (MTB not detected), use clinical judgement and conduct additional testing as described in Algorithm 1.

3. For patients not in the priority populations, collect two good quality sputum specimens and conduct smear microscopy or TB-LAMP examinations on both. Follow national guidelines for the detection of MTB based on smear microscopy.

   a. If one or both samples are positive, treat with a regimen of first-line TB drugs according to national guidelines.

      i. If resources allow, collect an additional specimen and refer for Xpert MTB/RIF testing and follow Algorithm 1 for interpretation and additional testing. One of the already collected specimens may be referred for Xpert MTB/RIF testing if sufficient volume is available.

      ii. If Xpert MTB/RIF testing is not available and if the infrastructure and resources for FL-LPA have been developed, a specimen may be referred for testing with FL-LPA to detect MTB and to assess resistance to isoniazid and rifampicin. Note that FL-LPA is recommended for use with smear-positive sputum samples only. FL-LPA results are interpreted as described in the WHO *Policy Update: use of molecular line probe assay for the detection of resistance to isoniazid and rifampicin*.

   b. If both samples are negative, re-evaluate the patient and conduct additional testing in accordance with national guidelines.

      i. Further investigations for TB may include chest X-ray, Xpert MTB/RIF test, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobials (fluoroquinolones should not be used), or culture.

ALGORITHM 2

ii. Consider the possibility of clinically defined TB (i.e., no bacteriological confirmation). Use clinical judgement for treatment decisions.

Suggested Reading

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16)

http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).

http://www.who.int/tb/publications/lamp-diagnosis-molecular

Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.03).

http://www.who.int/tb/publications/childtb_guidelines/en/

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).

http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).

http://www.who.int/tb/publications/molecular-test-resistance
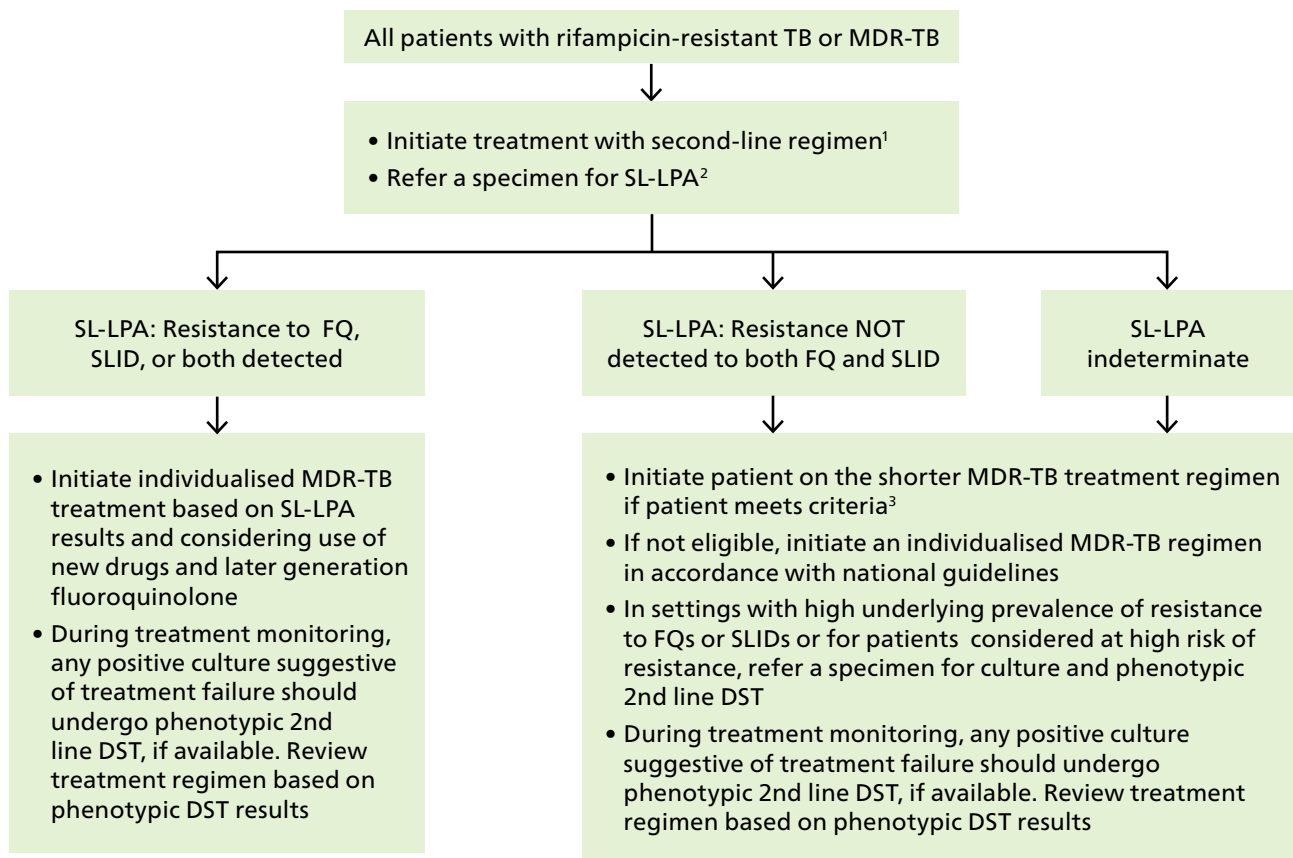
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.11).

http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Algorithm 3

Algorithm 3: Algorithm for testing for second-line drug resistance among rifampicin-resistant TB or MDR-TB patients

All patients with rifampicin-resistant TB or MDR-TB

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- Initiate treatment with second-line regimen[1]
- Refer a specimen for SL-LPA[2]

SL-LPA: Resistance to FQ, SLID, or both detected

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- Initiate individualised MDR-TB treatment based on SL-LPA results and considering use of new drugs and later generation fluoroquinolone
- During treatment monitoring, any positive culture suggestive of treatment failure should undergo phenotypic 2nd line DST, if available. Review treatment regimen based on phenotypic DST results

SL-LPA: Resistance NOT detected to both FQ and SLID

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- Initiate patient on the shorter MDR-TB treatment regimen if patient meets criteria[3]
- If not eligible, initiate an individualised MDR-TB regimen in accordance with national guidelines
- In settings with high underlying prevalence of resistance to FQs or SLIDs or for patients considered at high risk of resistance, refer a specimen for culture and phenotypic 2nd line DST
- During treatment monitoring, any positive culture suggestive of treatment failure should undergo phenotypic 2nd line DST, if available. Review treatment regimen based on phenotypic DST results

SL-LPA indeterminate

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[1] Patients may be initiated on the shorter MDR-TB regimen if the patient is assessed as being at low risk of having resistance to FQs and to SLIDs and meets the eligibility requirements. In patients at high risk of resistance or in settings with high underlying prevalence of resistance to FQs or SLIDs, selection or design of the treatment regimen to initiate may be guided by SL-LPA if the results can be obtained rapidly. See WHO *Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update.*

[2] Diagnostic accuracy is similar when SL-LPA is performed directly on sputum or from cultured isolates. SL-LPA can be used on smear-positive or smear-negative specimens although a higher indeterminate rate will occur when testing smear-negative specimens.

[3] The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions: 1) confirmed resistance, or suspected ineffectiveness, to a medicine (except isoniazid) in the shorter MDR-TB regimen for which there is reliable DST, 2) previous exposure for >one month to a second-line medicine included in the shorter MDR-TB regimen, 3) intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity, 4) pregnancy, or 5) extrapulmonary disease.

ALGORITHM 3

Algorithm 3 is for further evaluation of patients with RR-TB or MDR-TB. All patients with RR-TB or MDR-TB should be started on a second-line regimen. The results of DST for FQs and SLIDs should ideally be known for all RR-TB and MDR-TB patients before starting treatment, although this testing should not delay the start of treatment (see the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update* for more details on choice of regimen).

Decision Tree for Algorithm 3 in which SL-LPA is used as the initial diagnostic test for resistance to FQs and SLIDs for patients with RR-TB or MDR-TB

- The diagnostic accuracy SL-LPA is similar when it is performed directly on sputum or from cultured isolates. SL-LPA can be used on smear-positive or smear-negative specimens although a higher indeterminate rate will occur when testing smear-negative specimens.

- SL-LPA is only recommended for use with sputum specimens or MTB isolates. The laboratory testing of other specimen types should rely on culture and phenotypic DST.

- SL-LPA is suitable for use at the central or national reference laboratory level and may be used at the regional level if the appropriate infrastructure and human resources are available. Implementation of SL-LPA testing must ensure the availability of a reliable specimen transport system and efficient result reporting mechanism.

Note: If SL-LPA is not available, patients should be treated according to national guidelines. Patients may be evaluated for the use of a shorter MDR-TB regimen using criteria such as country drug-resistance patterns and the patient's treatment history. Algorithms that rely on culture and phenotypic DST are described in the WHO *Policy framework for Implementing Tuberculosis Diagnostics*. Phenotypic DST, if done, should include at a minimum testing for resistance to the FQs and SLIDs used in the country. If phenotypic DST to second-line drugs is not available in-country, specimens or isolates may be shipped to an external laboratory for testing (e.g., a WHO Supranational Reference Laboratory).

1. The patient should be promptly initiated on a MDR-TB regimen in accordance with national guidelines. Patients may be initiated on the shorter MDR-TB regimen if the patient is assessed as being at low risk of having resistance to FQs and to SLIDs and meets the eligibility requirements. In patients at high risk of resistance or in settings with high underlying prevalence of resistance to FQs or SLIDs, selection or design of the treatment regimen to initiate may be guided by SL-LPA if the results can be obtained rapidly.

2. Transport a sputum specimen or isolate to the appropriate laboratory for testing by SL-LPA.

3. If SL-LPA detects a mutation(s) associated with resistance to an FQ, SLID, or both, the patient should be initiated on an individualised MDR-TB treatment regimen considering use of new drugs and later generation fluoroquinolones. Note that cross-resistance between individual FQs or between individual SLIDs is complex and not fully understood; there are limited data on the ability of SL-LPA to assess the cross-resistance.

4. If SL-LPA is negative for mutations associated with resistance to FQs and to SLIDs, the patient should be assessed for eligibility for the shorter MDR-TB regimen.

   a. The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions 1) confirmed resistance, or suspected ineffectiveness, to a medicine (except isoniazid) in the shorter MDR-TB regimen for which there is reliable DST, 2) previous exposure for >one month to a second-line medicine included in the shorter MDR-TB regimen, 3) intolerance to one or more medicines

in the shorter MDR-TB regimen or increased risk of toxicity, 4) pregnancy, or 5) extrapulmonary disease.

i. Eligible patients should be placed on a shorter MDR-TB regimen according to national guidelines.

ii. For eligible patients at risk of having FQ-resistant or SLID-resistant TB (e.g., based on the country drug-resistance patterns), a specimen should be referred for culture and phenotypic DST, if such testing capacity is available. At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country.

iii. Reliable DST is available for the FQs and SLIDs. Although technically difficult, reliable DST for pyrazinamide is available, and resistance to pyrazinamide at the start of treatment may also be considered a criterion for exclusion. Reliable DST for ethambutol and the other drugs in the regimen (i.e., prothionamide, clofazimine) are not available and WHO does not recommend basing treatment decisions on the DST for these drugs. See WHO *Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions, Version: 20 December 2016* and WHO *Guidelines for the programmatic management of drug-resistant tuberculosis: 2016 update* for a detailed discussion.

b. If the patient is not eligible for the shorter regimen, the patient should be started on a MDR-TB regimen in accordance with national guidelines.

c. In settings with high underlying prevalence of resistance to FQs or SLIDS or for patients considered at high risk of resistance, a specimen should be referred for culture and phenotypic DST, if such testing capacity is available. If phenotypic DST to FQs and SLIDs is not available in-country, specimens or isolates may be shipped to an external laboratory for testing (e.g., a WHO Supranational Reference Laboratory). At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country. The regimen should be modified as needed based on the results of the phenotypic DST.

5. For all patients, treatment monitoring should include the collection of samples for culturing as described in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update*. Any positive culture suggestive of treatment failure should undergo phenotypic DST, if available. At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country. The regimen should be modified as needed based on the results of the DST.

Considerations for the use of SL-LPA:

When used to test directly sputum specimens from patients RR-TB or MDR-TB, SL-LPA will detect 86% of patients with FQ resistance and 87% of patients with SLID resistance and rarely give a positive result for patients without resistance, as described in the 2016 WHO policy guidance *The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs*. Because of this, WHO recommends that treatment decisions be made on the basis of the SL-LPA results with the following considerations:

• Despite good specificity and sensitivity of SL-LPA for the detection of FQ resistance (pooled sensitivity of 86% and specificity of 99% compared to phenotypic DST) and SLID resistance (pooled sensitivity of 87% and specificity of 99% compared to phenotypic DST), culture and phenotypic DST is required to completely exclude resistance to the individual drugs in these drug classes as well as to other second-line drugs. Phenotypic DST may be particularly needed in settings with a high pre-test probability for resistance to either FQs or SLIDs or both drugs to exclude resistance when the SL-LPA does not detect mutations associated with resistance.

ALGORITHM 3

- SL-LPA cannot determine resistance to individual drugs in the class of FQs. Resistance conferring mutations detected by SL-LPA are highly correlated with phenotypic resistance to ofloxacin and levofloxacin. However, the correlation of these mutations with phenotypic resistance or clinically significant resistance to moxifloxacin and gatifloxacin is unclear. The inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results.

- SL-LPA has high specificity for the detection of resistance conferring mutations in the *rrs* gene and these mutations are highly correlated with phenotypic resistance to each of the SLIDs (kanamycin, amikacin and capreomycin). However, mutations in the *eis* promoter region correlate with phenotypic resistance to kanamycin only. These mutations also confer an increase in the minimum inhibitory concentration (MIC) for amikacin, but the clinical significance of the increase in amikacin MIC is unknown.

Suggested Reading

The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).

http://www.who.int/tb/publications/lpa-mdr-diagnostics

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).

http://www.who.int/tb/publications/molecular-test-resistance

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).

http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.11).

http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions, Version: 20 December 2016. Geneva, World Health Organization. 2016.

http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf

Policy framework for implementing new tuberculosis diagnostics. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.11).
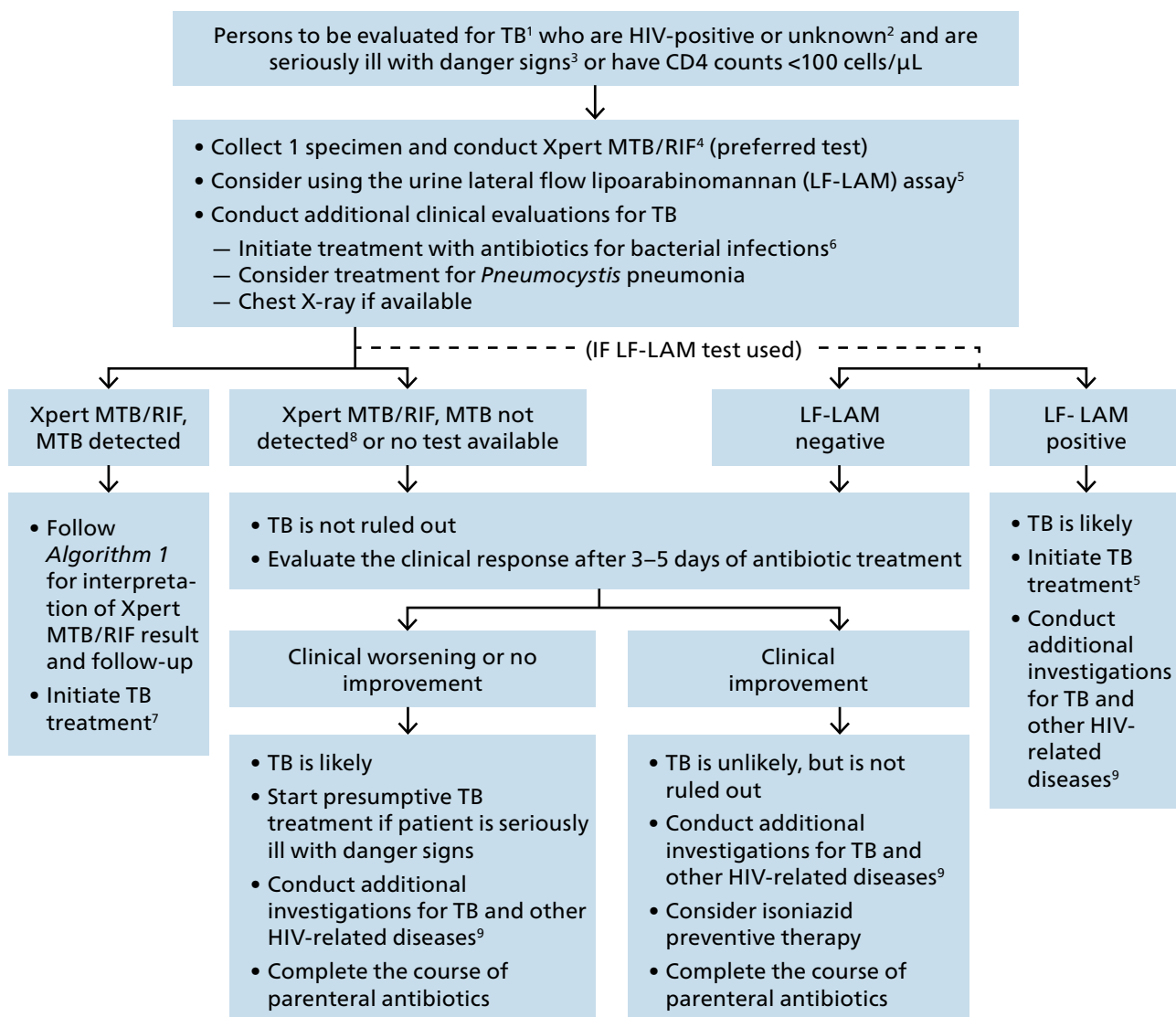
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

Training packages on culture on solid and liquid medium; on DST by phenotypic and molecular methods; on line probe assays (LPAs). Global Laboratory Initiative. 2012.

http://stoptb.org/wg/gli/trainingpackages.asp

Algorithm 4

Algorithm 4: Algorithm for evaluating persons for TB, among PLHIV who are seriously ill with danger signs or have CD4 counts ≤ 100 cells/μl

Persons to be evaluated for TB[1] who are HIV-positive or unknown[2] and are seriously ill with danger signs[3] or have CD4 counts <100 cells/μL

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- Collect 1 specimen and conduct Xpert MTB/RIF[4] (preferred test)
- Consider using the urine lateral flow lipoarabinomannan (LF-LAM) assay[5]
- Conduct additional clinical evaluations for TB
  — Initiate treatment with antibiotics for bacterial infections[6]
  — Consider treatment for *Pneumocystis* pneumonia
  — Chest X-ray if available

– – – – – – – (IF LF-LAM test used) – – – – – – –

Xpert MTB/RIF, MTB detected

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- Follow *Algorithm 1* for interpretation of Xpert MTB/RIF result and follow-up
- Initiate TB treatment[7]

Xpert MTB/RIF, MTB not detected[8] or no test available

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- TB is not ruled out
- Evaluate the clinical response after 3–5 days of antibiotic treatment

Clinical worsening or no improvement

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- TB is likely
- Start presumptive TB treatment if patient is seriously ill with danger signs
- Conduct additional investigations for TB and other HIV-related diseases[9]
- Complete the course of parenteral antibiotics

Clinical improvement

↓

- TB is unlikely, but is not ruled out
- Conduct additional investigations for TB and other HIV-related diseases[9]
- Consider isoniazid preventive therapy
- Complete the course of parenteral antibiotics

LF-LAM negative

LF- LAM positive

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- TB is likely
- Initiate TB treatment[5]
- Conduct additional investigations for TB and other HIV-related diseases[9]

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[1] Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the detection of MTB using CSF, lymph node and other tissue specimen from persons being evaluated for extrapulmonary TB.

[2] PLHIV (People living with HIV/AIDS) include persons who are HIV positive or 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 risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines. For all adults living with HIV/AIDS regardless of CD4 cell count or clinical stage, ART should be recommended and initiating co-trimoxazole preventive therapy should be considered.

[3] Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute, or unable to walk unaided.

[4] The Xpert MTB/RIF test is the preferred initial diagnostic test. For persons being evaluated for pulmonary TB, sputum is the preferred specimen.

[5] The LF-LAM assay may be used to assist in diagnosing active TB in both in-and out-patients who are seriously ill with danger signs, regardless of CD4 count. Testing with the LF-LAM assay may be especially useful for patients unable to produce a sputum specimen. Whenever possible, a positive LF-LAM should be followed up with other tests such as Xpert MTB/RIF. While awaiting results of other tests, clinicians could consider initiating TB treatment immediately based on the positive LF-LAM and their clinical judgment.

[6] Antibiotics with broad-spectrum antibacterial activity (except do not use fluoroquinolones) should be used.

[7] Initiate a treatment with first-line or second-line TB drugs based on the Xpert MTB/RIF result. See Algorithm 1.

[8] If the Xpert MTB/RIF test does not detect MTB, the test can be repeated using a fresh specimen. See Algorithm 1 for a discussion of possible follow-up testing for an Xpert MTB/RIF result of MTB not detected.

[9] Further investigations for TB may include chest X-ray, additional clinical assessments, a repeat Xpert MTB/RIF using a fresh specimen, or culture. If the patient is being evaluated for extrapulmonary TB, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

ALGORITHM 4

Algorithm 4 is used for PLHIV being evaluated for TB (pulmonary or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/μl or who are seriously ill regardless of CD4 count. This algorithm is based on Annex 15 of the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition.*

Decision Tree for Algorithm 4 is used for testing PLHIV being evaluated for TB who have a CD4 cell count less than or equal to 100 cells/μl or who are seriously ill regardless of CD4 count

- Follow Algorithm 1 or 2 for all persons being evaluated for TB except PLHIV who have a CD4 cell count less than or equal to 100 cells/μl or who are seriously ill regardless of CD4 count.

- Algorithm 4 may be used for persons being evaluated for pulmonary or extra-pulmonary TB.

- The Xpert MTB/RIF test is the preferred initial diagnostic test for Algorithm 4.

- The urine LF-LAM assay may also be used to assist in the diagnosis of TB in these individuals and may be especially useful in persons who cannot produce a good quality sputum specimen or when the Xpert MTB/RIF test is not available.

- Testing using the approved rapid methods should be given priority. Smear microscopy and culture may be useful, particularly when the rapid tests do not detect MTB.

1. Evaluate the patient for TB, determine HIV status, and assess presence of danger signs for being seriously ill. In PLHIV who are not seriously ill, it may also be necessary to measure CD4 cell counts to assess eligibility for testing with the LF-LAM assay.

   a. Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB (pulmonary or extrapulmonary) or with a chest X-ray with abnormalities suggestive of TB.

   b. PLHIV include persons who are HIV positive or 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 risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

   c. 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.

2. For PLHIV being evaluated for TB who have a CD4 cell count less than or equal to 100 cells/μl or who are seriously ill regardless of CD4 count:

   a. Collect a specimen and conduct the Xpert MTB/RIF test. Follow Algorithm 1 for result interpretation and follow-up testing.

      i. For persons being evaluated for pulmonary TB, induced or expectorated sputum (preferred), bronchoalveolar lavage, gastric lavage, and gastric aspirate specimens may be used. Data are limited for the sensitivity of the Xpert MTB/RIF with other samples such as nasopharyngeal aspirates, string test samples, or stool samples.

      ii. For persons being evaluated for extrapulmonary TB, the Xpert MTB/RIF test is recommended for use with CSF, lymph nodes and other tissue samples. However, the test has low sensitivity for pleural fluid specimens and data are limited for its sensitivity with stool, urine or blood specimens.

b. Collect a urine specimen and conduct the LF-LAM assay.

   i. If the Xpert MTB test is available on site, the LF-LAM testing should be done in parallel to the Xpert MTB/RIF test.

   ii. A positive LF-LAM result should be interpreted in the context of clinical judgment, chest X-ray findings (if available), and bacteriological results including Xpert MTB/RIF testing. While awaiting results of other tests, clinicians could consider initiating TB treatment immediately based on the positive result of the LF-LAM test and their clinical judgment.

   iii. If the LF-LAM result is negative, re-evaluate the patient and conduct additional testing in accordance with national guidelines. Further investigations for TB may include chest X-ray, repeat Xpert MTB/RIF test, additional clinical assessments, or culture.

c. Conduct additional clinical evaluations for TB such as initiating treatment for bacterial infections using antibiotics with broad-spectrum antibacterial activity (except do not use fluoroquinolones). Consider treatment for *Pneumocystis* pneumonia. Evaluate clinical response after 3–5 days of treatment.

   i. If clinical worsening or no improvement after 3–5 days of treatment, initiate further investigations for TB and other diseases and, if patient is seriously ill with danger signs, start presumptive TB treatment.

   ii. If clinical improvement, reassess for TB and other HIV-related diseases.

      1. Consider that clinical improvement may occur if the patient has TB and a bacterial infection, i.e., TB may not be ruled out.

      2. If there is high clinical suspicion of TB (clinical history and physical exam, history of previous TB that can be reactivated, chest ray suggestive) in the patient, use clinical judgement as to whether to initiate TB treatment.

   iii. All patients should complete the course of treatment for bacterial or *Pneumocystis* infections.

Considerations when using the LF-LAM test:

- The LF-LAM test should not be used to assist in the diagnosis of TB in populations other than described in Algorithm 4 and should not be used as a screening test for TB.

- LF-LAM is designed for use with urine samples. Other samples (e.g., sputum, serum, CSF or other body fluids) should not be used.

- LF-LAM does not differentiate between the various species of the genus *Mycobacterium*. However, in areas with a high prevalence of TB, the LAM antigen detected in a clinical sample is likely to be attributed to MTB.

- The use of the LF-LAM assay does not eliminate the need for other diagnostic tests for TB such as Xpert MTB/RIF or culture. These tests exceed the LF-LAM test in diagnostic accuracy and provide information on drug susceptibility. Whenever possible, a positive LF-LAM should be followed up with other tests such as Xpert MTB/RIF, WRD, or bacteriological culture and drug-susceptibility testing.

- Published studies revealed that the LF-LAM test may give a different result than the Xpert MTB/RIF test or culture (e.g., LF-LAM positive, Xpert MTB/RIF MTB not detected). This is not unexpected because the tests have different sensitivities and measure different analytes. Treatment decisions should rely on clinical judgement and all available information.

ALGORITHM 4

Suggested Reading

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. Geneva, World Health Organization. 2016.

http://www.who.int/hiv/pub/arv/arv-2016/

The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.25).

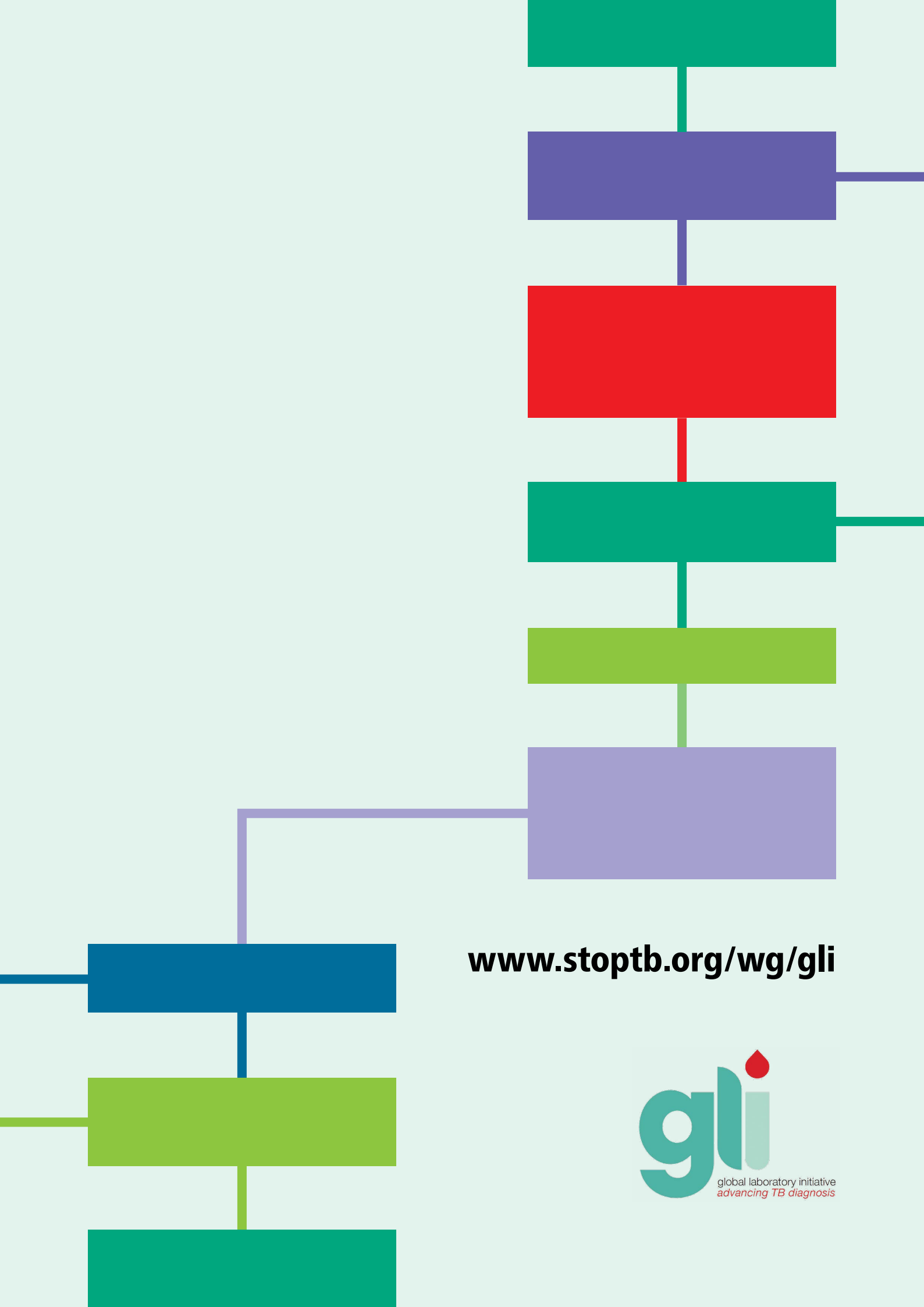http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv

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http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

Training package on Xpert MTB/RIF. Global Laboratory Initiative. 2014.

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global laboratory initiative
advancing TB diagnosis