

AN ACTIVIST'S GUIDE TO THE LAM TEST

VITAL FOR DIAGNOSING TB IN PEOPLE LIVING WITH HIV/AIDS



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WHY DIAGNOSING TB MATTERS

Tuberculosis (TB) is the number one killer of people living with HIV/AIDS, causing one in three of all AIDS-related deaths.¹ Yet, unlike HIV, TB is curable: each one of these 250,000 deaths annually is preventable.² All people living with HIV should be screened for TB, yet many countries do not report screening for TB in this vulnerable population.^{3,4}

Advocating for better TB diagnosis is essential to ending unnecessary suffering and deaths among people living with HIV/AIDS. In 2018, 860,000 people living with HIV fell ill with TB.⁵ People living with HIV are at increased risk of developing TB, and of dying from it—especially when they have advanced HIV disease, or AIDS (see text box).⁶

Most TB in people living with HIV is diagnosed very late, or not at all. A systematic review of data from Sub-Saharan Africa showed that prior to 2014, about half (45.8%) of people living with HIV who died of TB remained undiagnosed at death.⁷ Often people living with HIV do not get the TB treatment they need. This is in part because diagnosing TB in people living with HIV, especially those with AIDS who are most at risk of dying from TB, has been challenging in the absence of rapid, non-sputum-based, sensitive diagnostic tests for TB.

WHAT IS ADVANCED HIV?

Advanced HIV, also known as AIDS, is defined as a CD4 cell count of less than 200 cells/mm³ or a clinical stage 3 or 4 event (e.g., unexplained malnutrition, recurrent bacterial infections, etc.) at presentation for care for adults, adolescents, and children over five years of age. All children under five years should be considered as having AIDS at presentation, regardless of CD4 cell count or clinical events.⁸

WHY DO WE NEED NEW TB DIAGNOSTICS FOR PEOPLE LIVING WITH HIV/AIDS?

Most TB tests rely on sputum (mucus coughed up from the lungs). Sputum-based tests do not work well in people living with HIV/AIDS for three reasons. First, people living with HIV/AIDS are more likely than HIV-negative people to develop TB outside the lungs (40–80% versus 10–20%).⁹ Most adults (87.9%) with AIDS who died of TB had disseminated TB (TB throughout the body, rather than in the lungs).¹⁰

Second, the physical act of coughing up sputum for the test can be difficult and unpleasant for someone who is very ill. Lastly, people living with HIV/AIDS also tend to have fewer TB bacteria in their bodies, even when they are sick. This makes it harder for sputum-based tests to detect the TB bug.

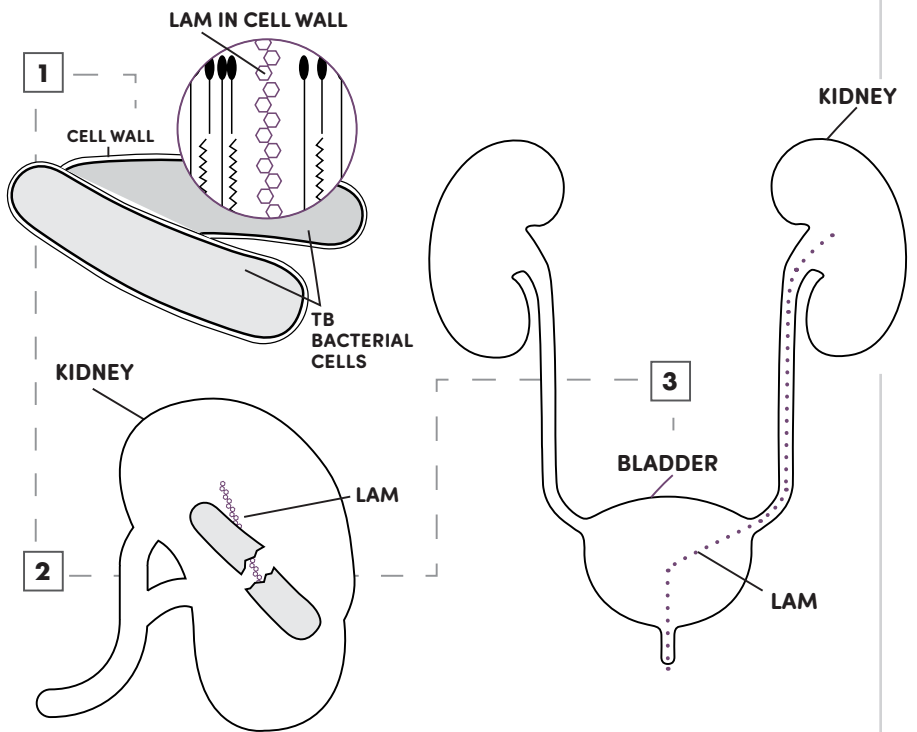
Rapid molecular tests like Xpert MTB/RIF Ultra or Truenat MTB Plus should be the number one test for all to detect TB. These tests can better detect TB in people living with HIV—including TB outside the lungs—than smear microscopy, which is no longer recommended by the World Health Organization (WHO) as an initial test for TB.¹¹ Rapid molecular tests are important tools for diagnosing TB in people living with HIV/AIDS, but they still rely on sputum or other samples from the body that are hard to obtain. Xpert and Truenat tests are not as simple, fast, or inexpensive as the LAM test. Using these tests together increases successful TB diagnoses among people living with HIV/AIDS, allows for early initiation of treatment, and saves more lives.¹²

THE LAM TEST

The LAM test is the only test available that can rapidly and easily diagnose active TB in people living with HIV/AIDS.¹³ The LAM test is simple: it looks like a typical urine-based pregnancy test. Abbott (formerly Alere) is currently the only company that commercially produces the LAM test, and it markets this test as the Determine TB LAM Ag test.^{14,15} In 2019, the WHO recommended that the LAM test be used to detect TB in all people living with HIV (1) who have signs and symptoms of TB, (2) who are seriously ill, or (3) who have AIDS, with less than 200 CD4 cells/mm³ for inpatients and less than 100 CD4 cells/mm³ for outpatients.¹⁶

WHAT IS LAM?

LAM stands for lipoarabinomannan. LAM is a component of the outer cell wall of TB bacteria. LAM is an antigen, meaning it causes an immune response when it enters the human body. LAM sheds off from TB bacterial cells in the body. Many people living with HIV/AIDS have disseminated TB spread throughout the body, including TB in their kidneys (renal TB).¹⁷ When TB bacteria in the kidneys shed off LAM, the kidney clears LAM into urine, which is how the urine LAM test can detect TB.



BENEFITS OF URINE LAM TESTING

- **Saves lives!**—the LAM test is the only TB test shown to reduce deaths.¹⁸ A randomized clinical trial of 2,000 hospitalized people living with HIV in South Africa, Tanzania, Zambia, and Zimbabwe showed that using LAM was associated with a four percent reduction in the number of people who died in the first eight weeks from any cause; LAM reduced the risk of dying by 17 percent. The LAM test did this by identifying people with TB earlier, which allowed them to receive TB treatment earlier. Another randomized control trial of over 2,500 hospitalized people living with HIV in Malawi and South Africa found that screening for TB using both LAM and Xpert MTB/RIF reduced deaths among people with AIDS and improved the overall rate of TB diagnosis among people living with HIV.¹⁹
- **Aimed at the most vulnerable**—the LAM test works best in those sickest with HIV, meaning it targets those most at risk of dying from TB. People living with HIV/AIDS previously lacked other good diagnostic options.
- **Affordable**—the LAM test costs just USD 3.50 per test. Unlike other TB tests, LAM requires no special reagents or equipment (other than cups and pipettes for the urine).
- **Noninvasive**—because the test uses urine, it does not require any of the uncomfortable procedures that other TB tests often do (such as inducing sputum or taking a biopsy).
- **Simple**—the LAM test is low tech and requires little training to use. It does not rely on electricity or any special equipment. As such, it is the only point-of-care TB test. It requires no sample preparation.
- **Fast**—the LAM test provides results in just 25 minutes, making it the fastest TB test.

LIMITATIONS OF URINE LAM TESTING

- **Low sensitivity**—the LAM test can miss TB, so a negative test must always be followed by other diagnostic tests for TB. When the LAM test is used in combination with other tests in people living with HIV/AIDS, more people with TB are detected. One study of hospitalized people living with HIV in South Africa showed that combining Xpert MTB/RIF on sputum plus urine LAM produced a diagnostic yield of 52.5%, compared with 26.6% for Xpert MTB/RIF alone, 38.1% for urine LAM alone, and 19.4% for sputum smear microscopy alone.²⁰ LAM and rapid molecular tests such as Xpert MTB/RIF Ultra or Truenat MTB Plus should be used together to optimize the diagnosis of TB among people living with HIV/AIDS.²¹
- **Does not provide information on drug susceptibility**—the LAM test is unable to test whether a strain of TB is drug resistant, and therefore it cannot detect multidrug-resistant TB (MDR-TB) or guide which treatment regimen is best.
- **Limited population**—LAM testing is recommended only for people living with HIV (1) who have signs and symptoms of TB, (2) who are seriously ill, or (3) who have AIDS with less than 200 CD4 cells/mm³ for inpatients, and less than 100 CD4 cells/mm³ for outpatients.²²
- **Differentiation**—LAM cannot distinguish between *Mycobacterium tuberculosis*, which causes TB, and other types of mycobacteria (which could be harmless or could require different treatment).
- **Not recommended for treatment monitoring**—after initial diagnosis, LAM is not used to test whether treatment against TB is working.

AVAILABILITY

Everyone has the right to health and the right to benefit from scientific progress. The Determine TB LAM Ag test marketed by Abbott has been commercially available since 2013 and recommended by the WHO since 2015, yet uptake of this test has remained limited. Five years after the WHO recommended the use of LAM testing, fewer than 10 countries have translated policy into practice by rolling out the use of LAM within their national programs.^{23,24} People living with HIV/AIDS have a right to access this life-saving test. The fact that LAM testing is still largely unavailable is a violation of their rights and a missed opportunity to save lives.



NEXT-GENERATION LAM TESTS

LAM in urine has proven to be a vitally important biomarker for detecting TB. Several next-generation urine-based LAM tests are currently under development and expected to offer improved sensitivity for TB detection.²⁵

One such test is SILVAMP TB LAM, manufactured by Fujifilm. According to a preliminary evaluation, SILVAMP TB LAM demonstrated a 30 percent increase in sensitivity over Abbott's Determine TB LAM Ag test.²⁶ The WHO is planning to review SILVAMP TB LAM in late 2020, and the test is expected to be commercially available by early 2021.²⁷ This new LAM test is constructed using more expensive materials and, as a result, is likely to enter the market at a price higher than Abbott's Determine TB LAM Ag, priced at USD 3.50 per test. SILVAMP TB LAM is also slightly less simple; it requires a 40-minute incubation period and an intermediary step to produce a result.

Though it may be tempting to wait for Fujifilm and others to deliver more sensitive LAM tests, it is imperative that we take action now, urgently and with the currently available LAM test to improve rates of TB diagnosis and to prevent unnecessary suffering and deaths among people living with HIV/AIDS.

TAKE ACTION

No TB diagnostic test is perfect, including the LAM test, but it is an important tool for saving people living with HIV/AIDS from dying of TB, with very few downsides. Make sure LAM testing is available where you live! If not, you can demand LAM by:

- Working with your government to incorporate LAM testing into Global Fund requests and U.S. President's Emergency Plan for AIDS Relief (PEPFAR) Country Operational Plans;
- Calling on your National AIDS Programs and National TB Programs to introduce and scale up LAM:
 - » Ask them to update their national TB and HIV guidelines and diagnostic algorithms to include LAM testing in line with WHO recommendations;
 - » Ask them to purchase LAM tests (both the Global Fund and PEPFAR will support this);
 - » Ask them to sensitize and train health care workers on the use of LAM; and

- » Ask them to roll out and scale up implementation of this life-saving test.
- Exploring whether registration with your national regulatory authority is necessary to use LAM. If so, encourage Abbott to register the LAM test in your country or ask your national regulatory authority to waive the registration requirement;
- Generating demand for LAM tests from TB/HIV-affected communities by creating awareness about the need for better TB diagnosis and about LAM testing;
- Encouraging donors to support countries in rolling out this test in high-TB/HIV-burden settings through special projects or centralized purchases.

To find out more about the status of LAM testing in your country and what you can do, contact TAG's TB Project Officer, David Branigan (david.branigan@treatmentactiongroup.org).

OVERCOMING RESISTANCE TO IMPLEMENTING THE LAM TEST

Globally, countries have lacked political will to implement LAM, resulting in low uptake of this life-saving test. When advocating for implementation of the urine LAM test in your country and at the regional and global levels, you may experience resistance and hear misconceptions from various stakeholders. Here are some potential reasons stakeholders may give for not wanting to introduce LAM where you live, and how you can respond:

REASON: We are scaling up the Test & Treat strategy for HIV, so people will not be presenting to the health care system with AIDS anymore.

RESPONSE: Even with proactive Test & Treat strategies, people will still present to the health care system with AIDS. Studies show that even in countries that rolled out Test & Treat years ago, many people living with HIV still present in health care facilities with very low CD4 cell counts. A 10-country analysis showed that one-third of people living with HIV are still presenting with CD4 cell counts of less than 200 cells/mm³;²⁸ in 2016 in Taiwan, 29% of people living with HIV presented with CD4 cell counts of less than 200 cells/mm³;²⁹ and in South Korea between 2013 and 2015, 17% presented with CD4 cell counts of less than 100 cells/mm³.³⁰ We are, unfortunately, many years away from a time when no one has AIDS. In the meantime, people are dying, and we need to use every tool we have to stop those deaths.

REASON: We are diagnosing TB among people living with HIV using other tests.

RESPONSE: LAM diagnoses TB faster, in a less invasive way, at little additional cost. LAM has been demonstrated to get people onto treatment faster and reduce mortality.³¹ LAM has also been demonstrated to greatly improve diagnostic yield when used in combination with other tests.³²

REASON: The evidence to support the use of the LAM test is not strong enough.

RESPONSE: There is sufficient evidence from multiple published studies in a range of countries to support the use of this test, and it is the only TB test shown to reduce mortality and accelerate TB treatment initiation.^{33,34,35,36} The body of evidence on LAM led the WHO to strongly recommend the use of LAM in 2019,³⁷ and the evidence base supporting this recommendation continues to grow.³⁸

REASON: We do not have funding for LAM.

RESPONSE: The test is very inexpensive (USD 3.50 per test), and there are no additional required materials/consumables/electricity (other than pipettes and cups for urine collection). One modeling study assessed the budget impact of implementing LAM testing and found LAM to be cost-effective even in resource-limited settings.³⁹ The Global Fund and PEPFAR will cover the purchase of LAM tests and their implementation in TB and HIV programs.⁴⁰ LAM tests can be procured in packs of 100 (USD 350) directly from Abbott or through the Stop TB Partnership's Global Drug Facility.⁴¹ There is no reason national programs should not be procuring and using LAM in these and larger quantities.

REASON: A new more sensitive LAM test will be available soon, so we are waiting to use that test.

RESPONSE: People with HIV/AIDS are dying of TB; we cannot afford to wait. Immediately procuring and implementing the currently available LAM test will save lives. The new LAM test, Fujifilm's SILVAMP TB LAM, is expected to be more sensitive, but in the meantime, the currently available LAM test, Abbott's Determine TB LAM Ag, can improve rates of TB diagnosis among people living with HIV and reduce deaths among people living with AIDS.⁴² It is the responsibility of national programs to immediately procure and implement the LAM test.

REASON: We do not know how to introduce this test.

RESPONSE: LAM is recommended for use in both hospital and outpatient settings. The WHO's 2019 policy update on the use of LAM includes a guide for how to integrate the LAM test into existing TB testing algorithms for people living with HIV/AIDS. Annex 1 of the policy update, *Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV*, details diagnostic algorithms for both hospital and outpatient settings.⁴³ Minimal training is needed for hospital or outpatient staff to implement these algorithms.

REASON: This test only works in a niche population, so it is not a high priority.

RESPONSE: This is the population with the highest risk of dying from TB, so it is a high priority. The right to health promotes access to the best available standard of care for all people, so even if the LAM target population is a small subset epidemiologically, it is still important to provide this population access to the best diagnostic and treatment tools available.

REASON: We do not know who will do the training for this test.

RESPONSE: You can contact TAG's TB Project Officer, David Branigan (david.branigan@treatmentactiongroup.org), who will facilitate introductions to individuals or organizations that can provide technical assistance and training for the health care workers in your country.

REASON: We are waiting for another country to lead the way.

RESPONSE: Several countries have already begun to use LAM in their national programs, and others should follow suit! While you are busy waiting for other countries to lead the way, people living with HIV/AIDS will unnecessarily suffer and die from TB. There will be blood on your hands.

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