

## **THE LAM TEST: VITAL FOR DIAGNOSING TB IN PEOPLE WITH ADVANCED HIV**

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### **WHY DIAGNOSING TB MATTERS**

Tuberculosis (TB) is caused by bacteria called *Mycobacteria tuberculosis*. TB is the number one killer of people with HIV, causing one in three of all AIDS-related deaths.<sup>1</sup> Yet, unlike HIV, TB is curable: each one of these 400,000 deaths annually is preventable.<sup>2</sup> All people with HIV should be screened for TB, yet many countries do not report screening for TB in people with HIV.<sup>3,4</sup>

Advocating for better TB diagnosis is essential to ending suffering for those living with HIV. In 2015, 1.2 million people with HIV fell ill with TB.<sup>5</sup> People living with HIV are at increased risk of developing TB, and of dying from it—especially when they have low CD4 counts.<sup>6</sup>

Most TB in people with HIV is diagnosed very late, or not at all. Studies from Sub-Saharan Africa show about half (45.8%) of the people with HIV who died of TB remained undiagnosed at death,<sup>7</sup> meaning people do not get the treatment they need. This is in part because diagnosing TB in people with HIV, especially those with low CD4 counts who are most at risk of dying from TB, has been challenging, until now, with the development of LAM testing (see text box).

#### **WHY WE NEED NEW TB DIAGNOSTICS FOR PEOPLE WITH ADVANCED HIV**

The most common TB test, sputum smear microscopy, does not work well in people with advanced HIV, for three reasons. First, it relies on sputum (mucus coughed up from the lungs). But people with HIV are more likely than HIV-negative people to develop TB outside the lungs (40–80% versus 10–20%), so sputum-based TB tests do not work as well in people with HIV.<sup>8</sup> Most adults (87.9%) with advanced HIV\* who died of TB had disseminated TB (TB throughout the body, rather than in the lungs).<sup>7</sup>

Second, people with HIV also tend to have fewer TB bacteria in their bodies even when they are sick. This makes it harder for the test, which is not very sensitive, to detect the TB bug. Third, the physical act of coughing up sputum for the test can be difficult and unpleasant for someone who is very ill.

Tests like GeneXpert MTB/RIF can better detect TB, including TB outside the lungs, in people with HIV. GeneXpert MTB/RIF is an important tool for diagnosing TB in people with advanced HIV, but it still relies on sputum or other samples from the body that are hard to obtain. GeneXpert is not as simple, fast, or inexpensive as the LAM test. **GeneXpert MTB/RIF and LAM should be used together for the best chance of diagnosing TB.**

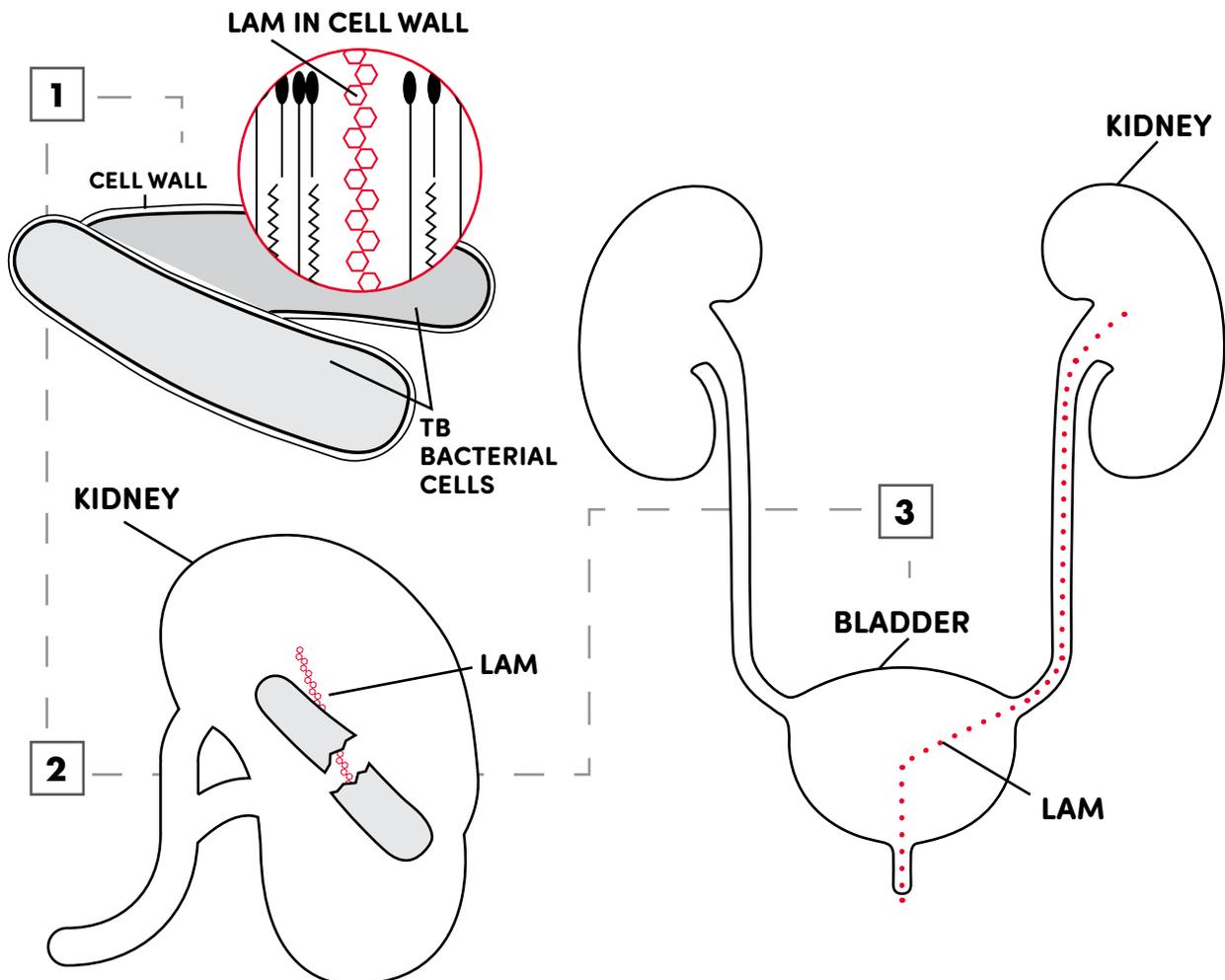
\* For adults, adolescents, and children over five years, advanced HIV disease is defined as a CD4 cell count <200 cells/mm<sup>3</sup> or a clinical stage 3 or 4 event at presentation for care.

## THE LAM TEST

For the first time ever, there is a test that can easily diagnose active TB in people with advanced HIV.<sup>9</sup> In 2015, the World Health Organization (WHO) recommended the use of a new test to efficiently detect TB in people with HIV with CD4 counts of  $\leq 100$  cells/mm<sup>3</sup> or who are severely ill, irrespective of their CD4 counts. This test is called the lipoarabinomannan (LAM) test. The LAM test is a simple urine dipstick test: it looks like a typical urine-based pregnancy test. Currently, Alere is the only company that produces the LAM test, and it markets this test as the Determine TB LAM Ag test.<sup>10</sup>

### WHAT IS LAM?

LAM stands for lipoarabinomannan. LAM is a compound that makes up part of the outer cell wall of the 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 with advanced HIV have disseminated TB, including TB in their kidneys (renal TB).<sup>11</sup> When TB bacteria in the kidneys shed off LAM, the kidney clears LAM into urine, which is how the LAM urine test can detect it.



## BENEFITS OF URINE LAM TESTING

- **Saves lives!**—the LAM test is the only TB test shown to reduce deaths.<sup>12</sup> A randomized clinical trial of 2,000 hospitalized people 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, allowing them to receive TB treatment earlier.
- **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 with advanced HIV 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 for the urine).
- **Noninvasive**—because the test uses urine, it does not require any uncomfortable procedures as other TB tests can (such as inducing sputum, drawing blood, 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 cases, so a negative test must be followed by other diagnostic tests for TB. When the LAM test is used in combination with other tests in people with advanced HIV, more TB cases are detected. One study of people living with HIV with low CD4 counts showed that combining GeneXpert MTB/RIF using sputum plus urine LAM led to a yield of 52.5%, in contrast to using GeneXpert MTB/RIF alone, which had a yield of 26.6%; only urine LAM, which yielded 38.1%; or just sputum microscopy, which yielded 19.4%.<sup>13</sup>
- **No drug susceptibility ability**—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.
- **Treatment monitoring**—after initial diagnosis, LAM cannot be used to test whether treatment against TB is working.
- **Limited population**—LAM testing is only recommended for people living with HIV who have low CD4 cell counts or are seriously ill.
- **Differentiation**—LAM cannot distinguish between *Mycobacterium tuberculosis*, which causes TB, and other types of mycobacteria (which could be harmless or could require different treatment).

## AVAILABILITY

As of August 2017, Uganda is the only country to have incorporated LAM into its policy for the diagnosis of TB in very sick HIV patients in hospitals. South Africa is planning on rolling out LAM later on this year.<sup>14</sup> Kenya, South Africa, and Uganda have introduced pilot projects. Alere has registered the LAM test for use in Brazil, Colombia, Guatemala, Kenya, Mexico, Peru, Thailand, Taiwan, and the European Union.<sup>15</sup>

Everyone has the right to health and to benefit from scientific progress. People with advanced HIV have a right to access this life-saving test. It is a violation of their rights that LAM testing is largely unavailable.

### COUNTRIES WITH HIGH BURDENS OF TB AND HIV

The following countries have high burdens of TB and HIV, and as such should be prioritized for implementation of the LAM test<sup>16</sup>:

Angola	Congo	Lesotho	South Africa
Botswana	DR Congo	Liberia	Swaziland
Brazil	Ethiopia	Malawi	Thailand
Cameroon	Ghana	Mozambique	Uganda
Central African Republic	Guinea-Bissau	Myanmar	UR Tanzania
Chad	India	Namibia	Zambia
China	Indonesia	Nigeria	Zimbabwe
	Kenya	Papua New Guinea	

## TAKE ACTION

No TB diagnostic test is perfect, including the LAM test, but it is an important tool for saving people with advanced HIV from dying of TB, with very few downsides. You can demand LAM by:

- Working with countries that have high TB/HIV burden on their Global Fund renewals and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) Country Operating Plans to ensure their plans include LAM rollout;
- Calling on your National AIDS Program and National TB Program to introduce LAM:
  - » Ask them to update their national TB treatment guidelines and HIV treatment guidelines to include LAM testing in line with WHO recommendations;
  - » Ask them to purchase LAM tests (Global Fund funding will allow for this);
- Exploring whether registration with your national regulatory authority is necessary to use LAM testing. If so, encourage Alere to register the LAM test in your country;
- Generating demand for LAM use from TB/HIV-affected communities by creating awareness among TB and HIV CSOs and CBOs;
- Encouraging donors, especially Unitaid and PEPFAR, to support countries in rolling out this test in high-TB/HIV-burden settings through special projects or centralized purchases.

## OVERCOMING RESISTANCE TO IMPLEMENTING THE LAM TEST

There has been low uptake of the test globally due to lack of political will. When advocating for the implementation of the urine LAM test in your settings, you may experience resistance and 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:

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

**Response:** Even with proactive Test & Treat strategies, people will still present to the health care system with advanced HIV. Studies show that even in countries that rolled out Test & Treat years ago, many people with HIV still present in health care facilities with very low CD4 counts. One-third of people with HIV are still presenting with CD4 counts of  $<200$  cells/mm<sup>3</sup> in a 10-country analysis;<sup>17</sup> in 2016 in Taiwan, 29% presented with CD4 counts of  $<200$  cells/mm<sup>3</sup>,<sup>18</sup> and in South Korea, 17% presented with CD4 counts of  $<100$  cells/mm<sup>3</sup> between 2013 and 2015.<sup>19</sup> We are, unfortunately, many years away from a time when no one has advanced disease. In the meantime, people are dying, and we need to use every tool we have to stop those deaths.

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**Reason:** We are diagnosing TB in the target population through 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.<sup>12</sup> LAM has also been demonstrated to greatly improve diagnostic yield when used with other tests.<sup>13</sup>

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**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 several countries to support the use of this test, and it is the only TB test shown to reduce mortality and accelerate treatment initiation.<sup>11,12, 20, 21</sup> The body of evidence on LAM led to the WHO endorsement of LAM in 2015 and has only been added to since—and the *Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy* emphasize the use of LAM in individuals with CD4 count  $\leq 100$  cells/mm<sup>3</sup> or who are seriously ill at any CD4 count.<sup>22</sup>

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**Reason:** We do not have funding for LAM.

**Response:** The test is very inexpensive (USD 3.50 per test), and there are no additional materials/consumables/electricity (other than cups for urine collection) required. The Global Fund and PEPFAR will also cover purchasing of LAM tests.<sup>23</sup>

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**Reason:** We do not know how to introduce this test.

**Response:** LAM is recommended for use in hospital or outpatient settings. The Global Laboratory Initiative's *Model TB Diagnostic Algorithms* algorithm 4 ([http://www.stoptb.org/wg/gli/assets/documents/GLI\\_algorithms.pdf](http://www.stoptb.org/wg/gli/assets/documents/GLI_algorithms.pdf)) provides a guide on how to adopt the LAM test in the TB testing algorithm for people with low CD4 counts.<sup>9</sup> The yield seen in hospital settings is very high, and minimal training is needed for hospital staff to implement the algorithm.

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**Reason:** This test only works in a niche population, so it's not a high priority.

**Response:** This is the population with the highest mortality rates, so it is a high priority. The right to health protects access to the best available health care for all people, so even if the LAM target population is a small subset epidemiologically, it is still important to give this population the best diagnostic and treatment tools possible.

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

**Response:** You can contact TAG's Erica Lessem ([erica.lessem@treatmentactiongroup.org](mailto:erica.lessem@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.

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

**Response:** Uganda is already leading the way, and South Africa is scheduled to follow suit! We really need to be proactive in saving lives and upholding human rights; there is no excuse as to why anyone should die of a curable disease due to lack of diagnosis and treatment.

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## END NOTES

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