THE LAM TEST:

ENSURING SCALED-UP, EXPANDED TB LAM TESTING FOR PEOPLE WITH ADVANCED HIV

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WHY DIAGNOSING TB MATTERS

Tuberculosis (TB) is the number one killer of people living with HIV (PLHIV), causing one in three of all AIDS-related deaths.[1] This amounts to 300,000 deaths per year, each of which is preventable.[2] The End TB Strategy from the World Health Organization (WHO) sets a target of reducing 95 percent of deaths caused by TB by 2035.[3] The political declaration from the first-ever United Nations General Assembly High-Level Meeting on TB in September 2018 calls for diagnosing TB in 40 million by 2022.[4] UNAIDS set a goal to reduce the number of TB-related deaths in PLHIV by 75 percent by 2020.[5] With almost four million of the estimated 10 million TB cases each year missing (never notified),[6] drastic improvements to TB diagnosis rates, including among PLHIV, are necessary to achieve these ambitious goals. And that will require a combination of tests.

WHY WE NEED TO USE IMPROVED TB DIAGNOSTICS FOR PEOPLE WITH ADVANCED HIV

People with advanced HIV are at extremely high risk of dying from TB, often without ever receiving a TB diagnosis. Relying on sputum-based testing poses major challenges to diagnosing TB in PLHIV, particularly those with advanced disease. PLHIV are more likely than HIV-negative people to develop TB outside the lungs (40–80% vs. 10–20%).[7] According to an analysis of 36 studies, most adults with advanced HIV (87.9%) who died of TB had disseminated TB (TB throughout the body, rather than in the lungs alone).[8] PLHIV are also more likely to have low levels of bacteria (paucibacillary disease), which can make TB more difficult to detect, and people with advanced HIV can have difficulty even producing sputum. Thus, the most frequently used sputum-based tests like microscopy and GeneXpert MTB/RIF Ultra on sputum miss many cases. TB tests

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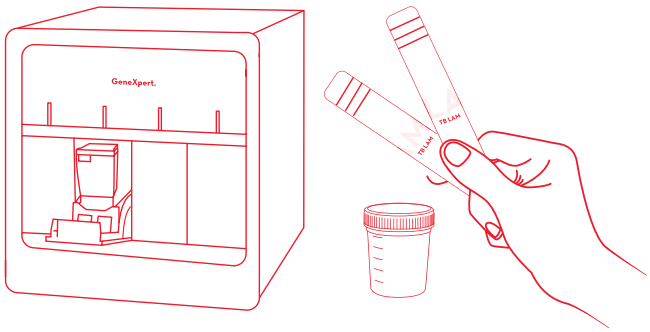
that do not rely on sputum are important to save lives. For these reasons, urine-based testing is a much easier sample, especially for diagnosing people with advanced HIV.

WHAT IS ADVANCED HIV? *People with advanced HIV disease are at extremely high risk of dying from TB and are in urgent need of faster diagnosis and linkage to care. For adults, adolescents, and children five years and older, the WHO defines advanced HIV disease as a CD4<200 cells/mm^3 or a WHO clinical stage 3 or 4 event at presentation for care.*[9]

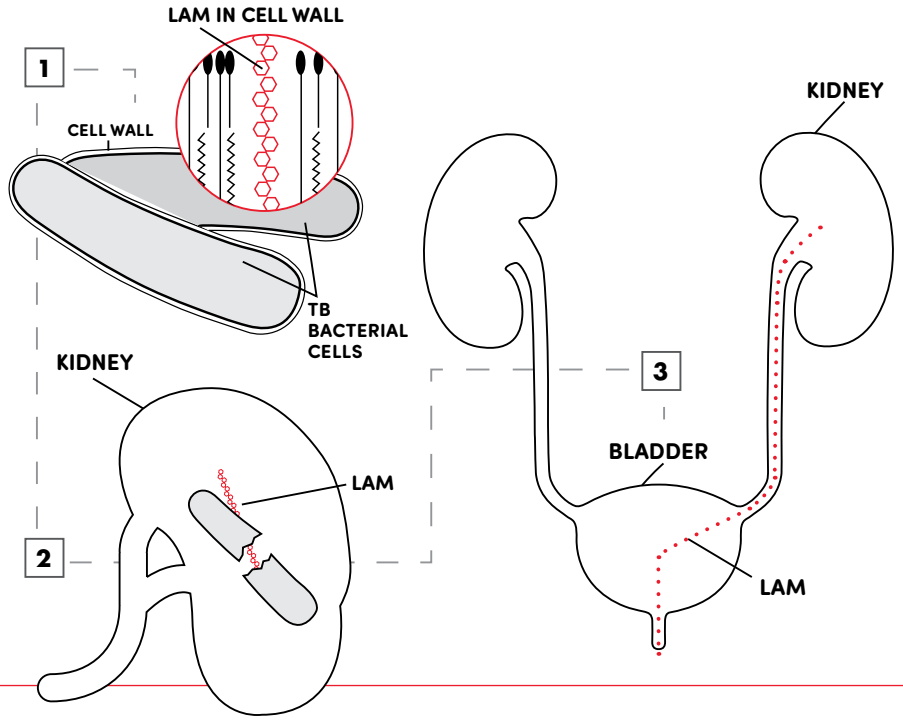
TB LAM TESTING

Currently, there is only one urine-based test for TB: TB lipoarabinomannan (LAM) testing. This test should be used in combination with GeneXpert MTB/RIF Ultra for the best chance of diagnosing TB in people with advanced HIV.



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). 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.



TB LAM testing has been endorsed by the WHO since 2015 for use in testing PLHIV with advanced disease. As of this writing, the WHO endorses the use of the Determine TB LAM Ag test, manufactured by Abbott (formerly Alere). The currently recommended test costs just US$3.50 and is a simple lateral flow assay. TB LAM testing does not require complex equipment or electricity—only urine collection cups, pipettes and pipette tips, and a timer.

NEXT-GENERATION TESTING

New tests to detect the LAM antigen are in development—tests that may offer improved sensitivity for detecting TB among all PLHIV (not just those with advanced disease). In 2019, the WHO is expected to review evidence for both the existing LAM test manufactured by Abbott, as well as preliminary evidence for a LAM test in development by Fujifilm. This review may result in a broader indication for LAM testing. In the meantime, TB and HIV programs should not wait to roll out the existing test, given its potential to save lives and its minimal cost.

SCIENTIFIC EVIDENCE & BENEFITS OF TB LAM TESTING

Evidence strongly suggests the dramatic benefits of using the TB LAM test in high TB/HIV burden settings. The test has demonstrated impact in all PLHIV admitted to the hospital regardless of CD4 count or symptoms, and for all PLHIV with advanced disease or CD4<200 cells/mm^3 presenting to ambulatory care. While the current LAM test has suboptimal sensitivity (a pooled sensitivity of 56% and a pooled specificity of 90% in PLHIV with CD4<100 cells/mm^3 compared with culture or nucleic acid amplification testing[11]), clinical trials have shown that it allows for earlier diagnosis in people with advanced HIV in both inpatient and outpatient settings and that it reduces TB mortality. TB LAM is the only TB diagnostic tool to date to show a mortality benefit in a randomized controlled trial: In a multicenter, multicountry study, adding TB LAM testing to standard TB testing (smear, culture, GeneXpert MTB/RIF, and culture) reduced the time to treatment, thereby reducing mortality in HIV-positive inpatients with symptoms of TB.[12]

Another multicountry, randomized trial, known as

the STAMP trial, showed that using TB LAM testing in addition to GeneXpert MTB/RIF in all HIV-positive, hospital-admitted adults resulted in a survival benefit in the most at-risk subpopulations in a pre-specified analysis, and in an increase in TB diagnosis and treatment initiation in the general study population.[13] TB LAM testing was found to increase life expectancy by half a year to 1.2 years and was cost-effective; using TB LAM testing in hospitals in Malawi and South Africa alone for five years would save 122,000 years of life.[14] These data support the value of using TB LAM to screen for TB among all hospitalized PLHIV. Further, a prospective observational cohort study of both ambulatory and hospitalized PLHIV in Kenya indicated that adding TB LAM testing to testing algorithms increased diagnostic yield in people with CD4<200 cells/mm^3.[15] These support the expansion of TB LAM testing to both inpatient and outpatient facilities for anyone with advanced HIV or with CD4<200 cells/mm^3.

These data not only reiterate the need for TB LAM uptake, but also favor expanding the use of TB LAM testing in both inpatient and outpatient settings. The available evidence strongly suggests the dramatic benefits of using the TB LAM test in high TB/HIV burden settings for all PLHIV admitted to hospitals regardless of CD4 count or symptoms (plus GeneXpert MTB/RIF Ultra), and for all PLHIV presenting to ambulatory care with signs of advanced disease or, if CD4 testing is available, with CD4<200 cells/mm^3.

COUNTRIES NEED TO TAKE ACTION

TB LAM testing has been WHO-endorsed since 2015 and is featured in the WHO's 2017 guidelines for managing advanced HIV disease.[16,17] Yet only a few countries have scaled up TB LAM testing nationally. 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.

A review of grant documents published on the Global Fund website—Global Fund countries' Funding Requests, Programmatic Gap Tables, Performance Frameworks, and Funding Landscapes—showed limited evidence of TB LAM testing scale-up. Of 55 Global Fund-supported countries, including 31 high HIV/TB burden countries, only six (Burundi, Cameroon, Eswatini, Guatemala, Ukraine, and Vietnam) included use of TB LAM testing in their grant documents. Furthermore, of 30 President's Emergency Plan for AIDS Relief (PEPFAR) Country Operational Plans (COPs) analyzed, only six countries (Côte d'Ivoire, Democratic Republic of the Congo, Eswatini, Kenya, Malawi, and Zambia) included use of LAM in their final COPs. None included expanded use of TB LAM in line with the best available evidence.

Countries must ensure increased access to TB LAM testing to prevent further needless deaths in PLHIV. National HIV and TB programs need to take action now to scale up and expand use of TB LAM testing by:

- **Updating national TB treatment guidelines and HIV treatment guidelines to include LAM testing**, regardless of CD4 count, in both inpatient and outpatient settings for people presenting with advanced HIV (plus any additional people with HIV with CD4<200 cells/mm^3 where CD4 testing is available), and to allow for the potential use of more sensitive future tests in all people with HIV per WHO guidance;
- **Including procurement, nationwide scale-up, and expanded use of TB LAM testing** in PEPFAR COPs and Global Fund funding proposals and annual plans;
- **Exploring whether registration with the national regulatory authority is necessary** to use LAM testing. If so, encourage Abbott to register the LAM test in your country;
- **Generating demand for LAM use** from health care providers and TB/HIV-affected communities by conducting trainings for health care providers, and creating awareness among TB and HIV civil society organizations and community-based organizations;
- **Encouraging donors to support your country in rolling out this test.** The Global Fund, Unitaid, and PEPFAR in particular play important roles. Even when donor funding is not available, **your country can purchase and implement inexpensive LAM testing using domestic funding**, either directly from Abbott or through the Global Drug Facility.

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