



Treatment Action Group

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TB TESTING IN 2021 PEPFAR COPS

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TREATMENT ACTION GROUP

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Recommended TB screening and diagnostic tests for PLHIV

WHO-recommended tests for TB screening among people living with HIV (PLHIV)

- WHO 4-symptom screen (current cough, fever, weight loss, or night sweats), chest X-ray, C-reactive protein (CRP) (**new!**), rapid molecular tests (**new!**)

WHO-recommended tests for TB diagnosis among PLHIV

- LAM tests + rapid molecular tests, clinical judgment based on TB signs and symptoms (in the absence of a positive test result)

WHO and PEPFAR algorithm for TB screening and diagnosis:

- TB screening using a WHO-recommended tool
- If screen-positive, LAM + rapid molecular testing / clinical judgment

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TB screening and diagnosis: what to push for in COP21

PEPFAR COP21 guidance states that:

- “All PLHIV must be screened at every clinical encounter for TB symptoms and using available technologies consistent with international guidelines.” p354
- “For individuals who screen positive for TB symptoms, a WHO-recommended rapid molecular diagnostic test (e.g., Xpert MTB/RIF Ultra, Truenat MTB Plus and Truenat MTB-Rif) should be used in conjunction with LF-LAM, if appropriate. Urinary LF-LAM is helpful for those who cannot produce sputum, but sputum testing with sensitive WHO-recommended rapid molecular diagnostic tests should always be attempted. LF-LAM should be performed in parallel to molecular diagnostic tests.” p348-349

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Urine LAM testing

What is LAM testing?

- LAM testing detects lipoarabinomannan (LAM), in urine. LAM is a component of the outer cell wall of TB bacteria that is a biomarker for the presence of TB.
- LAM tests are rapid, simple, inexpensive, point-of-care tests that use easy-to-obtain urine samples and return results in just 25 minutes. They are most sensitive in PLHIV with advanced HIV disease.
- LAM tests have a proven mortality benefit when used among PLHIV who present to care with advanced HIV disease, by supporting rapid same-day diagnosis and linkage to TB treatment (Gupta-Wright et al, Lancet, July 2018)

PEPFAR-recommended **indication for the use of LAM testing among inpatients AND outpatients** (based on the 2019 WHO recommendations):

1. All PLHIV with signs and symptoms of TB
2. All PLHIV who are seriously ill
3. All PLHIV with CD4 counts <200 cells/mm³

Slow uptake of urine LAM

LAM testing has been commercially available since 2013 and recommended by the WHO since 2015, yet **uptake of the test has remained low despite its low cost and proven mortality benefit.**

- More than five years after LAM testing was first recommended by the WHO, 62% (23/37) of countries surveyed by the MSF and Stop TB Partnership Step Up for TB 2020 report do not indicate TB LAM in their policies for routine use: <https://www.msf.org/step-tb-report-2020>
- Countries with high burdens of TB and HIV cite budget limitations as the primary barrier to adopting and implementing LAM testing, along with “lack of country-specific data and piloting, administrative hurdles such as regulatory agency approval, lack of coordination between National TB and HIV programs, and small perceived patient population,” according to a McGill International TB Centre survey 2018-2019: <https://gatesopenresearch.org/articles/4-24/v2>
- The currently available LAM test, Determine TB LAM Ag from Abbott, **costs only US\$3.50 per test.**

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Urine LAM in COPs: 2018-2020

	LAM in 2018 COP?	LAM in 2019 COP?	LAM in 2020 COP?
Cote d'Ivoire	Y	Y	Y
Democratic Republic of the Congo	Y	Y	Y
Eswatini	Y	Y	Y
Kenya	Y	Y	Y
Malawi	Y	Y	Y
Zambia	Y	Y	Y
Lesotho	N	Y	Y
Namibia	N	Y	Y
South Africa	N	Y	Y
Tanzania	N	Y	Y
Uganda	N	Y	Y
Ukraine	N	Y	Y
Botswana	N	N	Y
Brazil	N	N	Y
India	N	N	Y
Mozambique	N	N	Y
Nigeria	N	N	Y
South Sudan	N	N	Y
Zimbabwe	N	N	Y
TOTALS	6	12	19

Urine LAM: from inclusion in COPs to full implementation

Examples of the range of language in 2020 Strategic Direction Summaries of countries:

- **Cote d'Ivoire [3rd year]:** “incorporating TB LAM into the national diagnostic algorithm for TB, for seriously ill patients and those with advanced HIV disease, in addition to developing national tools and training materials”; “Funds were also allocated to procure WHO Approved TB LAM assay for about 72,000 units at \$371,059” **[specific]**
- **Namibia [2nd year]:** “As part of strategies to improve TB case finding, TB LAM has been rolled-out since December 2019. Implementation is done using the revised WHO November 2019 criteria for both in- and out-patient settings. In COP20, PEPFAR Namibia will support the full implementation of TB-LAM in all Regions”; “Laboratory support will include the procurement of 18,400 urine LAM assays.” **[specific]**
- **Zambia [3rd year]:** “PEPFAR Zambia will invest in... intensified TB case finding using GeneXpert and lipoarabinomannan” **[not very specific]**
- **South Sudan [1st year]:** “South Sudan requires... 100 TB LAM kits”; “Utilization of point-of-care TB lipoarabinomannan (TB LAM) testing as a “rule-in” test where available for PLHIV who are seriously ill or have a CD4 count less than 100 cells/ml.” **[specific but limited procurement quantities and indication]**

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Urine LAM: what to push for in COP21

PEPFAR COP guidance states that:

- “When more sensitive urinary assays for TB become available, PEPFAR will support their use if they are recommended by the WHO TB Program and prices are competitive. **In the meantime, programs should scale-up and implement the currently available LF-LAM test [!!!!].**” p349
- **“Procurement quantities of LF-LAM should exceed the number of PLHIV, including CLHIV, who present to care with signs and symptoms of TB or advanced HIV disease in inpatient and outpatient settings, and sufficient budget should be allocated accordingly [!!!!].”** p361
 - *Procurement quantities can be calculated using country-specific data and leveraged during regional PEPFAR planning meetings!*

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Rapid molecular testing

What is rapid molecular testing?

- Rapid molecular tests are rapid, accurate, cartridge-based tests that detect TB DNA or RNA in samples to diagnose TB and TB resistance to certain drugs.
- The WHO recommends rapid molecular tests as the initial test for confirmatory TB diagnosis and resistance to the first-line TB drug rifampicin.

WHO-recommended rapid molecular tests

- **Cepheid's Xpert MTB/RIF Ultra**
 - The most commonly available rapid molecular test, with extensive data and established test accuracy for a range of sample types.
 - Cepheid held a monopoly on rapid molecular testing for TB from 2010-2020, and high pricing has limited full roll-out and implementation of rapid molecular tests in accordance with WHO recommendations.
- **Molbio's Truenat MTB Plus + MTB/RIF Dx**
 - The most recent rapid molecular test recommended by WHO in 2020.
 - Truenat tests can be implemented at the microscopy center level, closer to the point of care than Xpert tests, which are positioned at the district lab level.

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Rapid molecular tests: what to push for in COP21

PEPFAR COP guidance states that:

- “All PLHIV with TB symptoms should be referred promptly for clinical evaluation and have quality specimens collected for diagnostic testing with a point-of care diagnostic test such as LF-LAM and WHO-recommended molecular diagnostic test with rapid patient results returned.” p354
- “Where appropriate, programs should ensure WHO-recommended rapid molecular TB diagnostic testing for children is done using both sputum and non-sputum specimen types (including stool) according to the WHO policy guidance for each test type.” p359
- “WHO-recommended molecular test (such as Xpert MTB/RIF Ultra, Truenat MTB Plus, or MTB-RIF Dx)” p360 – we should push to scale-up Truenat testing to break Cepheid’s monopoly and support TB testing closer to the point of care!

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Rapid ART initiation / TB testing

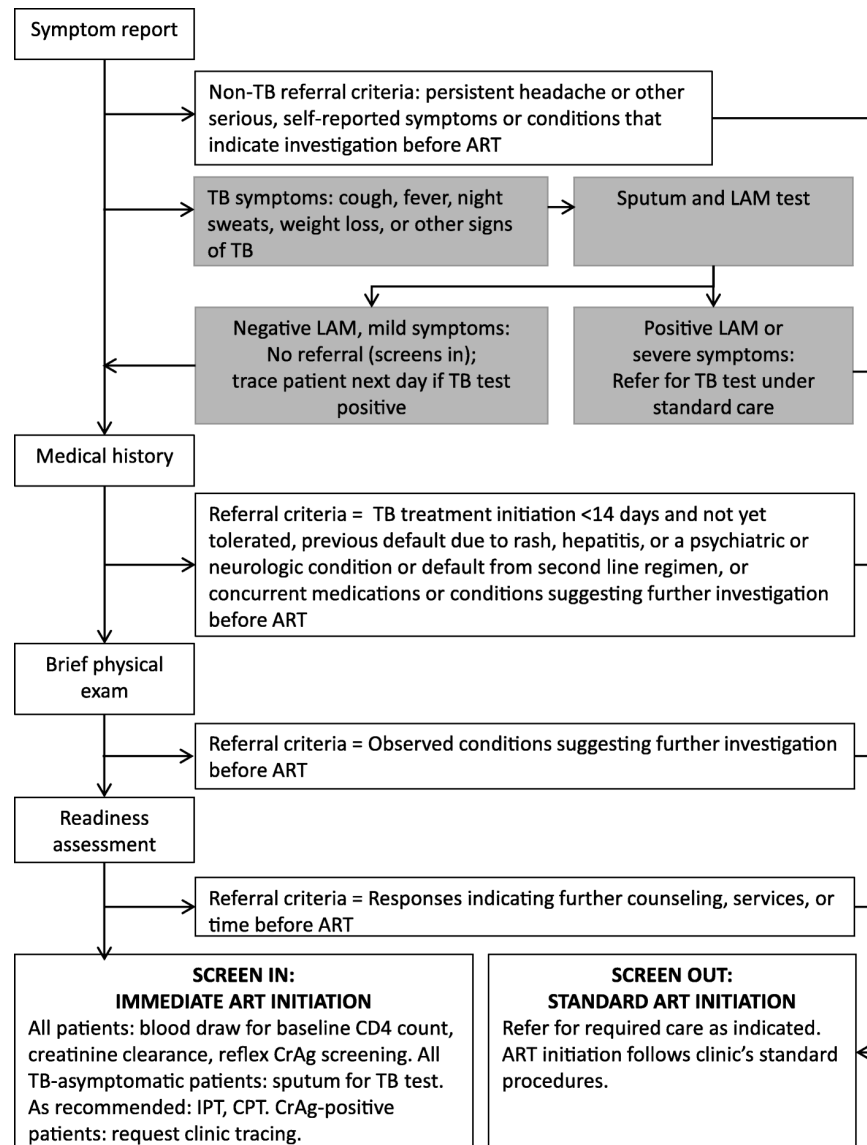
- **Rapid or same-day ART initiation has been shown to save lives** and is a priority of PEPFAR. High rates of TB symptom screen false positives and delays in TB testing can reduce rates of rapid or same-day ART initiation.
- PEPFAR COP guidance states that: “Delays in ART initiation should occur for only for meningitis, (tuberculous or cryptococcal) or other CNS infections,” and that **“[p]ending evaluations for tuberculosis should not delay ART initiation.”** p348
- PEPFAR COP guidance also states that: **“Treatment [for TB] should be initiated immediately if there is clinical suspicion and continued regardless of test result if the clinical symptoms are consistent with TB.”** (p349)
- Even in the case of immediate TB treatment initiation, **ART can still be rapidly initiated within 2 weeks of TB treatment initiation** (except in the case of TB meningitis, due to severe immune reconstitution inflammatory syndrome [IRIS] risk).
- WHO will release guidance on the timing of ART initiation and TB testing and treatment initiation in early 2021.
- The SLATE II study algorithm is one example of how to triage risk for TB, based on severity of symptoms and LAM results, to increase rates of same-day ART initiation. (Maskew et al, Plos Medicine, Aug 2020)

<https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003336>

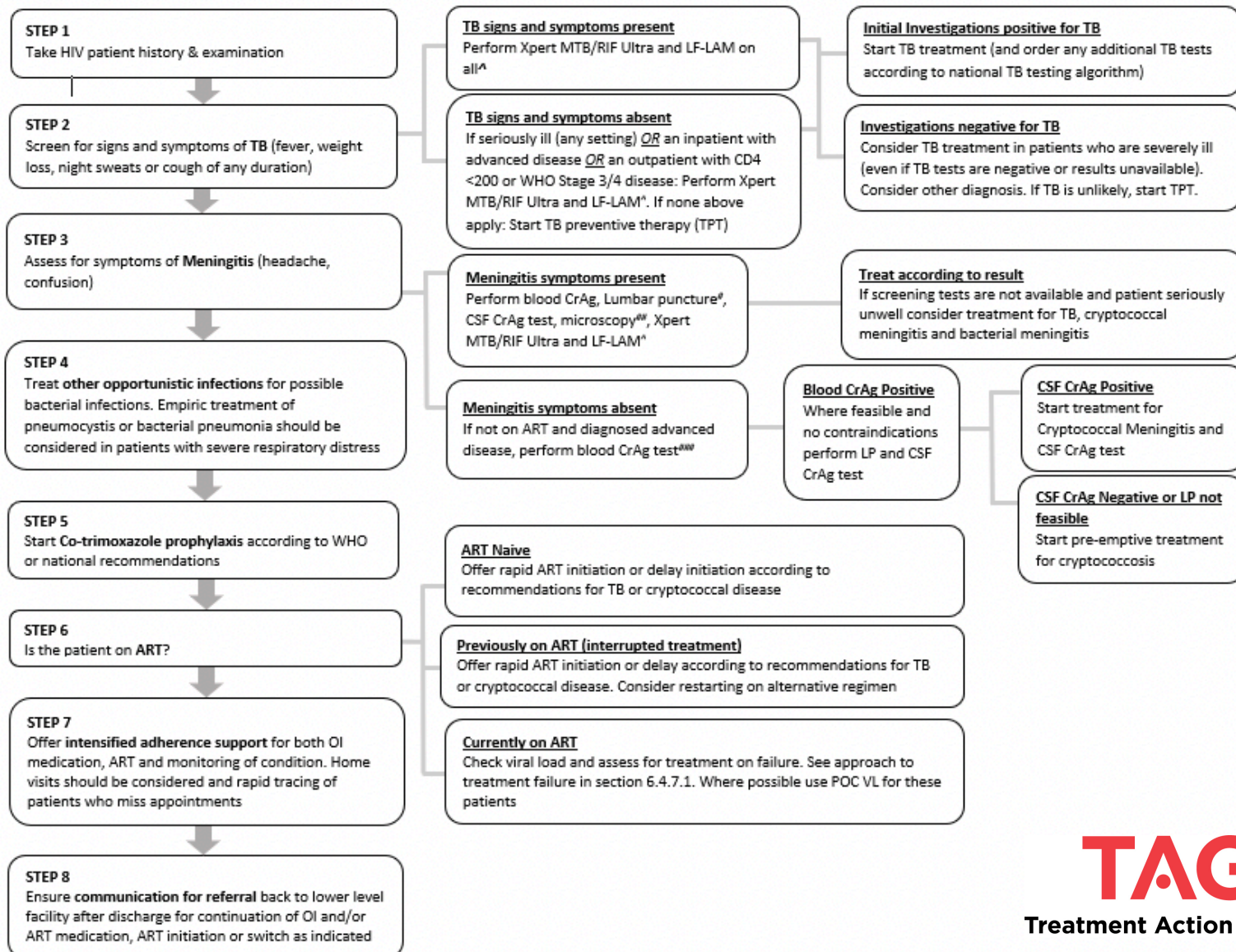


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SLATE II algorithm



Standard AHD algorithm



Rapid ART initiation / TB testing: what to push for in COP21

- **Rapid TB screening and testing, along with rapid (including same-day) ART initiation**, as appropriate according to new 2021 WHO guidance on the timing of ART and TB testing + treatment initiation.
- **Immediate LAM testing for all PLHIV and CLHIV** who present to care with signs of symptoms of TB, serious illness, or advanced HIV disease, in inpatient and outpatient settings.
- **For PLHIV who screen positive for TB**, same-day sputum sample collection (if able to produce sputum) or stool sample collection from CLHIV, for **immediate rapid molecular testing**.
- **“[TB] treatment should be initiated immediately if there is clinical suspicion** and continued regardless of test result if the clinical symptoms are consistent with TB.” p349

Excuses + counter-arguments

- Implementing both LAM + rapid molecular tests is too expensive.
 - LAM tests cost just \$3.50 per test and are simple to implement with minimal training; rapid molecular tests are recommended by the WHO as the initial TB diagnostic test and should be fully rolled out and implemented in countries.
- LAM tests are only for a limited population of PLHIV.
 - LAM tests are recommended by the WHO and PEPFAR for all PLHIV with signs and symptoms of TB or advanced HIV disease – those who are most at risk of dying from TB.
- Regulatory issues and pilot studies for LAM testing are complicated or expensive.
 - LAM testing has been studied extensively in multiple countries (e.g., South Africa, Kenya, Mozambique, etc.); regulatory and other requirements for local studies should be waived given strong WHO recommendations for the use of this life-saving test.
- Truenat tests have a more complicated workflow than Xpert tests.
 - Truenat tests are designed for use at the microscopy center level, which is closer to the point of care than Xpert tests; Truenat tests do have an extra micro-pipetting step, but this is easy to perform with minimal training; WHO recommended Truenat tests in 2020.
- Procuring TB test commodities is the responsibility of the TB program.
 - PEPFAR's COP guidance supports the use of PEPFAR funds to support procurement of LAM tests and other TB test commodities in quantities that exceed the number of PLHIV and CLHIV who present to care and require TB testing in accordance with WHO guidelines.

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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.

<https://www.treatmentactiongroup.org/publication/an-activists-guide-to-the-tb-lam-test/>



Thank you!

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