



IAS Educational Fund Webinar
Latest updates in TB and DR-TB in people living with HIV

18 February 2020

Q&A Session - Answers provided by WHO



I would like to know why people living with HIV are at high risk of acquiring TB?

People living with HIV can have more vulnerable immune systems if they have lower than normal CD4 cell counts and, as per the Global TB report of 2019, an estimated 19 times (range: 15-22) higher risk of acquiring TB than people without HIV.

Can blood in sputum affect the result of the Cepheid Xpert MTB/RIF test?

Blood is listed among substances which may interfere with the Xpert MTB/RIF test, causing a possible increase in false-negative or invalid results.^{1 2}

Can we monitor TB treatment based on LF-LAM?

No, LF-LAM is a diagnostic test only and should NOT be used for monitoring treatment. Other tests such as sputum smear microscopy and culture should be utilized for treatment monitoring, in accordance with national guidelines.

How are we going to monitor the treatment in the case that Cepheid Xpert MTB/RIF was negative and LAM positive?

In this case sputum smear microscopy and culture should be utilized, in accordance with national guidelines. It will be useful to perform baseline sputum smear microscopy or culture for monitoring purposes.

With a LAM positive result, can urine be processed using NALC-NaOH and tested for Rifampicin resistance on the Cepheid Xpert MTB/RIF test?

Given the difficulties in obtaining extra-pulmonary specimens and the technical limitations of conventional bacteriological methods to aid diagnosis, urine was evaluated as a non-pulmonary diagnostic specimen with promising results.³ At the moment, no particular processing method is recommended by WHO. More details on the use of urine as a non-pulmonary diagnostic specimen will be included in the WHO policy “Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance in adults and children. Policy update (2020)”, once it is publicly available.

What is the percentage of TB-HIV patients with CD4 <200 cells/uL in the TB-HIV co-infected population when diagnosed in the world?

Global data on the proportion of patients with HIV and TB with CD4 counts <200 cells/uL is not available (not reported globally); however, based on country level data analyses and reports from larger cohorts of HIV patients such as the IeDEA cohort, estimates of PLHIV with advanced HIV disease range from 15-40% of those presenting or re-presenting for care.⁴

Since you said LF-LAM is a rule-in test, do you mean it has higher specificity to be a confirmatory test like rapid point of care HIV tests?

WHO recommends using LF-LAM to assist in the diagnosis of active TB in selected HIV-positive adults, adolescents and children. Thus, LF-LAM should be used in combination with other WHO recommended diagnostic tests, in accordance with national TB algorithms for TB

¹ <https://www.cephheid.com/Package%20Insert%20Files/Xpert-MTB-RIF-ENGLISH-Package-Insert-301-1404-Rev-F.pdf>

² http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

³ <https://apps.who.int/iris/bitstream/handle/10665/330395/9789240000339-eng.pdf>

⁴ Carmona CID 2018: 32.9% IeDEA and COHERE CID 2018: 31-40% Lamp PLoS One 2019: 15-30%)



diagnosis. Because the specificity of LF-LAM is suboptimal in some patient populations, e.g. inpatients (82-87%), it cannot technically be called a rule-in test; however, TB treatment can be started based on a LF-LAM positive result while waiting for other tests, in accordance with national algorithms.⁵

Do you consider to do ultrasound TB FASH (focused assessment with sonography) for HIV-associated TB to exclude extra-pulmonary TB for outpatient cases with general symptoms with both TB LAM and Cepheid Xpert MTB/RIF tests being negative?

It is recommended to follow clinical diagnostic algorithms per national guidance. WHO and GLI guidance does not specifically include TB-FASH ultrasound within algorithms, as it was never evaluated for this role.⁶ At the same time at national and/or facility level, this may be indicated in some cases, where available, per clinical judgment.

How long can someone live with untreated MDR-TB in low resource settings?

This is a very complex question that requires consideration of many risk factors that affect survival, such as HIV co-infection, diabetes, disease severity, poverty, and resource-limited settings. This systematic review may be helpful to appreciate the complexity.ⁱ

What's your comment on management of patients with HIV/TB co-treatment on a PI-based regimen? The availability of Rifabutin seems to be the prevailing issue in LMICs.

WHO provides guidance on management of HIV/TB co-treatment addressing drug-drug interactions including between antiretrovirals and rifamycins (<https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/>). Regarding protease inhibitors specifically, if the patient is receiving a rifampicin-containing TB treatment regimen and is on a lopinavir-based ARV regimen, the lopinavir dose will need to be increased per WHO guidelines or the patient will need to be switched to an efavirenz-based regimen, dose-adjusted dolutegravir-based regimen (with an additional dose of DTG 50mg 12 hours apart from the ART dose) or other appropriate regimen, depending on age-based recommendations. The drug-drug interactions with other PIs are also described in WHO guidelinesⁱⁱ. Rifabutin has a lesser effect on the P450 system in the liver, and these dose adjustments are not required with a rifabutin-including TB treatment regimen.

Do I consider CD4 testing for the pediatric population?

WHO has published guidance for an advanced HIV disease (AHD) package of care for adults and childrenⁱⁱⁱ. In adults and children over 5 years of age, advanced HIV disease is defined as a CD4 count of less than 200 cells/mm³ or WHO stage 3 or 4 disease. At presentation, all children under the age of 5 years are considered high risk and deemed to have advanced HIV disease and thus do not require a CD4 cell test for this categorization, although it remains important to measure the level of immunosuppression. In these groups defined as having AHD, PLHIV seeking care should be offered LF-LAM for TB screening as well as other diagnostics and treatment prophylaxis as part of the AHD package of care.

What would be the recommendation for low resource settings with access to LF-LAM, but without Cepheid Xpert MTB/RIF testing available on-site?

Xpert MTB/RIF (Ultra) is currently recommended as an initial diagnostic test for TB for all groups of presumed TB patients and settings. If Xpert MTB/RIF (Ultra) is not available on site, the diagnostic specimen should be referred to the closest reference facility to perform

⁵ <https://www.who.int/tb/publications/2019/LAMPolicyUpdate2019/en/>

⁶ http://www.stoptb.org/wg/gli/assets/documents/GLI_algorithms.pdf



this testing, if at all possible. If only a LF-LAM test is available, based on recent WHO LF-LAM guidelines, the decision on TB diagnosis can be made based on a positive LF-LAM and the patient treated accordingly. If both LF-LAM and Xpert MTB/RIF are available, TB treatment can be initiated based on a positive LF-LAM while awaiting results of Xpert. Please refer to the clinical algorithm for LF-LAM test use.⁷

[I am a clinician from the Philippines, a country with a high TB prevalence. Are these recommendations for LF-LAM use in PLHIV useful to us?](#)

Yes, it is recommended as a diagnostic test for TB in PLHIV in all countries.

[I want to know when these guidelines will be in places like South Africa?](#)

Countries will adapt and adopt WHO guidelines in accordance with their usual national processes. WHO will launch updated WHO guidelines on DR-TB treatment in April 2020 and new LF-LAM guidelines have been released in October 2019.

[The latest WHO Rapid communication excludes linezolid \(LZD\). How do you see LZD being used in the current recommended short course regimen?](#)

Systematic reviews commissioned by WHO/GTB only yielded data on shorter regimens without LZD therefore the recommended regimen may not include LZD. When new evidence on the shorter regimen including both bedaquiline (BDQ) and LZD is available, it will be reviewed in accordance with WHO guideline policies. Operational research of the modified short-term regimen (including possibly LZD) is encouraged to support recommendation revisions in the future guideline updates.

[What are the WHO policies on countries conducting their evaluation studies on already prequalified lab diagnostics, or, for TB diagnostics, endorsement, in this case LF-LAM, for them to roll them out. This remains a major bottleneck to rapid roll out of this innovative approach.](#)

For technologies that have undergone WHO prequalification or endorsement assessments, typically WHO does not recommend each country conduct diagnostic accuracy or technical evaluation studies. This is already a component of the prequalification and endorsement processes and most products have significant data by the time of product listing and regulatory approval. Diagnostic accuracy studies typically delay implementation and scale-up and thus approaches should be re-considered for such products. Regional regulatory mechanisms, such as the Pan-African Harmonization Working Party, and WHO's newly developed Collaborative Registration Procedure for Diagnostics have been set up to share information and data across countries and regions to support faster regulatory approval and uptake in countries. Currently available LF-LAM assays, however, have not yet gone through the WHO prequalification process (set to introduce TB assays in their mandate in 2021), but one product has so far been endorsed by WHO's GTB program.

ⁱ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070694/>

ⁱⁱ <https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/>

^[i] <https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/>

⁷ <https://www.who.int/tb/publications/2019/LAMPolicyUpdate2019/en/>