Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV

Policy update (2019)

Report user perspectives on TB LAM testing: results from qualitative research

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1. Introduction

In ensuring access to effective diagnostics for TB care, we not only need to assess that these technologies are accurate but also that they are feasible, useable and acceptable. The users of diagnostics include patients, clinic staff, lab managers, ministries of health, NGOs, regulators and suppliers. If we do not take the perspective of all users into consideration, we risk that these technologies do not fit their intended use setting, cannot be made to work and scaled up, are not utilized or not accessible for those in need. User perspectives on new diagnostics, their preferences and values as well as their experiences with existing diagnostic systems, are important to take into account during WHO decision-making on new diagnostics, including guideline development and policymaking. Feedback from representatives of key stakeholders groups (including patients, health professionals and programme managers) is important.

Studies generating this kind of data are often qualitative in nature (i.e. they focus on meanings that people bring to a phenomena and how they act upon it). Qualitative studies use targeted sampling methods to capture diagnostic experiences across a range of users, diseases, tests and diagnostic settings (Davids et al., 2015; Engel et al., 2017; Engel et al., 2015; Engel et al., 2018; A. McDowell & Pai, 2016; Andrew McDowell et al., 2018; Miller, Parkhurst, Peckham, & Singh, 2012; Squire et al., 2005; Yellappa et al., 2017). They are an ideal method for making sense of user experiences with and perspectives on diagnostic tools within “real-world” situations because they avoid placing assumptions about what these tools are expected to accomplish at the outset (e.g., that a test is easy to use). By involving users (e.g., through interviews, usability tests, ethnographies and user feedback), qualitative studies can support decision-making on diagnostics and offer concrete insights into users’ values and preferences, as well as acceptability and feasibility of new diagnostics in intended use setting. Such data will also point out important considerations for scale-up.

In May 2019, the World Health Organization will be evaluating two point-of-care tests for diagnosing TB in people with HIV (Abbott (formerly Alere)’s Determine TB LAM test and FujifLAM). To inform those discussions, the WHO has commissioned a study into the perspectives, preferences, and experiences of users of diagnostics (including people living with HIV and people affected by TB, health professionals, and programme managers). To this end, we conducted a small qualitative study with participants in Kenya, Uganda, and South Africa. We interviewed clinicians, nurses, programme officers, laboratory staff, and patient advocates with the aim to understand their experiences of using TB LAM and diagnosing TB among people living with HIV (PLHIV) more generally and to contextualize users’ preferences about a new diagnostic.
This study is exploratory in nature and part of an ongoing inquiry into user perspectives of new TB diagnostics. More, in-depth ethnographic research on the ground is warranted to better understand perspectives and practices of different users including PLHIV and their caregivers.

2. Methodology

In February and March 2019, NE and MW conducted 15 semi-structured interviews with clinicians, nurses, programme officers, laboratory staff, and patient advocates in Uganda, Kenya and South Africa. These countries were selected based on the fact they have policies in place regarding TB LAM. Due to the short timeframe participants were purposively sampled and approached based on convenience through personal contacts and colleagues. The majority of participants were from Uganda where TB LAM is already available in routine use (see table 1). It was not possible to speak directly to patients via the phone as most are seriously ill and even patient advocates did not know anybody who had tested with TB LAM. The advocates highlighted that the voice of seriously ill PLHIV are not well represented within the overall HIV advocacy. This warrants more in-depth and on the ground research with face to face interviews to understand all user perspectives and practices of diagnosing TB in PLHIV.

All but one of the interviews (which was done in person) were conducted via the phone. We asked for the testing and treatment experiences as well as experiences on interaction between providers and patients to contextualize users’ preferences about a new diagnostic. Topics discussed included: current approach to diagnosing TB in PLHIV including specific challenges; experiences with using TB LAM, including details on steps taken in the diagnostic process, determining eligibility and treatment initiation as well as challenges and benefits; ways of interacting with patients about TB LAM; overall usefulness; the impact of TB LAM on equity and feasibility; and current policy context. We also tried to understand how a more complex test with longer turn-around time (TAT) (FujiLAM) would be perceived.

Interviews were audio-recorded, transcribed by MW, and coded by NE in NVivo. We each wrote memos on different topics, discussed these and collated them into themes which we present below. Professional roles are used to mask study participants’ identity.

Ethics

This study was approved by UMREC, the ethical review board of Maastricht University. Study participants were emailed an information sheet explaining the objectives of the study and an informed consent form which they signed prior to participation.

Table 1 Participants overview per country

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3. Results:

Below we discuss the results for current use of TB LAM separately for the three countries and then discuss overarching themes that emerged from the interviews across the different countries.
Current use of TB LAM in Uganda, Kenya and South Africa

Although TB LAM has been on the market since 2013, its adoption within national health systems of high TB/HIV burden countries has been very recent, if at all. As of 2018, South Africa, Kenya, and Uganda had each developed or began developing national guidelines for the test. South Africa’s guidelines state that it should be used for all PLHIV in hospital settings and among those with CD4 counts less than 100/mm3 in primary care settings (TBCAB, 2018). Kenya’s HIV programme recommends TB LAM be used as an adjunct rapid point-of-care diagnostic test for presumed TB among all PLHIV: (1) with advanced HIV disease (WHO stage 3 or 4 or CD4 count ≤ 200 cells/mm3 or CD4% ≤ 25% for children ≤ 5 years); or (2) any danger signs of severe illness; or (3) currently admitted to hospital (National AIDS and STI Control Programme, 2018). Uganda’s TB guidelines recommend the use of TB LAM in HIV positive adults in whom TB has not been picked by microscopy or Xpert MTB/RIF and who are very ill, with a CD4 count of less than 100/mm3 (Uganda National Tuberculosis and Leprosy Control Program, 2017).

National roll-out of TB LAM varies between the three countries. Uganda is the only one thus far to have rolled out the test to national and regional-level referral hospitals, but according to participants of the study, not all districts have received the test, and stock-outs in those that have it have been experienced. Actual in-country usage also seems to vary. According to a lab manager at a teaching hospital, TB LAM is being used for both HIV and non-HIV immunosuppressed patients who are suspected of having TB and are not able to expectorate sputum while a clinician working at a national referral hospital only uses TB LAM when other tests are not able to detect but the clinical suspicion is still high. Where the test is conducted also varies as some settings prefer the test be done in the lab due to frequent change-overs of ward staff, while others prefer to do it by the bedside. Although the Ugandan guidelines recommend a CD4 cut-off of 100/mm3, some hospitals appear to be using a cut-off of 200/mm3 (ID6, nurse 1) or conducting the test irrespective of CD4 counts (ID8, clinician 4). This may reflect the leeway the TB programme seems to have given local settings to run the system in the way that suits the context best (ID1, programme officer 1).

The Kenya TB programme will begin to roll out the test to county-level referral hospitals as a pilot project in 12 high-burden TB/HIV counties. The algorithm will recommend the test be used in conjunction with Xpert among PLHIV in hospital settings, with CD4 counts of less than 200/mm3. This criterion was extended from WHO’s cut-off of 100/mm3 on the rationale that expanding it will capture more patients and that in Kenya there is generally a good rate of adherence to ARV medicine, so limiting CD4s to WHO’s recommendation will only capture a handful of patients (ID15, programme officer 2). According to a TB programme manager, TB LAM will be conducted in the lab to enable uniformity in result interpretation, be close to GeneXpert machines, and streamline recording and surveillance practices.

According to a presentation given by Dr. Lindiwe Mvusi from the Ministry of Health during the TB 2018 pre-conference held on Sunday 22 July 2018 (Mvusi, 2018), South Africa has developed an algorithm for TB LAM and has rolled out the test as a pilot project in five hospitals to be used concurrently with Xpert MTB/RIF. According to an advocate of the present study, data from the pilot project are still in review.

TB LAM makes a difference in a hard to diagnose patient group

Participants discussed the difficulties in diagnosing TB in PLHIV in their settings, which is often extra-pulmonary TB, and how the introduction of TB LAM has improved on this. An advocate working in a high burden TB/HIV district in Uganda, for instance, states the critical difference the test makes in a hard to diagnose patient group with high numbers:

“it’s still an important test because we see like for the HIV in Uganda, we have about 89% of people on treatment but still we see like 10% of those having advanced HIV. And it is still the leading cause of mortality and morbidity among PLHIV, so definitely we still need it because with
the previous technologies we had we are not diagnosing enough, we still have capacity issues, and I feel we need it, though it has to be used in combination with other technologies, and it can’t be used in other populations but these populations are critical, and the numbers are high” (ID13, advocate 3).

Although TB case-finding among this population may have improved, follow-up testing is still difficult and clinical observation is particularly challenging as this population is vulnerable to co-morbidities and drug interactions (ID8 clinician 4). Furthermore, the characteristics of this patient group, namely being very ill, means that typically the TB LAM test is not explained and consent not taken. Only if the result is found positive a clinician might then say we tested (without going into details of the test) and are pretty sure you have TB. If the results are negative, clinicians would not mention it (ID2 clinician 1, ID8 clinician 4). Since patients are very ill and admitted in the hospital, clinicians work with implied consent and there is time to discuss some of the common patients concerns about their diagnosis and what the implications are for treatment, side effect, pill burden and transmission to others (ID10, clinician 5). In a regional referral hospital in Uganda, these concerns are then discussed with the nurses during counseling for TB treatment (ID6 nurse 1).

Characteristics of the test

Sample
Diagnosing TB in PLHIV is challenging as obtaining a viable sputum sample is often difficult because the patient is too ill to cough, or the disease is disseminated and the sputum sample may test negative. For these reasons, most of our study participants acknowledged the benefits of using urine to test for TB, citing it as a safe, pain-free, and non-invasive method for testing for TB that is easier to obtain than sputum. A nurse from Uganda illustrates these advantages on mortality (ID6, nurse 1):

“the challenges were, of course we were missing many cases, mostly these people who have HIV, they come in in their 3rd/4th stage, they cannot cough, they are not able to do the chest X-ray, they don’t have strength to stand to take them for the chest X-ray, and you just treat blindly. Most of the people died because, we didn’t know the diagnosis... because you can’t give HIV cases, who are really sick, bed-ridden, and the cough is mild, it is not strong for you to conclude that this patient has TB. [But] the LAM has impacted that such that these bed-ridden ones, we are having early diagnosis, and early treatment, with less mortality now in HIV/TB” (ID6, nurse 1)

A lab manager notes that obtaining urine instead of sputum from very ill patients does increase patient participation, as most are able to produce the latter over the former (ID9, lab manager 1). Additionally, a clinician emphasizes that when compared to sputum, urine presents less of an occupational health hazard to health workers and is less stigmatizing for patients (ID2, clinician 1). That being said, obtaining urine was not always easy. A clinician and a nurse noted that, at times, obtaining urine is a challenge when the patient is too ill or septic to produce it, when he/she has to be catheterized because collecting urine from diapers is impossible (ID7, clinician 3; ID12, nurse 2), or if the patient is in a hospital where there is no private and clean space to produce urine which is common in rural hospitals in Uganda (ID7, clinician 3). A lab manager highlights how he is not always sure how old the sample is and whether what he receives in the lab is a fresh urine sample (ID14, lab manager 2). The non-invasive nature of the sample also allows testing without explicit consent from the patient (see above).

Turn-around time
The fast turnaround time (TAT) of TB LAM was often cited by participants to have a notable impact within their settings. With a running time of 25 minutes, it was frequently discussed how treatment can be initiated sooner than if a test was run using existing technologies (ID1; ID12; ID13; ID14; ID6; ID7; ID9;
ID4). This in turn was linked to reduced loss to follow-up as patients do not have to wait extended periods of time for a diagnosis and treatment initiation. As a programme officer illustrates,

“If I am very ill, if my clinician can get a result in around 30 minutes, it basically makes the whole difference...I am in the ward very sick, I need to know [my] condition and then start treatment” (ID1, programme officer 1).

A lab manager also notes that due to the workload within the labs, clinicians in his setting prefer to request for TB LAM over smear microscopy (ID14, lab manager 2).

However, while the running time of TB LAM is standard, the time it takes between collecting the urine sample for testing and initiating treatment varies based on the reporting system, availability of anti-TB drugs in the pharmacy, and the time of day the test is requested and conducted. Once the decision is made to initiate treatment, it can be commenced within a few hours if the drugs are available at the pharmacy (ID12, nurse 2; ID1, programme officer 1). Yet, in several hospitals it seems to be the next day if clinicians have already finished their ward rounds for the day. So even if the LAM test is done near bedside, treatment might take another day to be initiated. It was also mentioned that if the test is done in the lab, the TAT would be faster if someone follows-up directly with the lab versus if they wait for normal reporting processes (ID10, clinician 5). A lab manager in Uganda noted that if the report is ready after the clinician has completed ward rounds -which in this particular hospital end at 1 or 2pm-, diagnosis and treatment initiation can only begin the next day (ID14, lab manager 2).

User-friendliness

TB LAM was frequently referenced as straightforward and easy-to-use, often likened to using a pregnancy dipstick test (ID2, clinician 1; ID7, clinician 3; ID11, clinician 6). The lack of technical expertise required to run the test was said to allow for task sharing especially in settings where the workload of the laboratory technicians is very high (ID1, programme officer 1; ID5, advocate 2; ID9, lab manager 1). Some found interpreting results to be straightforward, and appreciated the graded scorecard that accompanied the test kit (ID14, lab manager 2).

However, each of these benefits was not without challenges. For example, while the test is not technical, a lab manager mentioned that its timing is vital and that going beyond the recommended time could affect the results (ID14, lab manager 2). TAT was also said to influence the number of tests that could be run concurrently (ID12, nurse 2) and having a timer on while running the test was important (ID5 advocate 2; ID12, nurse 2; ID7, clinician 3). Additionally, the simplicity and specific timing of the test was mentioned to influence who could run the test, as those with a lot to do in their daily routine -such as clinicians- may forget they have began running a test and leave it to run longer than recommended (ID12, nurse 2).

Not everybody thought that interpretation of results which depends on visibility of the graded bands was easy. Several mentioned challenges with reading faint results, especially grade 1 and deciding on the result (ID2, clinician 1; ID8, clinician 4; ID9, lab manager 1; ID14, lab manager 2). In some settings this influenced whether the test was to be conducted in the laboratory or at the bedside, as the former was deemed a better environment for maintaining uniformity in result interpretation (ID2, clinician 1; ID15, programme officer 2), potentially affecting the future point-of-care status of the test.

Similarly, while the simplicity of TB LAM may enable non-laboratory staff to conduct the test, task sharing may not be feasible in settings where frontline staff conducting the test are frequently rotated through the system (e.g. nurses, students, clinical officers) (ID6, nurse 1). This could affect who in the end is able to conduct the test and how close to the bedside/patient it will be.

Lastly, although volume control for the test was perceived by some to be straightforward (ID14, lab manager 2), the fact that the kit does not come with a micropipette presents a challenge for others (ID8, clinician 4). It was therefore suggested that the manufacturer could provide detailed instructions of how to measure urine if a micropipette is unavailable (e.g. number of drops).
Cost and maintenance
When it comes to the logistics surrounding TB LAM, it was perceived by most participants to be better suited for their settings than existing technologies. For example, unlike Xpert MTB/RIF, TB LAM: (1) is cheap to buy and maintain (ID3); (2) does not require other reagents (ID13); (3) does not require much lab space (ID11); (4) does not require cold chain (ID14), and (5) does not require electricity to run (ID5). For these reasons, many understood the test to address infrastructural and logistical issues that currently prevent other technologies from being used at optimal capacity (ID7, 13, 14). That being said, the shelf-life of the test was perceived to be relatively short by some (ID1, 11), with a nurse recounting a recent instance when an expired test was used and the result was negative but a Xpert MTB/RIF result was positive (ID6, nurse 1). Additionally, accessories for running the test that do not come with the kit such as urine containers and micropipettes, presented challenges when not locally available (ID14, lab manager 2) and may lead to improvisation that could impact the reliability of results. Lastly, though TB LAM was largely perceived as inexpensive to procure, various settings in Uganda have experience stock-outs (ID6, nurse 1; ID14, lab manager 2), while private practitioners using the test in Kenya believe the test to still be too expensive for their patients (ID4, clinician 2; ID11, clinician 6).

Constructing confidence in diagnosing TB in PLHIV
Limited confidence due to sensitivity, cross reactions and faint results
The sensitivity of TB LAM limits the confidence in its results (ID3; ID5; ID11; ID13; ID2; ID4). According to a programme officer in Uganda, the confidence of clinicians in TB LAM is rather low given its low sensitivity that only improves with low CD4 count. This confidence decreases further because TB LAM can also give positive results due to cross-contamination in patients with candidiasis or with nontuberculous mycobacteria (ID1 programme officer 1). Furthermore, if somebody is weakly positive on TB LAM, when do you establish somebody as positive? Having the confidence that a grade 1 result is indeed a positive result is not given and according to a Ugandan programme officer some people argue that grade 1 should not be treated as a positive result (ID1, programme officer 1). While some mentioned they did not have any doubts in reading the results (ID12, nurse 2), others ensure coherence and consistency in reading results and interpretation of grade 1 by conducting the LAM in the laboratory by lab technicians who have established a routine as opposed to rotating clinicians (ID2, clinician 1). Yet, there is no additional microbiological confirmation of the TB diagnosis, only in a few cases can Xpert Ultra be done (i.e. patients are able to produce a sputum) (ID2, clinician 1).

Test is not made to stand alone
In communication about TB LAM with her patients, a nurse in South Africa explains how she is managing expectations of results among patients. She always establishes first whether a person had TB before or has been tested and then explains that her test only uses urine. Patients generally want to know what is going on with them and view TB LAM as one more step towards finding out and getting better. Upon receiving a positive TB diagnosis (on top of being HIV positive), some are disappointed and sad about the double diagnosis (which is particularly tricky in settings with double stigma of HIV/TB (Daftary, 2012)), others are accepting knowing they are very ill and these things are possible (ID12, nurse 2). According to an advocate, patients have the tendency to believe test results over those from clinical diagnosis (ID13, advocate 3). The nurse in a South African hospital explains the uncertainty of the LAM results and refers to the doctor who will come later on during the day and make a decision, or order further tests. In doing so, the test is not made to stand by itself but embedded in a battery of tests and considerations that the doctor makes, and not the nurse who is conducting the test (ID12, nurse 2).
“I do explain to the patient that even if my test is negative, the doctors will wait for the other
tests that they have done because my test doesn’t mean that there isn’t TB in the body, it just
means that the test that I am doing cannot pick it up. Not to say that they do have TB but the
possibility still does exist because I need to make ease as well that I am not coming there and
saying they do have TB. The possibility is there and that is why they want to test them.” (ID12,
nurse 2)

Interpreting the result with confidence: clinical suspicion is trump
Most clinicians we talked to seem to only act on a positive TB LAM result if they already suspect TB due
to clinical presentation or symptom screen.

“If I am struggling to confirm a diagnosis of TB, and the LAM comes back positive and my clinical
history fits, that may mean the life or death of that patient. Because that would mean I start my
treatment sooner rather than later.” (ID4, clinician 2)

In Uganda, the TB programme directs clinicians that just having a low CD4 count is not enough for acting
on a positive LAM result, they also need to have done the symptom screen and need to be suspecting TB
so that they interpret a positive TB LAM result with confidence (ID1, programme officer 1). Backing up a
positive LAM result with other follow up tests is hardly ever done, especially because the patients were
not able to provide that sample (and that might have been the reason for doing LAM in the first place).

“Usually what happens is that these clinicians are telling us that by the time they are asking for a
lab, they have already presumed TB. So even in the even in the event of cross contaminations,
they are ready to believe that this is TB because the person is already presenting with the TB
symptoms. That is why we are telling our clinicians that a low CD4 or me being very ill is not the
air ticket to a TB LAM, no, I should be a presumptive TB case. I might have a very low CD4 but
you need to screen me for TB, and if I have the signs and symptoms, then you go ahead and do
the LAM.” (ID1, programme officer 1)

A clinician in a Kenyan private hospital would still try to confirm a positive TB lam result with other ways
of looking for TB

“You know TB is just so difficult to diagnose, it [TB LAM] is an additional tool to our honorarium
of TB diagnostics. Right, so it’s just that. And it’s actually a really good one because if it’s
negative, then it’s less likely to be TB and that really helps I think” (ID11, clinician 6).

A nurse in research study in South Africa and a clinician involved in a study in a district hospital Uganda
echoed that sentiment; both observed that doctors would not start everybody on treatment with a
positive TB LAM result, but wait for other evidence (a sputum sample, a culture result) if the patient is
asymptomatic (ID12, nurse 2, ID2, clinician 1). A clinician argues that empirical suspicion will trump also
a negative TB LAM result (ID2, clinician 1).

Treating severely ill patients with improved level of confidence
TB LAM results are particularly reassuring (to be sure it is indeed TB) in patients that are already very ill,
have several co-morbidities and are therefore also much more susceptible to side effects and severe
complications during TB treatment (ID2, clinician 1, ID8, clinician 4). That particular usefulness of TB LAM
over empirical treatment might change if TB LAM would be made available for patients that are not so ill
or do not have as many co-morbidities. In those patients, a clinician suspects that one would feel more
comfortable to treat empirically and monitor whether indeed the patient improves (ID2, clinician 1).

“.. around the world lots of patients are treated empirically for TB and it’s kind of like, you are
not very sick but you know to be honest 6 months of these drugs are well-tolerated, here you go,
and we will see, you are going to go through 6 months of treatment and that’s ok. That happens
even in NYC, where you know, we are 70% sure you have TB but not 100% sure, and you know
what its ok. I mean you will take these drugs for 6 months, and we will check your liver function a
couple times and you will call us if you have any symptoms but you will be ok. And that’s just not the case when someone is sort of like super sick. That’s exactly who get all the side effects of the drug and will have a good chance like you say, multiple comorbidities going on, even if they truly do have TB they may very well have something else as well.” (ID2, clinician 1)

*Global guideline makers’ implicit confidence influences national and local level confidence in diagnostic*

According to an advocate, the language around innovations such as new diagnostics and drugs used in guidelines and communication from the WHO heavily influences country uptake, particularly in countries without progressive HIV or TB programme managers. A wait and see attitude is then taking place. The advocate particularly laments the fact that operational research on TB LAM and its effects, which could have changed that attitude, was ignored for several years (ID5 advocate 2).

“the people of WHO, their attitude towards TB LAM Alere, was not very positive, (...) and they partly contributed to low up take of the LAM, because they overemphasized talking about the lack of performance, and didn’t refer to the mortality benefit that we saw from especially the South African data. (...) if you as someone in the WHO has developed these guidelines, but you are not very convinced about the test... See now they are very excited about FujiLAM but when it was TB LAM they were like, “hmmm”. It trickles on to the countries, it really does.” (...) “I don’t necessarily think it is bad that they applied the caution that they applied, but it was very wrong of them to ignore operational research for, how many years, 4 years, waiting for FujiLAM. This is nonsense. If operational research is out there, it is showing that there is a mortality benefit, it is showing you that there is use of the test for those with CD4 counts of less than 200 especially, including in ambulatory settings, its showing you that there is task sharing that can be done, that is on WHO’s head...it was wrong of them to do that. Actually, ethically, it was very wrong, you see. That also slowed down the uptake of TB LAM Alere. Why should people die because people are waiting for a more specific and sensitive test?” (ID5 advocate 2)

*Eligibility criteria and CD4*

A clinician and researcher of LAM argues that everyone with HIV in hospital settings should get a TB LAM, whereas the usefulness for outpatient settings is not clear yet. She guesses that everybody who looks sick in outpatient should get a LAM as well.

“(...) TB is often missed particularly in inpatient settings. So, I think inpatients settings, anyone who is HIV positive probably deserves a LAM test to make sure they don’t have disseminated disease that could be better diagnosed with LAM. In outpatient settings, how you use LAM I think isn’t well understood.” (...) “I think that if you have someone presenting to clinics who are HIV positive, who look sick, you should certainly do a LAM test, if you are considering hospitalizing them. So, the people who look relatively well who are positive, you can do some kind of a test to understand what their baseline CD4 is” (ID7, clinician 3).

It would need more in-depth research on the ground to understand how different healthcare providers decide when somebody is serious ill.

*CD4 counts are not routinely available*

According to a clinician in Uganda, LAM has been made conditional on another test that is not routinely available (ID7, clinician 3). CD4 counts are not routinely done in Uganda (ID1, programme officer 1) and it is very rare a clinician would base their LAM request on a CD4 count (ID1, programme officer 1; ID14, lab manager 2), even if available in a hospital laboratory, in order to avoid delays of a couple days and because patients generally look sick (ID14, lab manager 2). In a district hospital everybody who is
admitted and HIV positive is tested on LAM irrespective of CD4 count (ID8, clinician 4). In a private
hospital in Kenya where CD4 counting is easily available, the clinician would order the CD4 count and TB
LAM concurrently but based on clinical suspicion. This is done to avoid delays when ordering a CD4
count which takes 1 or 2 days. Also, being a TB endemic country, the clinician has seen TB with all sorts
of CD4 counts (ID11, clinician 6).

Unintended effects of CD4 below 100 cut-off
According to an advocate, the restrictive use of CD4 count below 100 had the undesired effect that
countries would not like to admit that they have many patients that are that ill, because it reveals poor
HIV programme performance (ID5, advocate 2):

“..about 30% of PLHIV in high HIV endemic countries, about 30% will have advanced HIV, in a lot
of these low- and middle-income countries. So, they don’t want to roll out a test that will show
the enormity of the problem, ..(ID5, advocate 2).

It also gave the national programme officers the opportunity to argue that these are very few people
and therefore downplay the priority of the test which is why, according to an advocate, it is important to
follow operational research results and widen eligibility criteria to above CD4 count of 200 (ID5,
advocate 2). Given the restrictive eligibility and niche applicability of the test, it might be further
downgraded in programming and budgeting for it (ID3, advocate 1) and not be made as accessible as it
should be, according to an advocate in Uganda only 25% of those eligible receive a TB Lam, and this
might have to do with the niche and strict eligibility criteria. It also lowered confidence among clinicians
who initially are unsure about who the test is for and what results mean (ID14, lab manager 2). An
advocate would like to see LAM used in smaller city-level hospitals as well, not just the big hospitals
(ID3, advocate 1). But seriously ill PLHIV that are mostly affected by LAM are not the ones that usually
are represented well by advocacy of PLHIV:

“..and unfortunately, with LAM it is not one of those that can get patients groups to shout
too much about, because what do you say. Like we’ve said yes, we want LAM now blah blah, but
PLHIV, those people who know what they want because they know that the treatment works, in
those groups, they don’t always deal with the advanced cases. “ (ID3, advocate 1)

Fuji LAM

Weighing TAT, complexity and sensitivity
A Kenyan programme officer argues that finding a right balance between the existing and future TB LAM
test involves finding a balance between the applicability of the test in terms of TAT and accuracy (like
between Xpert MTB/Rif and Ultra) and also depending on where a country is in its decision-making with
adopting TB LAM. A less sensitive test may still be useful if it is operational within the country.
“Sensitivity depends on what a country wants” is how he put it (ID15, programme officer 2).
Clinicians and lab managers seem to value higher sensitivity, especially in settings where the Alere/Abott
TB LAM is presently conducted in the laboratory and not at the bedside (ID11, clinician 6; ID14 lab
manager 2)). A Ugandan programme officer argues that additional user steps (which he envisions to be
still easier than doing a microscopy) are a small price to pay for a higher sensitivity, even if this means it
defeats the purpose of POC and needs to be moved back to the lab (ID1, programme officer 1). Others
specify and argue a longer waiting time up to 2 hours would be acceptable but many more complex user
steps (including for instance amplification) and moving it to a central lab would mean the strength of the
test would be lost (ID2, clinician 1). A clinician argues she is more interested in a sensitive test if patients
are in a hospital setting with a very short TAT to initiate treatment with the patient still in front of you
(ID10; clinician 5). Additional complexity might also make the test not feasible for small labs attached to
wards in terms of the required equipment, quality controls, staff capacity, sample preparation steps and overall cost (ID4, clinician 2).

An advocate argues that a better performing test will generally be picked up quicker by policymakers (ID5, advocate 2). Another advocate cautions that a more complex and longer TAT would mean programmatic drawbacks, as these aspects have been essential advantages of the ALere/Abott TB LAM (ID13, advocate 3). If the test should be rolled out in primary care settings a higher complexity is not warranted (ID5, advocate 2).

TAT is also linked to how many tests a healthcare provider can run simultaneously and when they are run during a working day. A nurse in South Africa explains that if TAT would increase to an hour she would be able to run more than two tests simultaneously (currently she conducts maximum two at the same time). Yet, additional user steps might eat into that time again. (ID12, nurse 2). A clinician refers to the difference between ZN and LED microscopy where the additional handling and user steps mean the testing is often done in batches at the end of the working day to run them simultaneously, increasing overall TAT to a day (ID7, clinician 3).

**Possible reasons for slow policy implementation and how to overcome it**

Although TB LAM has been on the market for about six years, the uptake of the test within national, high-burdened health systems has been remarkably slow. When asked why they think this has been the case, many participants cited the perceived low performance of the test by clinicians and policymakers (ID4, clinician 2; ID5, advocate 2), largely shaped by the initial communication about the test published by WHO and related agencies (ID5, advocate 2). Even once guidelines for TB LAM were published, prioritizing the operationalization of those guidelines did not happen, unless there was high-level advocacy taking place as well (ID3 advocate 1, 5 advocate 2, 13 advocate 3). In many settings, this type of advocacy seems to be missing due to the absence of strong advocacy voices for this particular patient group (TB among *advanced* HIV individuals; ID5, advocate 2) or the lack of awareness among frontline healthcare workers that such a test even exists (ID4 clinician 2, 13 advocate 3). Additionally, the cumbersome process of operationalizing global guidelines and developing context-specific algorithms may discourage many resource-tight TB/HIV programs (ID7 clinician 3, ID15 programme officer 2). For this reason, countries may be awaiting operational research from those settings that are currently implementing it before adopting it within their own systems (ID3 advocate 1, 9 lab manager 1). It was also speculated that perhaps national programs have not prioritized TB case-finding among severely ill PLHIV. As a programme officer put it:

“*if you really think that this [TB] is really a disease of serious public health importance amongst the PLHIVs, you would use all necessary tests to make sure that you identify this in this group*”

(ID1 programme officer 1).

To overcome the relatively slow uptake of life-saving technologies, they must first be prioritized by policy-makers and the language within the policy should be carefully constructed so as to not unduly or unintentionally discourage uptake. At a global level, there should be greater integration between relevant programs surrounding the communication of such a test. For example, although TB LAM benefits both TB and HIV populations, if only the global TB or the global HIV programme provides communication regarding the test, the other programme at the national level will assume that it is not its responsibility. Both global HIV and TB programmes should communicate jointly and in a coordinated fashion as to clearly indicate responsibilities. Lastly, implementing partners could also partner with national TB/HIV programs to sponsor the operationalization of international guidelines and the development of accompanying reporting and surveillance tools.
4. Conclusion and recommendations user perspective TB LAM

The results show that TB LAM clearly addresses a need and makes a difference in a population in which TB is very hard to diagnose. The characteristics of the test, the sample, TAT, ease of use, cost and infrastructure/maintenance requirements are differently discussed among the participants. While global health actors including the participants of this study generally herald TB LAM as an easy to use, low maintenance/equipment requiring, quick test that crucially does not rely on sputum but a much more easily available and safer sample (urine), those very same characteristics can also pose their specific challenges as experiences of those using the test show. The sample, for instance, is safe, more easily available, and less stigmatized than sputum, but not everybody can collect it (in bedridden patients catheters are required); produce it (dehydrated patients with sepsis cannot urinate); adequately measure it (in some instances the dropper provided in the test kit was not accurate enough and a micropipette was required) or has a private and clean space to provide it (rural hospitals do not necessarily have toilets or running water available to patients). Similarly, the infrastructure requirements are minimal but stock outs, lack of urine containers and shelf live still pose challenges. While the TAT is supposed to be just 25 minutes, treatment initiation in many settings only happens the next day.

Another important challenge that users struggle with is the low sensitivity of the test, cross-reactions and the difficulty of reading faint results (grade 1). We show how clinicians and nurses construct confidence in the results by 1) ensuring that the test is not made to stand by itself but embedded in a battery of tests and considerations that the doctor makes, and not the nurse who is conducting the test; and 2) using test results in combination with clinical suspicion of TB or other evidence in case of asymptomatic patients. Could the implications of these practices mean that patients are still being missed?

And yet, in severely ill patients where pill burden, side effects and severe complications during treatment are a real challenge, TB LAM provides some much-needed confidence beyond clinical suspicion. Would this need for increased level of confidence change if the test would be made available to less ill patients in outpatient settings? Answering these questions would require more in-depth and on the ground research.

In the way confidence in the test is perceived, the global guideline making by WHO and the language that is used has very important consequences that trickle down to country and user levels. Several participants blame the negative language for the slow uptake of TB LAM and general hesitation by countries to implement. In the future, it should be carefully considered how guidelines around a new test are being communicated and drawbacks and benefits weighed against each other and presented. Both global HIV and TB programmes should communicate jointly and clearly indicate responsibilities.

Prior consultations with users and policymakers could aide that process.

Our results also reveal that the restrictive eligibility criteria of the WHO guidelines mean the test is perceived as so niche and at the same time carries the implicit risk of revealing poor performance of HIV programs that it is not made accessible to the extent it should be. What is more, CD4 counting is not widely used to determine eligibility for LAM testing. Currently symptom screen, hospitalization and assessing whether a patient looks ill are used to decide whether a patient is eligible for TB LAM testing rather than CD4 count which in many places is not routinely available or if available not ordered to avoid time delays.

While our participants would value improved sensitivity in a new test such as Fuji LAM, they also caution against increasing complexity and TAT if the test should be made to work in primary care settings.
5. Recommendations to include qualitative research into guideline making on diagnostics

The GRADE-CERQual approach provides guidance for assessing synthesized qualitative evidence. The WHO has formally commissioned and included qualitative evidence into the Optimize guidelines on healthworkers role for maternal and newborn health, including thematic analysis of an email discussion list, in-depth case studies of country programs and four systematic reviews of qualitative evidence (Colvin, 2014; World Health Organization, 2012). Since then, similar qualitative evidence has been used for several other guidelines by WHO (i.e. on healthworkers role in providing safe abortions; use of ARVs for treating and preventing HIV infection; antenatal care guidelines; health promotion interventions for maternal and newborn health, etc.). Note, that at times the qualitative evidence synthesized is from similar interventions rather than the exact same intervention (f.i. experiences with task shifting or adherence to treatment in related fields). This is useful to keep in mind for decision-making on new diagnostics, where qualitative studies on the utilization of the specific diagnostic in question are scarce and thus insufficient qualitative evidence is available to synthesize.

To overcome these limitations and to generate evidence on end-user and professional user experiences, preferences and values, three measures are proposed:

1. **Identify and acknowledge all cadres of users**: Focus on user perspectives and experiences that include end-users (such as patients), but also professional users such as laboratory technicians, clinicians, nurses, local suppliers and decision-makers (Shah, Robinson, & AlShawi, 2009).

2. **Engage users in decision-making about diagnostics**: Commission qualitative studies that draw on their perspectives and experiences to support WHO decision-making process around new diagnostic guidelines: assign a technical team to prepare a file on user experience, values and preferences using: qualitative evidence synthesis (where evidence is available); interviews/FGDs/ethnographies with user groups; in-depth case studies of country programmes, trials, or demonstration studies; moderate and conduct thematic analysis of online discussions forums;

3. **Mandate qualitative evaluations for diagnostic regulatory approval**: Mandate qualitative evidence as a routine part of studies evaluating diagnostics for WHO regulatory approval. Adding a survey at the end of an RCT or another quantitative study is not sufficient. Instead, the qualitative part could be embedded in a mixed method design or be a stand-alone study.

The general aim of these qualitative studies should be to examine:

- The experiences and challenges with diagnostic testing for TB (and HIV or other co-morbidities)
- Feasibility and acceptability of the new diagnostic in question or a similar diagnostic
- Values and preferences with regard to diagnosing TB and how new diagnostics change these

Such qualitative data will produce a whole range of potential issues the various users will have with a diagnostic technology and will point to possible uptake scenarios, potential pitfalls and barriers to utilization and access. These measures would create opportunities for meaningful engagement of users in WHO guideline development meetings, beyond the presence of one patient representative. It would allow gathering more diverse user perspectives and it could support defining additional PICO questions, for instance on operational dilemmas or ethical challenges for scale up.

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6. References


