# Low tuberculosis treatment initiation after positive tuberculosis lipoarabinomannan results

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*To the Editor:*

Urine-based tuberculosis (TB) lipoarabinomannan (LAM) testing can increase the yield of TB case finding and TB treatment initiation when added to commonly used sputum-based TB diagnostics among people living with HIV (PLHIV) [1, 2]. Since 2019, the World Health Organization recommends TB-LAM testing in all outpatient PLHIV with TB symptoms, a $CD4^+$ cell count <100 per µL or signs of serious illness [3]. Alere Determine TB-LAM (AlereLAM) (Abbott, Chicago, IL, USA) is the one available TB-LAM test [4]. Guideline implementation and AlereLAM testing uptake are poor. In 2021, 11 (44%) out of 25 surveyed African countries had a TB-LAM policy but only South Africa (4%) reported widespread facility use [5]. In 2022, 19 (86%) out of 22 surveyed high TB/HIV burden countries had a TB-LAM policy, but only 47% (nine out of 19) reported health facility use [6]. Testing with AlereLAM is only useful if a positive test leads to TB treatment initiation [3]. Evidence on the effect of a positive AlereLAM result on starting TB treatment is scarce.

We previously reported inclusion criteria, study procedures and the feasibility of implementing the advanced HIV disease care package in PLHIV during near-facility passive TB-case finding (TB-TRIAGE+ Accuracy, www.clinicaltrials.gov identifier NCT04666311) [7, 8]. Briefly, adults with TB symptoms presenting to health facilities in rural/semirural South Africa and Lesotho were included. All participants received sputum Xpert MTB/RIF (Xpert RIF) and Xpert MTB/RIF Ultra (Xpert Ultra) (Cepheid, Sunnyvale, CA, USA) and culture in a mycobacterial growth indicator tube (MGIT) (Becton Dickinson, Franklin Lakes, NJ, USA). In PLHIV, Omega VISITECT CD4 Advanced Disease (Accubio Limited, Alva, UK) was performed on venous blood and AlereLAM on urine. Participants were referred with results for management following national guidelines. TB-LAM guidelines have existed in South Africa since 2018 and Lesotho since 2019 [6].

12-week (10–14 weeks) survival and TB treatment status were assessed by telephone call and clinic file review. We found it feasible to implement the advanced HIV disease care package, with high AlereLAM uptake [8]. Using data from that cohort, here, we estimated AlereLAM (index test) diagnostic accuracy compared to different TB reference standards, and the increase in diagnostic (number diagnosed with TB including with AlereLAM/number diagnosed with TB excluding AlereLAM) and therapeutic yield (number started on TB treatment/number started on TB treatment excluding those with only AlereLAM positive) when adding AlereLAM to a composite reference standard (CRS). We estimated the proportion of PLHIV with a positive AlereLAM test who initiated treatment and assessed prediction of TB treatment initiation in PLHIV with any positive TB test (Xpert, MGIT or AlereLAM positive, or records showed empirical TB diagnosis at 12 weeks). Sensitivity and specificity were calculated in PLHIV who had a test result for AlereLAM and a TB reference test. We defined two CRSs: CRS1 was positive if Xpert or MGIT was positive; and CRS2 if Xpert or MGIT was positive, or records showed TB had been empirically diagnosed at 12 weeks. We compared categorical variables with Chi-squared or Fisher's exact test. We created a variable that combined AlereLAM and Xpert results (either one positive/negative) and included this variable in a multivariable logistic regression model to assess the effect of baseline predictors on TB treatment initiation in PLHIV with any positive TB test. Models were compared with $r^2$ and Aikake's and Bayesian information criterions. Ethics boards in Switzerland, Lesotho and South Africa provided ethical approval [8]. Included participants gave informed consent [8].

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**A positive urine TB-LAM result should lead to TB treatment initiation. TB treatment uptake was low after a positive TB-LAM but negative Xpert test. A lack of trust in TB-LAM results by clinicians and false-positive results may contribute to these results.** https://bit.ly/3VGHekC

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**TABLE 1** Characteristics and outcomes of people living with HIV with a positive tuberculosis (TB) test by TB treatment status

| Vital status | Total, n (column %)[#] | On treatment, n (row %)[#] | Not on treatment, n (row %)[#] | | | | |
|---|---|---|---|---|---|---|---|
| **Total TB diagnosis** | 148 (100) | 118 (80) | 30 (20) | | | | |
| **Vital status at 12 weeks** | | | | | | | |
| Dead | 3 (2) | 3 (100) | 0 (0) | | | | |
| Alive | 133 (90) | 108 (81) | 25 (19) | | | | |
| Unknown | 12 (8) | 7 (58) | 5 (42) | | | | |
| **Characteristics and test results** | | | | **Univariable analysis** | | **Multivariable analysis** | |
| | | | | **OR (95% CI)** | **p-value** | **aOR (95% CI)[¶]** | **p-value** |
| **AlereLAM** | | | | | | | |
| Negative | 62 (42) | 57 (92) | 5 (8) | 1 | | NA | |
| Positive | 86 (58) | 61 (71) | 25 (29) | 0.21 (0.07–0.60) | 0.003 | | |
| AlereLAM grading, n (%) among positives | | | | | | | |
| 1+ | 45 (52) | 25 (56) | 20 (44) | NA | | | |
| 2+ | 8 (9) | 8 (100) | 0 (0) | | | | |
| 3+ | 7 (8) | 6 (86) | 1 (14) | | | | |
| 4+ | 26 (30) | 22 (85) | 4 (15) | | | | |
| **Age, years, median (IQR)** | 43 (35–50) | 40 (34–49) | 49 (44–53) | 0.96 (0.93–1.00) | 0.040 | 0.99 (0.94–1.04) | 0.662 |
| **Sex** | | | | | | | |
| Male | 76 (51) | 61 (80) | 15 (20) | 1 | | NA | |
| Female | 72 (49) | 57 (79) | 15 (21) | 0.93 (0.42–2.08) | 0.868 | | |
| **Country** | | | | | | | |
| Lesotho | 83 (56) | 71 (86) | 12(14) | 1 | | 1 | |
| South Africa | 65 (44) | 47 (72) | 18 (28) | 0.44 (0.19–1.00) | 0.050 | 0.34 (0.11–1.04) | 0.058 |
| **$CD4^+$ cell count on VISITECT, per µL** | | | | | | | |
| >200 | 81 (55) | 56 (69) | 25 (31) | 1 | | 1 | |
| ⩽200 | 66 (45) | 61 (92) | 5 (8) | 5.45 (1.95–15.20) | 0.001 | 3.68 (1.11–12.2) | 0.033 |
| Unknown | 1 (1) | 1 (100) | 0 (0) | | | | |
| **Xpert RIF** | | | | | | | |
| Negative | 80 (54) | 54 (68) | 26 (33) | 1 | | NA | |
| Positive | 62 (42) | 59 (95) | 3 (5) | 9.49 (2.70–33.08) | 0.000 | | |
| Unknown | 6 (4) | 5 (83) | 1 (17) | | | | |
| **Xpert Ultra** | | | | | | | |
| Negative | 78 (53) | 53 (68) | 25 (32) | 1 | | NA | |
| Positive | 67 (45) | 63 (94) | 4 (6) | 7.43 (2.43–22.70) | 0.000 | | |
| Unknown | 3 (2) | 2 (67) | 1 (33) | | | | |
| **AlereLAM/Xpert** | | | | | | | |
| AlereLAM and Xpert positive | 30 (20) | 29 (97) | 1 (3) | 1 | | 1 | |
| AlereLAM positive and Xpert negative | 54 (36) | 31 (57) | 23 (43) | 0.05 (0.01–0.37) | 0.004 | 0.04 (0.01–0.38) | 0.005 |
| AlereLAM negative and Xpert positive | 41 (28) | 37 (90) | 4 (10) | 0.32 (0.03–3.01) | 0.318 | 0.48 (0.05–4.74) | 0.527 |
| Other | 23 (16) | 21 (91) | 2 (9) | 0.36 (0.03–4.26) | 0.419 | 0.57 (0.05–7.12) | 0.661 |
| **MGIT** | | | | | | | |
| Negative | 80 (54) | 53 (66) | 27 (34) | NA | | | |
| Positive | 58 (39) | 56 (97) | 2 (3) | | | | |
| Unknown | 10 (7) | 9 (90) | 1 (10) | | | | |

A positive TB test is defined as Alere Determine TB lipoarabinomannan test (AlereLAM), Cepheid Xpert MTB/RIF (Xpert RIF), Cepheid Xpert MTB/RIF Ultra (Xpert Ultra) or mycobacterial growth indicator tube (MGIT) positive or an empirical TB diagnosis at 12 weeks. aOR: adjusted odds ratio; NA: not applicable; IQR: interquartile range; VISITECT: Omega VISITECT CD4 Advanced Disease. [#]: unless otherwise stated; [¶]: variables with an odds ratio p-value ⩽0.05 were retained in the multivariable model.

Characteristics and test results of 676 included PLHIV were reported. One person refused AlereLAM and one could not produce urine [8]. Compared to Xpert RIF, Xpert Ultra and MGIT, respectively, the sensitivity of AlereLAM in 651, 657 and 607 PLHIV was 48.4% (95% CI 35.5–61.4%), 44.8% (95% CI 32.6–57.4%) and 45.8% (95% CI 32.7–59.2%), and the specificity 90.8% (95% CI 88.2–93.0%), 90.3% (95% CI 87.7–92.6%) and 90.0% (95% CI 87.1–92.3%). Compared to CRS1 and CRS2, respectively, the

sensitivity of AlereLAM in 597 PLHIV was 40.5% (95% CI 29.9–51.8%) and 35.1% (95% CI 25.6–45.4%), and specificity 90.5% (95% CI 87.6–92.8%) and 90.2% (95% CI 87.3–92.7%). The addition of AlereLAM increased the TB diagnostic yield of CRS2 1.6-fold, from 16.2% (97/597) to 25.5% (152/597), and the therapeutic yield 1.2-fold, from 15.1% (90/597) to 18.9% (113/597).

12-week information was available for 148 (97.4%) out of 152 participants with any positive TB test. Of four not reached, three participants had only AlereLAM positive and one MGIT. Of 148, 118 (79.7%) were on TB treatment at 12 weeksand 30 (20.3%) were not (table 1). Among 86 participants with a positive AlereLAM result, 61 (70.9%, 95% CI 60.1–80.2%) were initiated on TB treatment and 25 (29.1%, 95% CI 19.8–39.9%) were not (p=0.003). Among 54 PLHIV with AlereLAM-positive but Xpert-negative results, 31 (57.4%) were initiated on TB treatment and 23 (42.6%) were not (p=0.004). Compared to having positive AlereLAM and Xpert results, having AlereLAM-positive, Xpert-negative results was negatively associated with TB treatment initiation (adjusted odds ratio (aOR) 0.04, 95% CI 0.01–0.38), while having AlereLAM-negative, Xpert-positive results was not significantly associated (aOR 0.48, 95% CI 0.05–4.74).

Among AlereLAM-positive participants, a higher grading (>1+ *versus* 1+) was associated with TB treatment initiation (p=0.008). In South Africa and Lesotho, 33 (97.1%) out of 34 and 12 (23.1%) out of 52 AlereLAM-positive participants had grade 1+, respectively (p=0.000). Among AlereLAM-positive participants, 54 (88.5%) out of 61 of those on treatment and 21 (84.0%) out of 25 of those not on treatment were alive at 12 weeks (p=0.526).

The diagnostic accuracy of AlereLAM we found is consistent with literature; in outpatients with TB symptoms, AlereLAM sensitivity was 29% (95% CI 17%–47%) and specificity 96% (95% CI 91%–99%) in a review [9], and 44% (95% CI 34–54%) and 86% (95% CI 83–88%), respectively, in a recent study [4]. This comparison is limited by the lack of a good TB reference standard [10] and AlereLAM should remain complementary to sputum-based tests.

In our cohort, a positive AlereLAM result often did not trigger treatment initiation, especially when combined with a negative Xpert. This translated into a 1.6-fold increase in diagnostic yield but only a 1.2-fold increase in therapeutic yield when adding AlereLAM. Low TB treatment uptake after positive AlereLAM results has been reported [11, 12]. Reasons for not initiating TB treatment could include a lack of trust in AlereLAM results, which may be stronger when grading is low and when Xpert is negative. Clinicians confronted with a AlereLAM-positive, Xpert-negative results will weigh these and the presence/absence of other risk factors with the risks/benefits of TB treatment to make a clinical decision. For these patients, despite a test indicating TB, the clinician's treatment threshold may have not been reached [13]. Respondents from the South African National TB Programme reported incomplete roll-out of TB-LAM guideline implementation, a lack of staff training and clinicians' reluctance to treat based on an AlereLAM result [6]. The Lesotho TB programme reported having been excluded from guidelines roll-out and poor training [6]. Our staff nurses were uncertain about result interpretation and grading, and correct midstream urine sampling for AlereLAM, leading to fears of incorrect TB treatment initiation [8]. False-positive AlereLAM results are possible, sometimes due to other bacterial contamination during sampling [14]. Since 21 out of 25 AlereLAM-positive participants not on treatment were still alive at 12 weeks, these may not have had disseminated TB, which has high early mortality [15]. PLHIV for whom we could not ascertain their vital status may have died early, impeding treatment.

We found low TB treatment initiation following positive AlereLAM results when Xpert was negative, despite acceptable AlereLAM diagnostic performance and existing TB-LAM guidelines. A lack of trust in AlereLAM results by clinicians and false-positive results may contribute to treatment hesitancy. Research is needed on barriers to TB treatment initiation to optimise the added value of TB-LAM testing to reduce mortality.

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