International Journal of Infectious Diseases 79 (2019) 37–43

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Does the use of adjunct urine lipopolysaccharide lipoarabinomannan in HIV-infected hospitalized patients reduce the utilization of healthcare resources? A post hoc analysis of the LAM multi-country randomized controlled trial

Poobalan Naidoo[a], Aliasgar Esmail[b], Jonathan G. Peter[c], Malika Davids[b], Mohammed Fadul[b], Keertan Dheda[b,d,*]

[a] Department of Internal Medicine, RK Khan Hospital, Department of Internal Medicine, University of Kwa-Zulu Natal, Chatsworth, Kwa-Zulu Natal, South Africa
[b] Centre for Lung Infection and Immunity, Division of Pulmonology and University of Cape Town Lung Institute, Department of Medicine, University of Cape Town, Cape Town, South Africa
[c] Division of Allergology and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa
[d] Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 15 July 2018
Received in revised form 25 September 2018
Accepted 28 September 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
HIV-infected
Urine lipopolysaccharide
lipoarabinomannan

ABSTRACT

Background: The World Health Organization (WHO) recommends the use of adjunctive urine lipopolysaccharide lipoarabinomannan (LAM) testing in hospitalized HIV-infected persons with suspected tuberculosis (TB) and a CD4 count <100 cells/ml. However, the recommendation is conditional, and uptake by individual treatment programmes depends on perceived additional benefit. The aim of this study was to determine whether adjunctive LAM testing has additional clinical benefits including a reduction in healthcare-related use of resources.

Methods: A post hoc analysis was performed of a published multicentre, multi-country, randomized controlled trial that showed an approximate 20% mortality benefit in HIV-infected hospitalized patients who underwent adjunctive LAM testing as part of their diagnostic workup. In that parent study, adult HIV-infected hospitalized patients with suspected TB ($n = 2528$) were randomly allocated to either routine diagnostics (smear microscopy, Xpert MTB/RIF, and culture; $n = 1271$), or routine diagnostics plus adjunctive urine LAM testing ($n = 1257$). Data were further analyzed to determine whether there were other potential benefits of LAM usage based on CD4 count and illness severity. Aspects evaluated included: (1) the reduction in number of diagnostic sputum samples tested, (2) the utilization of additional imaging, (3) disease resolution based on follow-up signs and symptoms of illness severity, and (4) the reduction in hospital readmission.

Results: Adjuvant LAM did not reduce the number of diagnostic sputum samples requested, the need for additional imaging, or the hospital readmission rate. However, adjunctive LAM was associated with a more rapid rate of disease resolution (dyspnoea) in the severely ill subgroup. Higher LAM grade (grades 4 and 5), compared to lower grade positivity (≤ 3), was associated with lower use of ultrasound, lower Karnofsky performance score, lower CD4 cell count, and shorter time to culture positivity.

Conclusions: Although, adjunct LAM was associated with a mortality benefit in the parent study, no benefit could be demonstrated in the secondary analysis with respect to the number of diagnostic sputum samples requested, the use of additional imaging, or hospital readmission rates. However, given the limitations of the present study, further appropriately designed studies are required to determine the effect of adjunct urine LAM on the utilization of healthcare resources.

* Corresponding author at: University of Cape Town, H47 Old Main Building, Groote Schuur Hospital, Observatory 7925, South Africa.
E-mail addresses: poobalan1naidoo@yahoo.com (P. Naidoo), a.esmail@uct.ac.za (A. Esmail), jonny.peter@uct.ac.za (J.G. Peter), malika.davids@uct.ac.za (M. Davids), mohammed.fadul@uct.ac.za (M. Fadul), keertan.dheda@uct.ac.za (K. Dheda).

https://doi.org/10.1016/j.ijid.2018.09.024

Introduction

Tuberculosis (TB) is a major cause of mortality and morbidity in HIV-infected patients (Cohen et al., 2010; Lawn et al., 2013; Dheda et al., 2016). A major limitation of current mainstream TB diagnostic tests is their resource intensiveness and the turnaround time of tests (Wasserman and Meintjes, 2014). Furthermore, it is often difficult to obtain sputum samples from HIV-infected patients and the production of aerosols is a potential danger to healthcare workers, hospital staff, and other hospitalized patients (Wasserman and Meintjes, 2014).

Point-of-care urine testing offers rapid test turnaround times and is less resource-intensive than currently used TB diagnostic tests (Drain et al., 2014). Lipopolysaccharide lipoarabinomannan (LAM) testing at the point of care has been shown to have mortality benefit in HIV-infected patients with advanced immunosuppression, likely because of a shorter time to treatment and greater proportion of patients receiving anti-TB treatment (Peter et al., 2016). Furthermore, LAM testing may be useful for prognostication, since a positive result is associated with higher mortality (Gupta-Wright et al., 2016).

Thus, the World Health Organization (WHO) recommends the use of adjunctive urine LAM testing in HIV-infected persons with a CD4 count <100 cells/ml or in those who are seriously ill (WHO, 2015). However, the recommendation is conditional, and uptake by individual treatment programmes depends on perceived additional benefit. Additional potential benefits may include a reduction in number of sputum sample requests, additional imaging (beyond X-rays), signs and symptoms of illness (dyspnoea, night sweats, pain, and haemoptysis), the use of empiric antibiotics, and hospital readmission. The reduction in use of healthcare resources (antibiotics, imaging, sputum testing, readmission rates, etc.) may have cost savings. This may inform resource allocation and public health strategy and impact decisions about the rollout and use of urine

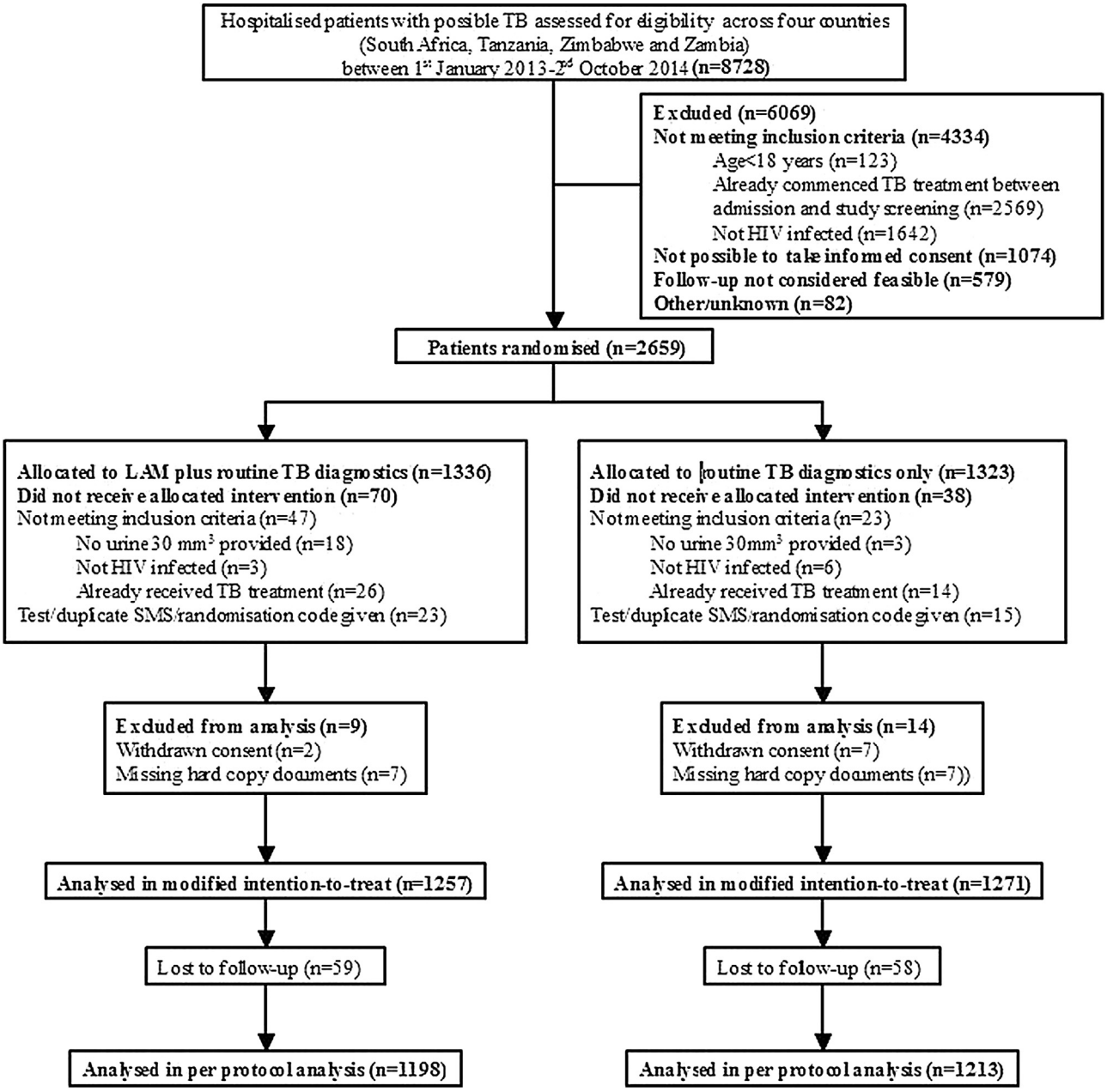

Figure 1. Study overview and flow diagram.

LAM by TB programmes, given that the WHO recommendations on LAM usage are conditional. However, there are hardly any data about the impact of adjunctive urine LAM on healthcare resource utilization. This study aimed to address the aforementioned knowledge gap. It was hypothesized that adjunctive LAM testing would reduce the number of sputum samples, reduce utilization of additional imaging, quicken disease resolution (based on follow-up signs and symptoms of illness severity), and reduce hospital readmission.

Methods

Study design and conduct

This study analyzed data from a published pragmatic, randomized, parallel-arm, multicentre, multi-country study that investigated the utility of adjunctive LAM testing in HIV-infected hospitalized patients in South Africa, Tanzania, Zambia, and Zimbabwe (Peter et al., 2016). Patients were randomized to a LAM-guided or conventional arm, thus functionally eliminating the bias introduced by physician practice.

The study received regulatory and ethical clearance from the relevant authorities and was aligned with the Declaration of Helsinki. Informed consent was received from all participants in their first language. This trial is registered with Clinicaltrials.gov, number NCT01770730.

Study patients and enrolment criteria

Patients admitted to 10 urban or peri-urban hospitals in South Africa, Tanzania, Zambia, and Zimbabwe were screened for study inclusion. The inclusion criteria were (1) HIV-infected persons; (2) at least one of the following symptoms: current fever or cough, drenching night sweats, and self-reported loss of weight; (3) illness severe enough to necessitate hospitalization; (4) age ≥18 years; (5) granting of informed consent. The exclusion criteria were: (1) persons not infected with HIV, (2) patients receiving any anti-TB medication in the 60 days prior to testing, and (3) unable to provide at least 30 ml of urine.

Procedures and clinical management

On enrolment of patients, a spot urine specimen (>30 ml) or a spot catheter sample was collected. Alere Determine TB LAM Ag lateral flow strip testing was performed at the bedside for patients allocated to the LAM testing arm.

Patients were asked to expectorate a minimum of two sputum samples for routine TB diagnosis. For patients unable to self-expectorate, sputum was induced. A clinical assessment and chest X-ray facilities were available in most cases. Additional radiology (e.g., ultrasound or computed tomography (CT) scanning) and non-sputum sampling were differentially available in study hospitals; the request for these investigations was at the discretion of the attending clinical team.

The attending clinical team made all decisions regarding patient therapy, use of additional radiology, request of non-sputum sampling, and initiation of anti-TB treatment and the timing thereof, including acting upon the LAM test results.

Database and analysis

A total of 8728 patients were screened and 2659 eligible patients were randomized; 2528 were included in the final analysis (1257 in the LAM group and 1271 in the non-LAM group).

Data were analyzed to determine whether there were other potential benefits (beyond mortality) of LAM usage in all study participants and in subgroups of patients with a CD4 count <50, 50–100, and >100 cells/ml, and severely ill (respiratory rate >30, heart rate >120, temperature >39 °C). Research staff assessed symptoms at 8 weeks after randomization (within a range of 14 days). Figure 1 outlines the study overview.

Statistical methods

The median and interquartile range (IQR) were calculated for continuous variables and the frequency (percentage) for categorical variables. Continuous variables were compared with the Wilcoxon rank sum test and categorical variables with the Chi-square test. When comparing the adjuvant LAM group to the non-LAM group, quantitative and qualitative variables were compared using the Mann–Whitney *U*-test and the Chi-square test or Fisher's exact test, respectively. A Chi-square test was performed to determine whether LAM grade correlated with mortality, and the Mann–Whitney test was used to determine whether adjunctive LAM reduced the number of sputum samples collected. Logistic regression analysis included variables that were significantly associated with the LAM grade. A significance value of $p < 0.05$ was used. Statistical analyses were conducted in Stata (version 13).

Results

Adjunctive LAM and sputum samples

In patients receiving adjuvant LAM, there was no reduction in the number of sputum samples requested by clinicians (1034 vs. 1019, $p = 0.7680$).

Use of additional imaging

In patients receiving adjuvant LAM, there was no reduction in the use of additional imaging (ultrasonography and CT) in the entire cohort or in the subgroups (CD4 cell count >100 cells/ml, 50–100 cells/ml, and <50 cells/ml, and severely ill patients). Stratification by country did not show a reduction in usage of ultrasound or CT scans. A total of 85 CT scans were performed (52 of the head, 13 of the chest, 13 of the abdomen, and 7 unspecified). South Africa used the most additional imaging. The aforementioned results are presented in Tables 1 and 2.

Disease resolution based on follow-up signs and symptoms of illness

During follow-up, there were significantly fewer patients with dyspnoea in the severely ill group receiving adjuvant LAM. In patients receiving adjuvant LAM, there was no reduction in

Table 1
Radiographic imaging obtained in all countries combined (South Africa, Zimbabwe, Tanzania, and Zambia) for those who did and did not receive adjunctive LAM testing.

	No LAM	Adjunctive LAM	*p*-Value
Ultrasound			
Entire cohort	311/1162 (26.8%)	335/1163 (28.8%)	0.272
CD4 cells >100	128/510 (25.1%)	129/469 (27.5%)	0.392
CD4 cells 50–100	49/195 (25.1%)	52/185 (28.1%)	0.511
CD4 cells <50	89/388 (22.9%)	96/429 (22.4%)	0.848
Severely ill	168/534 (31%)	172/522 (33%)	0.7577
CT scan			
Entire cohort	46/1204 (3.8%)	40/1187 (3.4%)	0.554
CD4 cells >100	22/522 (4.2%)	23/484 (4.7%)	0.680
CD4 cells 50–100	10/196 (5.1%)	6/189 (3.2%)	0.343
CD4 cells <50	10/400 (2.5%)	10/432 (2%)	0.862
Severely ill	13/471 (3%)	16/471 (3%)	0.7187

LAM, lipopolysaccharide lipoarabinomannan; CT, computed tomography.

Table 2
Ultrasound and computed tomography utilization stratified by country.

Country	Adjunctive LAM Number of US/number of patients	No adjunctive LAM Number of US/number of patients	*p*-Value[a]
US			
South Africa	111/254 (44%)	110/253 (43%)	1.000
Zimbabwe	9/460 (2%)	4/460 (1%)	0.263
Tanzania	0/205 (0%)	1/211 (0%)	1.000
Zambia	215/338 (64%)	196/347 (56%)	0.0614
Country	Adjunctive LAM Number of CT/number of patients	No adjunctive LAM Number of CT/number of patients	*p*-Value[a]
CT scan			
South Africa	38/254 (15%)	43/253 (17%)	0.547
Zimbabwe	1/460 (0.2%)	1/460 (0.2%)	1.000
Tanzania	0/204 (0%)	0/209 (0%)	–
Zambia	1/269 (0.4%)	2/282 (1%)	1.000

LAM, lipopolysaccharide lipoarabinomannan; US, ultrasound; CT, computed tomography.
[a] Fisher's exact test.

dyspnoea, night sweats, pain, or haemoptysis in the entire cohort or in any of the CD4 cell count subgroups (>100 cells/ml, 50–100 cells/ml, and <50 cells/ml). The aforementioned results are presented in Table 3.

Table 3
Symptoms at follow-up for the group receiving LAM versus the group not receiving LAM. The groups were stratified into participants with a CD4 count >100, 50–100, and <50 cells/ml, and those severely ill.

Entire cohort	LAM (n = 877)		No LAM (n = 824)		*p*-Value[a]
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	
Dyspnoea	13.1 (115)	86.9 (762)	13.1 (108)	86.9 (716)	0.990
Night sweats	9.4 (82)	90.6 (795)	9.5 (78)	90.5 (746)	0.935
Pain	14.3 (125)	85.7 (751)	12.9 (106)	87.1 (718)	0.398
Hemoptysis	1.0 (9)	99.0 (868)	0.7 (6)	99.3 (816)	0.514
CD4 >100 cells/ml	LAM (n = 393)		No LAM (n = 390)		*p*-Value[a]
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	
Dyspnoea	11.9 (47)	88.1 (346)	13.6 (53)	86.4 (337)	0.494
Night sweats	10.2 (40)	89.8 (353)	9.2 (36)	90.8 (354)	0.654
Pain	14.5 (57)	85.5 (336)	11.0 (43)	89.0 (347)	0.145
Hemoptysis	1.2 (5)	98.8 (388)	0.7 (2)	99.3 (387)	0.260
CD4 50–100 cells/ml	LAM (n = 124)		No LAM (n = 150)		*p*-Value[a]
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	
Dyspnoea	13.7 (17)	86.3 (107)	14.7 (22)	85.3 (128)	0.843
Night sweats	6.5 (8)	93.5 (116)	9.3 (14)	90.7 (136)	0.382
Pain	8.0 (10)	92.0 (114)	11.2 (23)	88.8 (127)	0.066
Hemoptysis	0.8 (1)	99.2 (123)	0	100 (150)	0.271
CD4 <50 cells/ml	LAM (n = 298)		No LAM (n = 241)		*p*-Value[a]
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	
Dyspnoea	12.1 (36)	87.9 (262)	12.1 (26)	87.9 (215)	0.640
Night sweats	9.1 (27)	90.9 (271)	9.9 (24)	90.1 (217)	0.723
Pain	14.8 (44)	85.2 (253)	13.3 (32)	86.7 (209)	0.611
Hemoptysis	0.7 (2)	99.3 (295)	1.6 (4)	98.4 (237)	0.279
Severely ill	LAM (n = 344)		No LAM (n = 315)		*p*-Value[a]
	Yes % (n)	No % (n)	Yes % (n)	No % (n)	
Dyspnoea	11.6 (40)	88.4 (304)	18.1 (57)	91.9 (258)	0.019
Night sweats	8.7 (30)	91.3 (314)	10.8 (34)	89.2 (281)	0.369
Pain	14.3 (48)	85.7 (295)	19.7 (62)	80.3 (253)	0.051
Hemoptysis	0.9 (3)	90.1 (341)	1.0 (3)	99.0 (311)	0.911

LAM, lipopolysaccharide lipoarabinomannan.
[a] Chi-square test.

Readmission

In patients receiving adjuvant LAM, there was no reduction in the frequency of readmission in the entire cohort or in the subgroups (CD4 cells >100 cells/ml, 50–100 cells/ml, and <50 cells/ml, and severely ill patients). The aforementioned results are presented in Table 4.

LAM grade

Higher LAM grade (grades 4 and 5) was associated with lower use of ultrasound (p = 0.001), lower Karnofsky performance score (p = 0.005), lower CD4 cell count (p = 0.001), and shorter time to culture positivity (p = 0.005). The aforementioned results are presented in Table 5 and Figure 2. There was no significant difference in time to death in patients with low versus high LAM grade (p = 0.647). A multivariable analysis for variables associated with high positive LAM grade (grades 4 and 5) is presented in Table 6.

Discussion

The aim of this study was to determine whether adjunctive LAM testing has benefits other than a mortality benefit. However, it was found that adjuvant LAM did not reduce the number of diagnostic sputum samples requested or the need for additional imaging and had no impact on hospital readmission. Adjunctive LAM was associated with a more rapid rate of disease resolution (dyspnoea) in the severely ill subgroup, and higher LAM grade was associated with prognostication (factors known to be associated with mortality).

In patients receiving adjunctive LAM testing, there was no reduction in usage of ultrasound or CT scanning. This remained so even when stratified by country (South Africa was the greatest user

Table 4
Patient readmission for those who did and did not receive adjunctive LAM testing.

	No LAM	Adjunctive LAM	*p*-Value
Entire cohort	76/1195 (6%)	95/1162 (8%)	0.1335
CD4 cells >100	11/519 (2%)	12/462 (3%)	0.0672
CD4 cells 50–100	10/205 (5%)	12/200 (6%)	0.6518
CD4 cells <50	29/421 (7%)	30/446 (7%)	0.8317
Severely ill	26/50 (52%)	41/54 (76%)	0.8253

LAM, lipopolysaccharide lipoarabinomannan.

Table 5
Relationships between LAM grade and CD4 cell count, weight, smear result, previous TB, Karnofsky performance score, mortality, TBscore, and ultrasound and computed tomography usage.

	Low positive grade (1–3) $n = 186$	High positive grade (4 and 5) $n = 81$	p-Value
CD4 count			0.001
<50	85 (52.2%)	59 (75.6%)	
50–100	28 (17.2%)	11 (14.1%)	
>100	50 (30.7%)	8 (10.3%)	
Weight			0.32
≤50	95 (51.1%)	36 (44.4%)	
>50	91 (48.9%)	45 (55.6%)	
Smear result			0.01
Negative	92 (60.5%)	32 (42.7%)	
Positive	60 (39.5%)	43 (57.3%)	
Previous TB			0.49
No	147 (79.0%)	67 (82.7%)	
Yes	39 (21.0%)	14 (17.3%)	
Mean Karnofsky score	51.3 (20–90)	46.7 (20–90)	0.005
Mortality			0.238
Dead	48 (27.3%)	27 (34.6%)	
Alive	128 (72.7%)	51 (65.4%)	
TBscore	80	44	0.772
Ultrasound (yes)	64 (39.3%)	14 (18.4%)	0.001
CT (yes)	3 (1.7%)	1 (1.3%)	0.830

LAM, lipopolysaccharide lipoarabinomannan; TB, tuberculosis; CT, computed tomography.

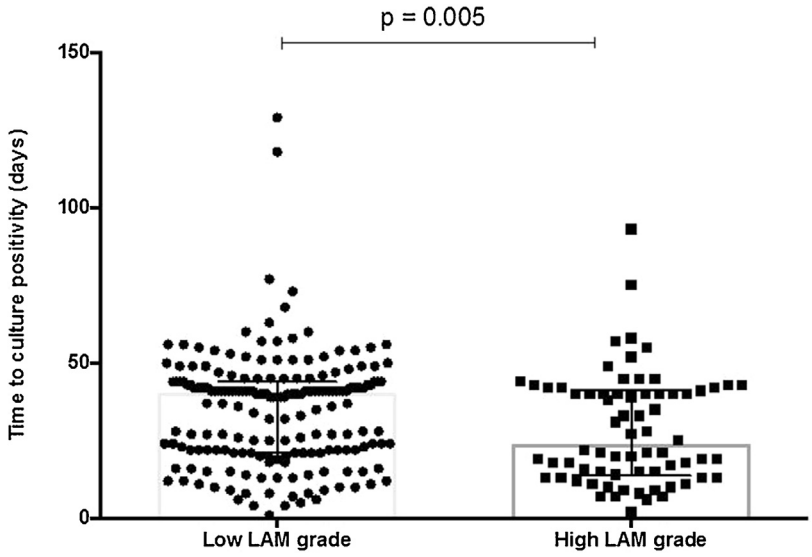

Figure 2. Time to tuberculosis culture positivity in participants with low versus high LAM grade.

Table 6
Multivariable analysis for variables associated with high positive LAM grades (grades 4 and 5).

	OR	p-Value	95% CI
CD4 cell count category	0.6214	0.083	0.3626–1.0649
Smear result	1.9582	0.037	1.0422–3.6795
Karnofsky score	0.9789	0.066	0.9569–1.0014
Ultrasound	0.3316	0.013	0.1391–0.7902

LAM, lipopolysaccharide lipoarabinomannan; OR, odds ratio; CI, confidence interval.

of additional imaging). This may be because the LAM test does not specifically identify the site/sites of TB and imaging may add clinically useful additional information. Indeed, imaging informs about the site of TB, which often affects downstream management including the selection of drugs, dose, and use of adjunctive steroids (e.g., TB pericarditis and TB meningitis, which may require drainage or surgical intervention, and drug selection, dosage, and duration may differ with intracranial TB) (Marx and Chan, 2011). Furthermore, if the patient has neurological signs, a CT scan of the brain may determine whether there is TB-associated hydrocephalus or other space-occupying lesions (Marx and Chan, 2011; Thwaites et al., 2009). Indeed, the British Infection Society recommends that every patient with intracranial TB should have a CT brain scan (Thwaites et al., 2009). South Africa performed far greater numbers of CT scans than the other study sites, probably because of greater availability of imaging resources in a middle-income country. Secondly, imaging is often required to rule out other diseases that may co-exist with TB or to exclude other differential diagnoses, e.g., lymphoma (Heller et al., 2010). In short, adjunctive LAM does not differentiate between pulmonary and extrapulmonary TB, and radiological investigation is still required, where clinically indicated.

There are several other possible reasons for the failure to demonstrate a reduction in healthcare utilization. Firstly, we did

not expressly collect the data and it was not an a priori primary or secondary aim of the parent study. Secondly, as outlined above, physicians may have requested investigations for other clinical reasons including ruling out or ruling in other opportunistic infections, or other clinical indications. In addition, at the time of the study, the mortality benefit of LAM was unknown and so clinicians were more likely to continue their normal practices regardless of LAM.

In patients receiving adjuvant LAM, there was no reduction in the frequency of readmission in the entire cohort or in the subgroups. Speculative reasons for this finding include the short study duration, the relatively small number of patients who were readmitted, poor health-seeking behaviour, and management of these patients at non-trial centres.

During follow-up, there were significantly fewer patients with dyspnoea in the severely ill group receiving adjuvant LAM. This may be due to the possibly higher rate of extrapulmonary rather than pulmonary involvement in those with advanced HIV, or it may be a chance finding, as adjunctive LAM was not associated with a reduction in other symptoms, i.e., night sweats, pain, and haemoptysis. It is challenging to compare these results with published data because such a study has not been performed previously. Bark et al. (2011) investigated symptoms in a previously published international phase 3 trial of TB therapy in 394 ambulatory HIV-uninfected subjects (Johnson et al., 2009). Bark et al. (2011) found that self-reported symptoms at baseline included dyspnoea (30%), cough (81%), and fever (51%). After the first 2 months of treatment, the proportion of subjects with symptoms declined by 94% for fever, 59% for cough, 77% for chest pain, 94% for sweats, and 81% for dyspnoea. The reduction of dyspnoea mirrors the result in the present study. In patients receiving adjunctive LAM testing, a reduction in TB symptoms may be attributed to appropriate patients receiving correct and timely anti-TB therapy.

Higher LAM grade (grades 4 and 5) correlated with poor prognostic characteristics (lower Karnofsky score and lower CD4 cell count). This may assist with prognostication and targeting such patients (more likely to die) with more aggressive therapy and follow-up. This requires further exploration and investigation. The findings of this study are aligned with those of Kerkhoff et al. (2014), who found that in "patients with HIV-associated TB, concentrations of LAM in urine were strongly associated with a range of poor prognostic characteristics known to be associated with mortality risk." Drain et al. (2015) showed that there was a significantly greater mortality risk in patients with a LAM grade of $\geq$2 after 2 months of anti-TB therapy. However the study, which had a limited sample size, did not determine the effect of LAM grade on prognosis before the initiation of anti-TB therapy. No other published study that has investigated the prognostic value of LAM grade could be identified.

There are several limitations to this study. This was a post-hoc analysis and thus the results must be interpreted with caution. The study sites had heterogeneous patients with differing severity of disease. Furthermore, the study duration was 8 weeks; a longer duration study may have better captured readmission rates. It is thus possible that adjunctive LAM may still have beneficial effects on healthcare utilization. A major limitation is the absence of capturing antibiotic utilization. There is currently a focus on antibiotic stewardship and it would have been useful to know whether patients receiving adjuvant LAM would have had a reduction in the utilization of antibiotics. It is likely this might be the case, as a positive LAM test would negate the use of empiric antibiotic therapy. Further studies are required to address this question.

In conclusion, although in the parent study adjunct LAM was associated with a mortality benefit, in the subgroup analysis no benefit could be demonstrated with respect to the number of diagnostic sputum samples requested, the use of additional imaging, or hospital readmission rates. However, given the limitations of the study, further appropriately designed and prospective studies are required to determine the effect of adjunct urine LAM on the utilization of healthcare resources.

Ethical approval and consent to participate

The study received regulatory and ethical clearance from the relevant authorities and was aligned with the Declaration of Helsinki. Informed consent was received from all participants in their first language. This trial is registered with Clinicaltrials.gov, number NCT01770730.

Consent for publication

Not applicable.

Funding

The European & Developing Countries Clinical Trials Partnership, the South African Medical Research Council, and the South African National Research Foundation.

Conflict of interest

None.

Trial registration

This trial is registered with ClinicalTrials.gov, number NCT01770730.

Availability of data and material

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

Author contributions

KD, AE, and JGP conceptualized and designed the study. The data analysis was performed by MF and MD. Substantial contribution was made by all authors, all of whom gave final approval of the version to be submitted.

Acknowledgements

We acknowledge the patients and study personnel who participated and contributed to the primary study.

References

Bark CM, Dietze R, Okwera A, Quelapio MI, Thiel BA, Johnson JL. Clinical symptoms and microbiological outcomes in tuberculosis treatment trials. Tuberculosis (Edinb) 2011;91(November (6)):601–4.

Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. PLoS Med 2010;7(June (6)) e1000296, doi:http://dx.doi.org/10.1371/journal.pmed.1000296 PubMed PMID: 20582324; PubMed Central PMCID: PMC2889914.

Dheda K, Barry CE, Maartens G. Tuberculosis. Lancet 2016;387(March (10024)):1211–26.

Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. Lancet Infect Dis 2014;14 (March (3)):239–49.

Drain PK, Gounder L, Grobler A, Sahid F, Bassett IV, Moosa MY. Urine lipoarabinomannan to monitor antituberculosis therapy response and predict mortality in an HIV-endemic region: a prospective cohort study. BMJ Open

2015;5(April (4))e006833, doi:http://dx.doi.org/10.1136/bmjopen-2014-006833.
Gupta-Wright A, Peters JA, Flach C, Lawn S. Detection of lipoarabinomannan (LAM) in urine is an independent predictor of mortality risk in patients receiving treatment for HIV-associated tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. BMC Med 2016;14(March (1)):53, doi:http://dx.doi.org/10.1186/s12916-016-0603-9.
Heller T, Goblirsch S, Wallrauch C, Lessells R, Brunetti E. Abdominal tuberculosis: sonographic diagnosis and treatment response in HIV-positive adults in rural South Africa. Int J Infect Dis 2010;14(September (6)):e108–12, doi:http://dx.doi.org/10.1016/j.ijid.2009.11.030.
Johnson JL, Hadad DJ, Dietze R, Maciel EL, Sewali B, Gitta P, et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. Am J Respir Crit Care Med 2009;180(September (6))558–63, doi:http://dx.doi.org/10.1164/rccm.200904-0536OC Epub 2009 June 19.
Kerkhoff AD, Wood R, Vogt M, Lawn SD. Prognostic value of a quantitative analysis of lipoarabinomannan in urine from patients with HIV-associated tuberculosis. PLoS One 2014;9(July (7))e103285, doi:http://dx.doi.org/10.1371/journal.pone.0103285.
Lawn SD, Meintjes G, McIlleron H, Harries AD, Wood R. Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. BMC Med 2013;11(December):253, doi:http://dx.doi.org/10.1186/1741-7015-11-253.
Marx Grace E, Chan Edward D. Tuberculous meningitis: diagnosis and treatment overview. Tuberc Res Treat 2011;2011:798764, doi:http://dx.doi.org/10.1155/2011/798764.
Peter JG, Zijenah LS, Chanda D, Clowes P, Lesosky M, Gina P, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. Lancet 2016;387(March (10024)):1187–97, doi:http://dx.doi.org/10.1016/S0140-6736(15)01092-2.
Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009;59(September (3)):167–87, doi:http://dx.doi.org/10.1016/j.jinf.2009.06.011.
World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. Policy guidance. WHO/HTM/TB/2015.25. Geneva: World Health Organization; 2015 http://www.who.int/tb/areas-of-work/laboratory/policy_statement_lam_web.pdf. [Accessed 13 July 2018].
Wasserman S, Meintjes G. The diagnosis, management and prevention of HIV-associated tuberculosis. S Afr Med J 2014;104(December (12)):886–93.