Algorithm-guided empirical tuberculosis treatment for people with advanced HIV disease: the "TB Fast Track" cluster-randomised trial: supplementary web appendix

Development of the TB Fast Track algorithm

To refine the TB Fast Track algorithm and find appropriate cut-off values, we used data from a study evaluating the diagnostic performance of a urine lipoarabinomannan (LAM) ELISA assay among hospitalised patients in South Africa with signs or symptoms of tuberculosis, in which haemoglobin and body mass index were measured, and the gold standard comprised sputum microscopy and mycobacterial culture, and mycobacterial blood culture in all patients, with additional diagnostic investigations as clinically indicated. We restricted the analysis to HIV-positive patients with CD4 counts ≤150 cells per μL. The sensitivity and positive predictive values for each item (urine LAM ELISA positive, body mass index ≤18·5 kg/m^2 and haemoglobin <80g/L) and for a composite comprising any of the three items are shown below:

Table 1: Diagnostic performance of urine LAM, body mass index, haemoglobin and a composite of any of the three items versus a gold standard of microbiologically-confirmed TB among hospitalised HIV-positive patients with CD4 ≤150 cells/μL

	Sensitivity, n/N	% (95% confidence interval)	Positive predictive value, n/N	% (95% confidence interval)
LAM ELISA positive	84/111	75·7% (66·6–83.3%)	84/111	75·7% (66·6–83·3%)
Body mass index <18·5kg/m^2	33/97	34·0% (24·7–44·3%)	33/73	45·2% (33·5–57·3%)
Haemoglobin <100g/L	56/90	62·2% (51·4–72·2%)	56/99	56·6% (46·2–66·5%)
Any of the three items	100/109	91·7% (84·9–96·1%)	100/185	54·0% (46·6–61·4%)

LAM=lipoarabinomannan.

Data for this analysis were kindly provided by Dr Manaunk Shah, from his previously-published study
Shah M, Variava E, Holmes CB, et al. Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a High HIV prevalence setting. *J Acquir Immune Defic Syndr* 2009; **52**(2): 145-51.

Table 2: Baseline characteristics of intervention arm participants, by category of TB probability

Intervention (n=1506*)		**TB probability category assigned by research nurse**		
		High (n=689)	**Medium (n=475)**	**Low (n=342)**
Sex, female	n (%)	398 (57·8%)	238 (50·1%)	184 (53·8%)
Age, years	Median (IQR)	37 (32–44)	39 (33–45)	36 (31–43)
CD4, cells per μL	Median (IQR)	62 (26–102)	76 (39–115)	89 (55–124)
CD4 <50 cells per μL	n (%)	285 (41·4%)	152 (32·0%)	71 (20·8%)
BMI, kg/m^2	Median (IQR)	19·0 (17·3–33·3)	21·9 (20·0–25·3)	23·8 (20·9–27·5)
BMI <18·5 kg/m^2	n (%)	315 (45·7%)	2 (0·4%)	3 (0·9%)
Hb <100 g/L	n (%)	426 (61·8%)	1 (0·2%)	1 (0·3%)
Urine LAM positive	n (%)	180 (26·2%)	1 (0·2%)	0 (0%)
At least one TB symptom	n (%)	605 (87·8%)	438 (92·2%)	51 (15·0%)
Previous TB	n (%)	81 (11·8%)	47 (9·9%)	23 (6·7%)
Taking IPT	n (%)	18 (2·6%)	11 (2·3%)	22 (6·4%)
Taking co-trimoxazole	n (%)	320 (46·4%)	230 (48·4%)	141 (41·4%)
TB tests in last 6 months	n (%)	367 (53·3%)	240 (50·5%)	129 (37·8%)
Control (n=1039)**		**TB probability category, assigned retrospectively**		
		High (n=512)	**Medium (n=339)**	**Low (n=188)**
Sex, female	n (%)	323 (63·1%)	183 (54·0%)	105 (55·8%)
Age, years	Median (IQR)	35 (30–42)	37 (32–44)	36 (30·5–45)
CD4, cells per μL	Median (IQR)	59 (30–110·5)	67 (33–109)	84 (54–124)
CD4 <50 cells per μL	n (%)	206 (40·2%)	120 (35·4%	43 (22·9%)
BMI, kg/m^2	Median (IQR)	19·6 (17·3–23·0)	22·2 (20·3–25·5)	23·0 (20·6–26·2)
BMI <18·5 kg/m^2	n (%)	210 (41·0%)	0 (0%)	0 (0%)
Hb <100 g/L	n (%)	305 (59·6%)	0 (0%)	0 (0%)
Urine LAM positive	n (%)	156 (30·5%)	0 (0%)	0 (0%)
At least one TB symptom	n (%)	365 (71·4%)	339 (100%)	0 (0%)
Previous TB	n (%)	51 (10·0%)	35 (10·3%)	17 (9·0%)
Taking IPT	n (%)	63 (12·3%)	30 (8·8%)	28 (14·9%)
Taking co-trimoxazole	n (%)	288 (56·2%)	185 (54·6%)	86 (45·7%)
TB tests in last 6 months	n (%)	261 (51·1%)	178 (52·8%)	65 (34·6%)

* n=1 in intervention arm does not have an assigned probability of TB due to missing data; ** n=476 in control arm do not have an assigned probability of TB due to missing data
TB=tuberculosis. IQR=interquartile range. BMI=body mass index. LAM=lipoarabinomannan. IPT=isoniazid preventive therapy. TB symptoms defined as any of cough, fever, unintentional weight loss, night sweats.

Table 3: mortality rates by clinic

Intervention					Control				
Site code	Stratum	Deaths	py	rate/100py	Site code	Stratum	Deaths	py	rate/100py
I1.1	1	17	63·95	26·58	C1.1	1	3	30·63	9·79
I1.2	1	12	66·40	18·07	C1.2	1	16	62·92	25·43
I1.3	1	7	52·19	13·41	C1.3	1	20	69·67	28·71
I1.4	1	16	65·60	24·39	C1.4	1	8	61·96	12·91
I1.5	1	9	38·90	23·14	C1.5	1	20	66·51	30·07
I1.6	1	13	68·91	18·87	C1.6	1	12	66·27	18·11
I1.7	1	9	76·31	11·79	C1.7	1	6	60·55	9·91
I1.8	1	12	66·69	17·99	C1.8	1	9	37·31	24·12
I1.9	1	10	39·79	25·13	C1.9	1	12	63·75	18·82
I1.10	1	3	30·94	9·70	C1.10	1	13	48·68	26·70
I2.1	2	15	64·59	23·22	C2.1	2	16	61·58	25·98
I2.2	2	11	69·93	15·73	C2.2	2	16	69·13	23·14
Overall		134	704·20	19·03	Overall		151	698·97	21·60
Geometric mean				18·17	Geometric mean				19·80

py=person-years.

Table 4: Subgroup analyses for the primary outcome of all-cause mortality at six months

		Intervention	Control						
		Rate/100 py (deaths/py)	Rate/100 py (deaths/py)	Unadjusted RR	95% CI	P-value	Adjusted RR	95% CI	P-value
CD4*, cells per µL	<50	33·9 (77/227)	33·5 (78/233)	0·99	(0·64–1·51)	0·95	0·91	(0·59–1·41)	0·65
	≥50	12·0 (57/476)	15·6 (73/466)	0·86	(0·56–1·32)	0·47	0·81	(0·50–1·30)	0·37
Previous TB†	No previous TB	18·6 (118/634)	21·2 (135/636)	0·91	(0·67–1·26)	0·57	0·87	(0·59–1·27)	0·45
	Previous TB	22·8 (16/70)	25·3 (16/63)	ND	ND	ND	ND	ND	ND
BMI‡, kg/m^2	<18·5	32·8 (47/143)	34·2 (41/120)	1·00	(0·54–1·83)	0·99	1·00	(0·56–1·80)	0·99
	≥18·5	15·5 (87/561)	18·9 (109/578)	0·85	(0·61–1·19)	0·33	0·84	(0·59–1·20)	0·32
Hb¶, g/L	<80	37·3 (29/78)	50·3 (22/44)	ND	ND	ND	ND	ND	ND
	≥80	16·8 (105/626)	20·1 (91/454)	0·76	(0·49–1·19)	0·22	0·75	(0·48–1·18)	0·20

* CD4 strata: 1030 CD4<50 cells per µL (522 in control, 508 in intervention), 1992 CD4≥50 cells per µL (994 in control, 998 in intervention). †Previous TB strata: 2735 no previous TB (1380 in control, 1355 in intervention), 287 previous TB (136 in control, 151 in intervention). Six clinics (four control and two intervention) all in the previous TB stratum with zero deaths. ‡BMI strata: 591 BMI<18·5 kg/m^2 (271 in control, 320 in intervention), 2429 BMI≥18·5 kg/m^2 (1242 in control, 1187 in intervention). Two clinics (both control [C1.1, C1.7], BMI<18·5 kg/m^2) with zero deaths. 0·5 deaths added to all clinics. ¶Hb strata: in the control arm there were three clinics where >75% participants have missing Hb (C1.2, C1.6, C2.1) zero deaths and one clinic with no Hb measurements. In the control arm Hb<80 g/L strata there were two clinics with zero outcomes (C1.1, C1.2) and one clinic with a denominator of zero (C2.1). In the intervention arm with Hb<80 g/L strata there were two clinics with zero outcomes (I1.5, I1.10)

Hb=haemoglobin. BMI=body mass index. CI=confidence interval. py=person-years. HR=hazard ratio. ND=not done.

P values for interaction: CD4 0·61; BMI 0·64

Table 5: Mortality rate over 12 months, intervention vs. control arm

	Intervention n=1507)	Control (n=1515)						
	Rate/100 py (deaths/py)	**Rate/100 py (deaths/py)**	**Unadjusted HR**	**95% CI**	**P-value**	**Adjusted HR***	**95% CI**	**P-value**
Mortality rate over 12 months	13·1 (178/1314)	14·7 (187/1269)	0·97	(0·75–1·25)	0·78	0·92	(0·69–1·24)	0·57

py=person-years. HR=hazard ratio. CI=confidence interval.

* Analyses adjusted for sex, age, body mass index, CD4 count, taking isoniazid preventive therapy at baseline, tuberculosis symptoms, tuberculosis tests in last six months, previously treated for tuberculosis, and randomisation stratum.

Table 6: Details of study-defined serious adverse events with outcome recorded as fatal

Study arm	Age, sex, baseline CD4 (cells per µL)	TB treatment start (days after enrolment)	ART start (days after enrolment)	Event onset (days after enrolment)	Nature of adverse event	Description of adverse event	Relationship of event to intervention (empirical TB treatment)
Intervention AE1	31y, F, 72	not started	2	88	Pain in legs, possible peripheral neuropathy; hospitalisation	Worsening pain in legs: eventually unable to walk. Admitted to hospital 116 days post-enrolment with cough, diarrhoea, vomiting, fever, epistaxis. On examination pale, dehydrated with neck stiffness and oral candida. Hb 29 g/L. Died 118 days after enrolment. Panel-assigned CoD: non-tuberculous mycobacterial disease.	Not associated
Intervention AE2	44y, M, 86	0 (same day)	15	74	Nausea / vomiting grade 3; hospitalisation	Vomiting for about two months prior to admission, painful feet. Admitted to hospital 74 days post-enrolment with abdominal pain, vomiting and painful legs. On examination febrile (40.1°C), tachycardic (144 beats/minute), pale, bilateral coarse crackles in lung fields. Hb 55 g/L. Died 83 days after enrolment. Hospital diagnosis: lower respiratory tract infection. Panel-assigned CoD: thrombotic thrombocytopaenic purpura.	Possibly associated
Intervention AE3	36y, M, 19	0 (same day)	14	14	Pain in feet, possible peripheral neuropathy; hospitalisation	Participant reported pain in legs at the two week visit. He had started pyridoxine prior to study enrolment. He reported worsening numbness in his feet at a routine clinic visit 119 days after enrolment. Admitted to hospital 170 days after enrolment with a 10-day history of weakness and vomiting. On examination, dehydrated, wasted, pale, jaundice, epigastric tenderness. Weight 35kg. No liver function tests recorded during admission. Died 181 days post-enrolment. Hospital-assigned diagnosis: diarrhoea and difficulty breathing. No panel-assigned CoD.	Possibly associated
Intervention AE4	25y, F, 115	66	128	144	Vomiting grade 3; hospitalisation	Assigned low probability of TB at enrolment so, per study algorithm, empirical TB treatment not started. 25 days post-enrolment attended hospital out-patient department with genital ulcer, dysuria and cough. Mother reported TB treatment initiated 66 days post-enrolment, not confirmed in medical records. Started vomiting 144 days post-enrolment, admitted to hospital 146 days post-enrolment with breathlessness and vaginal swelling; she reported having seen a traditional healer. On examination cachexic, pale, breathless, labial ulcer. Died 147 days post-enrolment. Hospital diagnosis: lobar pneumonia, septic labial ulcer. No panel-assigned CoD.	Not associated; study algorithm did not assign empirical TB treatment

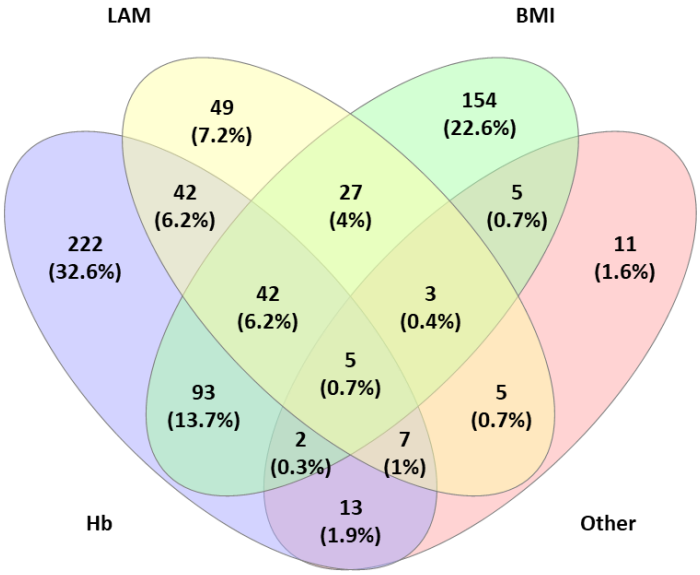
Study arm	Age, sex, baseline CD4 (cells per µL)	TB treatment start (days after enrolment)	ART start (days after enrolment)	Event onset (days after enrolment)	Nature of adverse event	Description of adverse event	Relationship of event to intervention (empirical TB treatment)
Intervention AE5	41y, M, 5	0 (same day)	NA (never started)	0	Nausea and vomiting grade 3; hospitalisation	Participant described vomiting and diarrhoea starting the same day he started TB treatment. 35 days post-enrolment clinic notes lost to follow-up from TB treatment. Admitted to hospital 48 days post-enrolment with vomiting and diarrhoea for 2 days, weak and drowsy. On examination confused, dehydrated, neck stiffness. Lumbar puncture normal. Died 48 days post-enrolment. Hospital-assigned CoD: meningitis and renal failure. Autopsy: Mtb (sensitive to isoniazid and rifampicin) isolated from liver and spleen but not CSF. Panel-assigned CoD: disseminated TB.	i) Nausea and vomiting definitely associated ii) death not associated*
Intervention AE6	32y, F, 83	0 (same day)	14	i) 64 ii) 74	i) Painful feet, possible peripheral neuropathy; ii) hospitalisation	i) Attended clinic 64 days post-enrolment, describing painful feet. Pyridoxine had been given since the start of TB treatment. ii) Admitted to hospital 74 days post-enrolment with breathlessness, weakness, chest pain and general body pain. On examination, tachycardia (pulse 122 beats/minute), afebrile, respiratory distress, bilateral crackles in lung fields. Hb 57 g/L, bicarbonate 16 mmol/L. Hospital diagnosis: gastroenteritis. Treated with intravenous antibiotics and fluids. TB treatment and ART continued. Discharged 78 days post-enrolment. Readmitted 86 days post-enrolment with chest pains and weakness of both legs. Discharged 98 days post-enrolment. No hospital file found. Died 126 days post-enrolment. No CoD information available. No panel-assigned CoD.	i) Probably associated ii) Possibly associated
Control AE7	30y, F, 48	not started	not started	i) 8 ii) unknown	i) Pain in feet, possible peripheral neuropathy; ii) hospitalisation	i) Seen in clinic 8 days post-enrolment reporting painful feet. Prescribed co-trimoxazole, co-amoxiclav, fluconazole, vitamin B complex. ii) Admitted to hospital with swollen feet; died 31 days post-enrolment. Family reported diagnosis of cervical cancer. No panel-assigned CoD.	Not applicable (control arm)
Control AE8	42y, M, 53	not started	22	166	Hepatotoxicity, hospitalisation	Pre-ART blood monitoring tests (pre-enrolment) showed ALT 570 and creatinine 1519; 9 days after enrolment these had improved (ALT 107, creatinine 145). Admitted 166 days post-enrolment with cough, fever, chest pain, yellow eyes. On examination tachycardic, hypotensive, oxygen saturation 60%. Hb 62 g/L, creatinine 541 mmol/L,	Not applicable (control arm)

Study arm	Age, sex, baseline CD4 (cells per µL)	TB treatment start (days after enrolment)	ART start (days after enrolment)	Event onset (days after enrolment)	Nature of adverse event	Description of adverse event	Relationship of event to intervention (empirical TB treatment)
						bicarbonate 8 mmol/L, ALT 167 iu/L, AST 171 iu/L, bilirubin 216 mmol/L, alkaline phosphatase 216 iu/L. 169 days post-enrolment: potassium 6·5 mmol/L, urea 75 mmol/L, creatinine 740 mmol/L, bicarbonate 4 mmol/L. Died 170 days after enrolment. Hospital-assigned diagnosis: drug-induced liver injury, possible pneumocystis pneumonia. No panel-assigned CoD.	

* One adverse event of nausea/vomiting (AE05) is recorded as definitely associated with a fatal outcome because there was no documentation of resolution. Patient was lost to follow-up from TB treatment, subsequently admitted to hospital with vomiting and diarrhoea and died 48 days post-enrolment. Hospital-assigned cause of death was meningitis and renal failure. Autopsy: *Mycobacterium tuberculosis* (sensitive to isoniazid and rifampicin) isolated from liver and spleen but not cerebrospinal fluid. Panel-assigned cause of death was disseminated TB. Therefore, the adverse event (nausea and vomiting) was considered associated, but death was considered not associated with the intervention.

Abbreviations: ALT=alanine transaminase. AST=aspartate transaminase. ART=antiretroviral therapy. CoD=cause of death. Hb=haemoglobin. TB=tuberculosis.

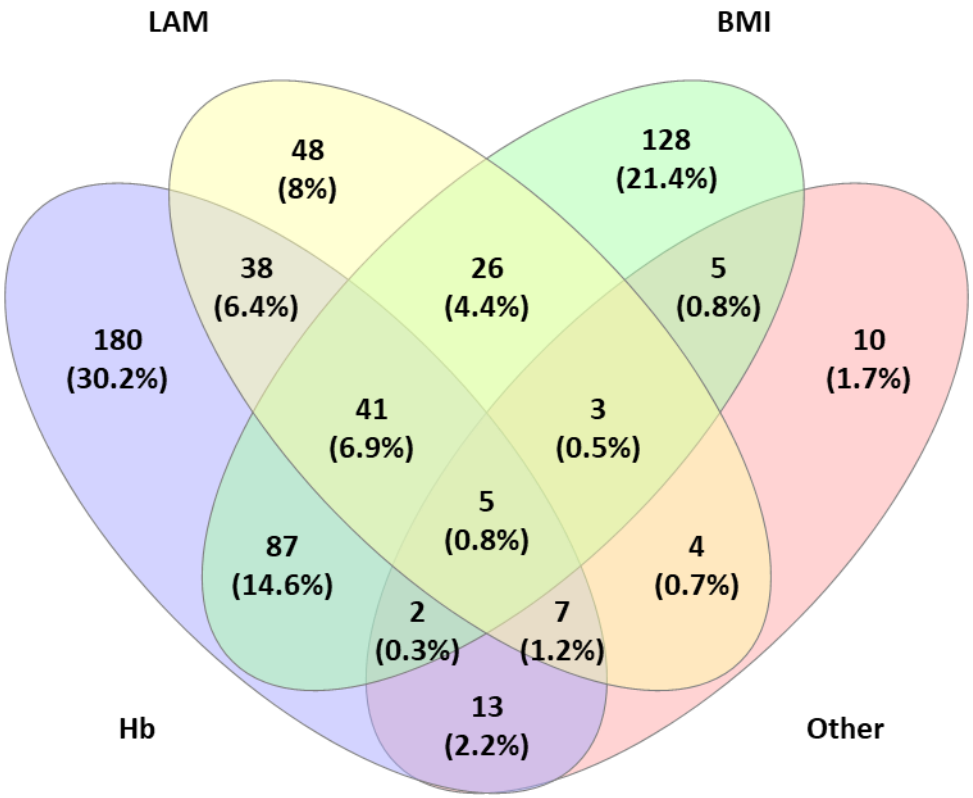
Figure 1A: Intersection between components of the intervention algorithm, intervention arm participants assigned high probability of TB (N=680)*



LAM=positive grade 1 or above on urine lipoarabinomannan lateral flow assay. BMI=body mass index <18.5 kg/m^2. Hb=haemoglobin<100g/dL. Other=evidence from chest radiograph or positive sputum test on a routine sample.

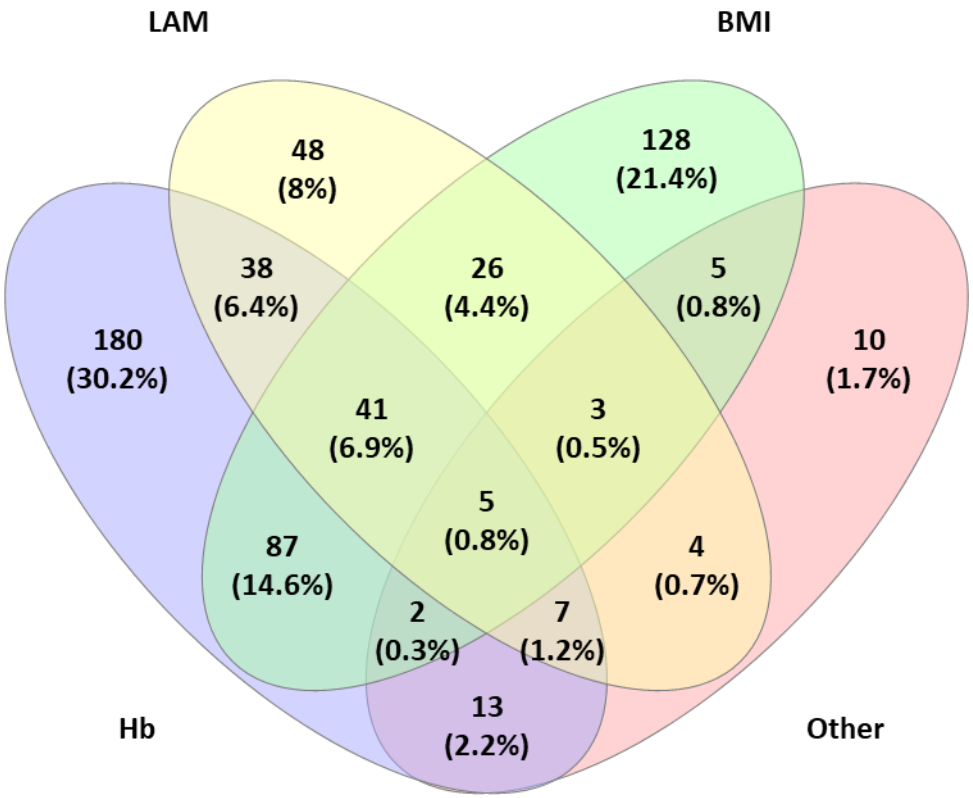
*Nine participants, not summarized in the diagram, did not meet the algorithm criteria based on urine LAM result, body mass index or haemoglobin, but were assigned high probability based on clinical judgement.

Figure 1B: Intersection between components of the intervention algorithm, intervention arm participants assigned high probability of TB, restricted to those reporting at least one TB symptom (N=597)



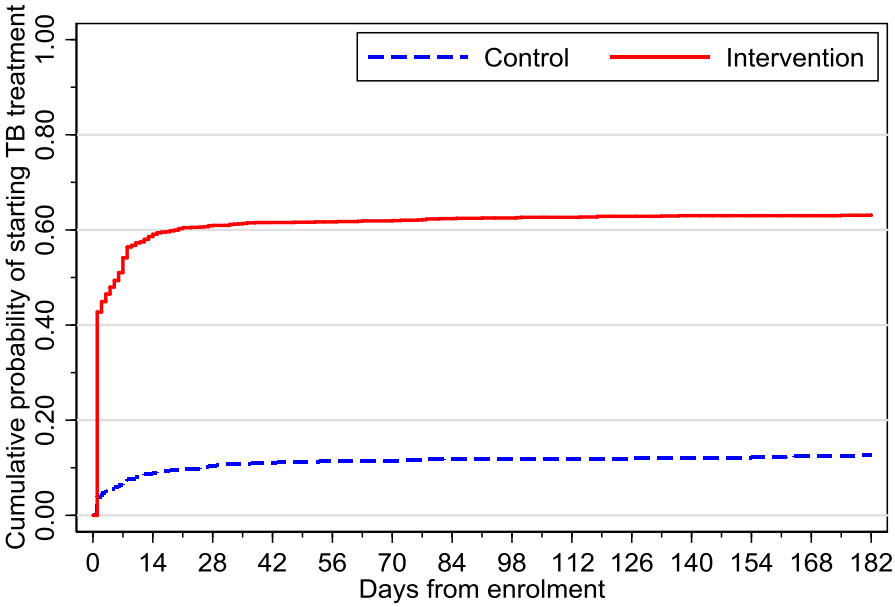
LAM=positive grade 1 or above on urine lipoarabinomannan lateral flow assay. BMI=body mass index <18.5 kg/m^2. Hb=haemoglobin<100g/dL. Other=evidence from chest radiograph or positive sputum test on a routine sample.

Figure 1C: Intersection between components of the intervention algorithm, intervention arm participants assigned high probability of TB, restricted to those reporting no symptoms (N=83)



LAM=positive grade 1 or above on urine lipoarabinomannan lateral flow assay. BMI=body mass index <18.5 kg/m^2. Hb=haemoglobin<100g/dL. Other=evidence from chest radiograph or positive sputum test on a routine sample.

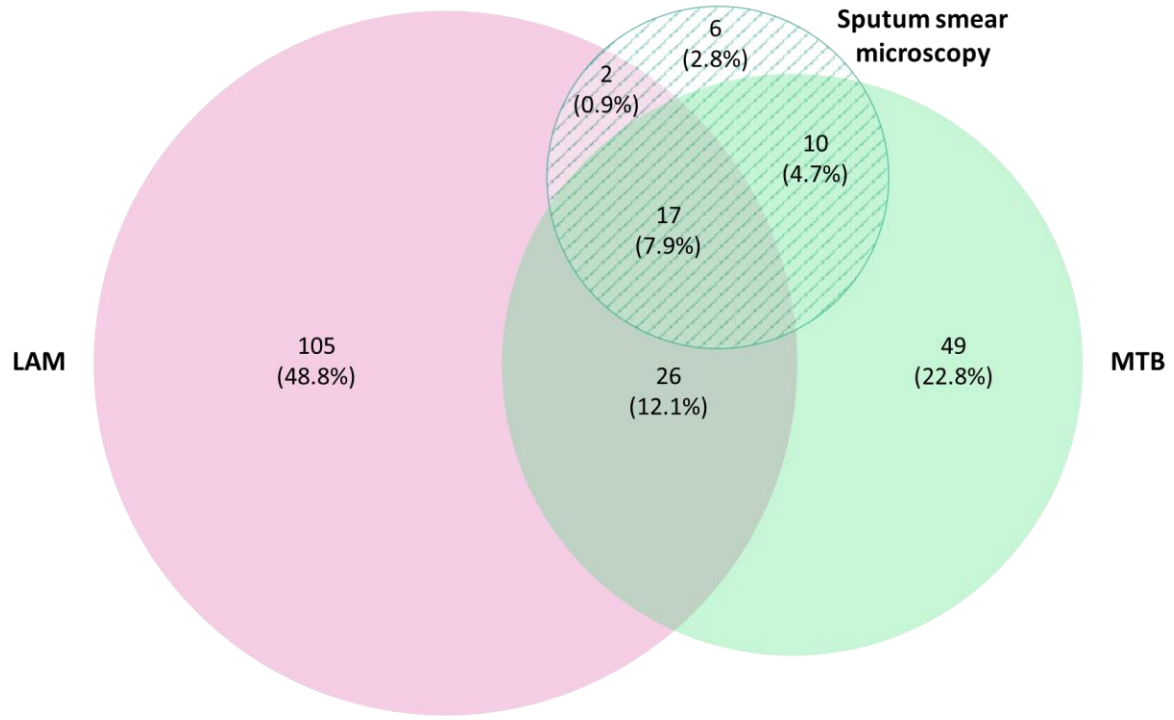
Figure 2: Time from enrolment to tuberculosis treatment start, by study arm (ignoring clustering)



Number at risk:

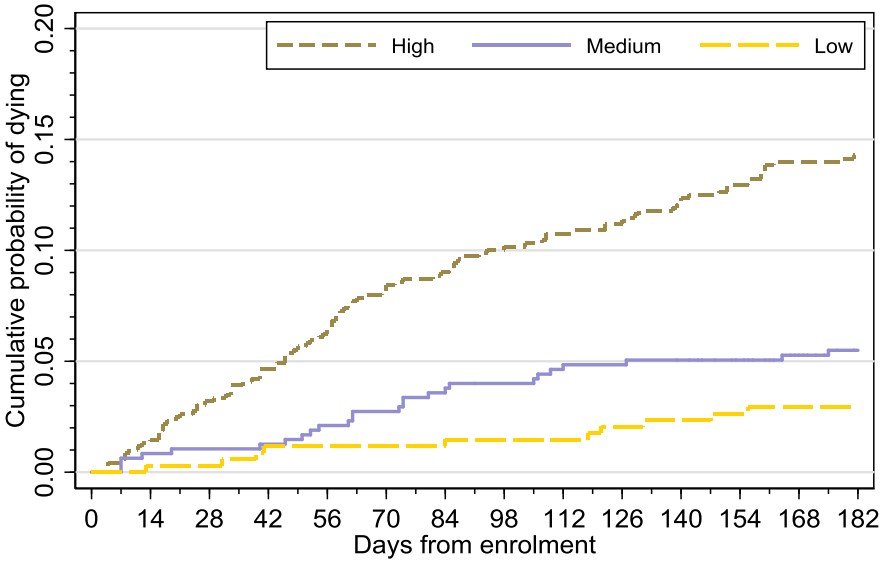
Control	1515	1321	1270	1236	1218	1198	1145
Intervention	1507	584	563	547	538	527	501

Figure 3: Intersection between sputum smear and culture results and urine LAM results, intervention arm only (N=968)



LAM=lipoarabinomannan. MTB= positive *Mycobacterium tuberculosis* culture.

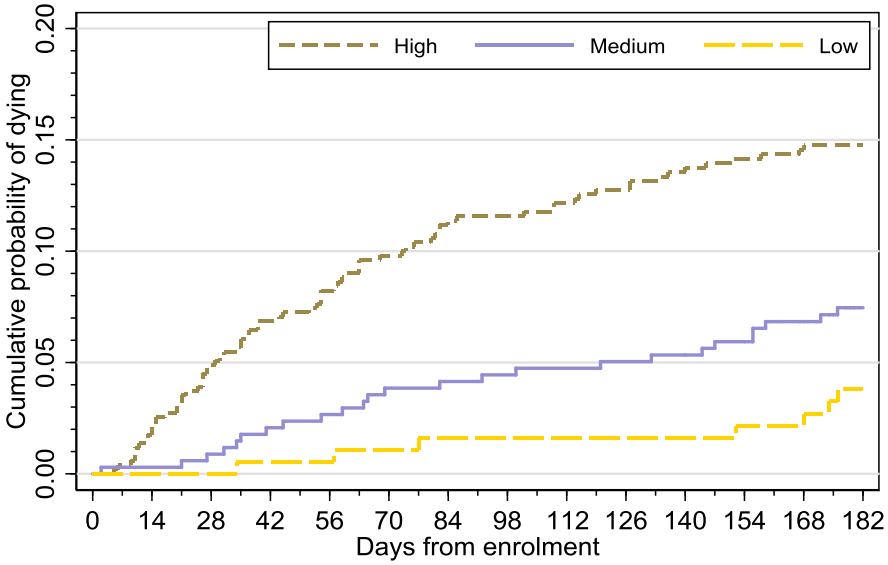
Figure 4A: Mortality by probability of tuberculosis (assigned at baseline), intervention arm only (N=1506)



Number at risk:

High	689	666	645	626	614	603	563
Medium	475	470	465	458	452	449	432
Low	342	341	336	336	335	331	319

Figure 4B: Mortality by probability of tuberculosis (at baseline, assigned retrospectively), control arm only (N=1039)



Number at risk:

High	512	485	467	452	445	437	420
Medium	339	336	328	323	320	318	305
Low	188	188	187	185	185	184	177