Tuberculosis in hospitalised patients with HIV: clinical characteristics, mortality, and implications from the STAMP trial

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Brief Summary:
322 HIV-positive inpatients with tuberculosis were characterised. 2-month mortality was 31%, and dissemination was common. Older age, being male, taking antiretroviral therapy at admission, poor nutritional status and positive urine-diagnostics were associated with mortality. Interventions to reduce mortality are needed.

Abstract:

Background: TB is the major killer of people living with HIV globally, with suboptimal diagnostics and management contributing to high case-fatality rates.

Methods: A prospective cohort of confirmed (Xpert MTB/RIF and/or Determine TB-LAM Ag positive) TB patients identified through screening HIV-positive inpatients with sputum and urine diagnostics in Malawi and South Africa (STAMP trial). Urine was tested prospectively (intervention) or retrospectively (standard of care arm). We defined baseline clinical phenotypes using hierarchical cluster analysis, and also used Cox regression analysis to identify associations with early mortality (≤56 days).

Results: Of 322 patients with TB confirmed between October 2015 and September 2018, 78.0% had ≥1 positive urine test. Antiretroviral therapy (ART) coverage was 80.2% among those not newly diagnosed, but with median CD4 count 75 cells/μL and high HIV viral loads. Early mortality was 30.7% (99/322), despite near-universal prompt TB treatment. Older age, male sex, ART before admission, poor nutritional status, lower haemoglobin, and positive urine tests (TB-LAM and/or Xpert MTB/RIF) were associated with increased mortality in multivariate analyses. Cluster analysis (on baseline variables) defined 4 patient subgroups with early mortality ranging from 9.8% to 52.5%. Although unadjusted mortality was 9.3% lower in South Africa than Malawi, in adjusted models mortality was similar in both countries (HR 0.9, p=0.729).

Conclusions: Mortality following prompt inpatient diagnosis of HIV-associated TB remained unacceptably high, even in South Africa. Intensified management strategies are urgently needed, for which prognostic indicators could potentially guide both development and subsequent use.

Keywords: HIV, TB, hospital inpatients, mortality, urine LAM, Xpert

Introduction

HIV-associated tuberculosis disease (HIV/TB) is a leading cause of mortality, accounting for 370,000 deaths globally in 2016 [1]. Much of this burden resides in patients admitted to hospitals in high HIV-prevalence settings in Africa [2]. A meta-analysis estimated that TB caused 24% of admissions and 27% of deaths amongst HIV-positive inpatients, with 30% case fatality [3]. Post-mortem data suggest an even greater burden, as almost half of fatal TB remains undiagnosed [4]. However, these data predate widespread access to antiretroviral therapy (ART) and improved diagnostics such as the Xpert MTB/RIF assay.

There remains a scarcity of data on factors associated with mortality in HIV/TB. Post-mortems suggest TB as the predominant cause of death [4], but substantial co-morbidity from other opportunistic infections and non-infectious conditions means that death *with* confirmed TB does not necessarily imply death *from* TB. Observational cohorts report low CD4 cell count and older age as associated with mortality, but these data mainly relate to ART naïve individuals, and include patients without bacteriologically-confirmed TB disease [5–7]. Disseminated HIV/TB, as indicated by MTB detection in blood or urine, is also common and is an independent predictor of mortality [8–10].

Understanding factors associated with mortality in hospitalised patients with HIV/TB in the context of high ART coverage, rapid TB diagnostics with better yield, and prompt TB treatment could help inform strategies to identify high-risk patients, and interventions to reduce mortality. Here we describe characteristics of patients diagnosed with TB from the STAMP (Screening for TB to reduce AIDS related Mortality in hospitalised Patients) randomised controlled trial of urine-based TB screening in HIV-positive inpatients in Malawi and South Africa.[11]

Our specific aims were to describe the clinical phenotypes, mortality and risk factors for mortality in hospitalised HIV/TB patients; the prevalence and mortality of disseminated TB; and the impact of ART and study site on mortality.

Methods

This prospective cohort study was nested within the STAMP trial [11,12], which recruited adult HIV-positive patients, irrespective of clinical presentation, at admission to medical wards in two hospitals in Malawi and South Africa. Upon enrolment, patients were randomised to TB screening using sputum testing alone (standard of care, SOC), or sputum and urine testing (intervention). Primary outcome was all-cause mortality at 2-months, and secondary outcomes included TB diagnosis and treatment. Patients were excluded if they had TB treatment within 12 months, isoniazid preventative therapy (IPT) within 6 months, unable to provide informed consent, or been admitted for >48 hours at the time of screening.

Trial procedures are outlined in the Supplementary Methods [11,12]. After enrolment, urine and spontaneously expectorated sputum samples were obtained and tested for TB according to trial arm. Patients allocated to the intervention arm underwent sputum testing (if produced) with Xpert MTB/RIF assay (Xpert), unconcentrated urine was tested with Determine TB-LAM Ag assay (TB-LAM), and concentrated urine was tested with Xpert [13]. Patients allocated to the SOC arm had sputum Xpert testing only: with urine immediately frozen. Clinical events during admission were recorded, and patients followed-up once at 2-months by interview. Patients not attending follow-up were contacted by telephone and/or home visit, with interview of next-of-kin to establish vital status if necessary.

Patients diagnosed with TB in the SOC trial arm (i.e. no real-time urine TB testing) had TB-LAM and Xpert testing performed on stored urine (Supplementary Methods). Patients were enrolled in this sub-study if they were diagnosed with TB and had positive laboratory tests (≥1 positive specimen on microscopy for AFB, Xpert, culture or TB-LAM) on any sample. Patients diagnosed or treated for TB without positive tests were excluded. The study was approved by the research ethics committee of the London School of Hygiene & Tropical Medicine, and local research ethics committees in Malawi and South Africa.

Definitions

Patients were defined as 'clinically suspected TB' if TB was recorded in the admitting differential diagnosis. Disseminated urinary TB was defined by any positive urine TB assay (TB-LAM or Xpert), and non-disseminated TB was a positive sputum TB assay with negative urine TB assays.
A urine 'TB score' was calculated based on the number of positive urine TB tests (TB-LAM or Xpert, possible values 0-2) [14]. The Supplementary Methods outlines other definitions.

Statistical analysis

Mortality risk was calculated 56-days from admission. All baseline demographics, clinical variables, laboratory results and physiological measurements were considered for association with mortality using Cox proportional hazards models. An explanatory model was built excluding the most proximal factors on the causal pathway to mortality (notably, functional impairment). Separate models were built to assess associations of recruitment site with mortality. Models used step-wise backward elimination (variables with $p>0.1$ were excluded) and were restricted to complete cases. Non-linearity of continuous variables was assessed using fractional polynomials.

Clinical phenotypes of HIV/TB patients were identified using unsupervised (i.e. without mortality outcome) hierarchical cluster analysis, with the number of clusters determined by stopping rules. Clusters were then described by comparing means and proportions to the overall population, and associations with mortality assessed using Kaplan-Meier curves, and Cox regression. Supplementary Methods describe the analysis in further detail.

Results

Patient characteristics

Between October 2015 and September 2017, 506 HIV-positive patients were diagnosed with TB, of whom 322 were laboratory-confirmed and included in this analysis. Similar numbers were from Malawi (155, 48.1%) and South Africa (167, 51.9%), with two-thirds (63.7%) clinically suspected to have TB (Table 1).

At admission, median CD4 cell count was 75 cells/µL, and 93% had advanced HIV (as defined by WHO). 139 (43.2%) patients had ≥1 WHO danger sign, and 77 (23.9%) had signs of sepsis. Patients had substantial functional impairment, with 165 (51.2%) being unable to perform usual activities and 74 (23.0%) assessed as severely disabled (Karnofsky score ≤40), and poor nutritional status (median BMI 18.2). Anaemia was very common, only 30 (9.3%) patients had normal haemoglobin and 62 (19.3%) had life-threatening anaemia (haemoglobin <6.5 g/dL).

267 (82.9%) patients knew their HIV status before admission, of whom 214 (80.1%) were taking ART. Median duration taking ART was 1.0 year (interquartile range [IQR] 0.3-4.2) and 68 (21.1%) were on ART for <3 months. Most (58.4% [125/214]) patients reporting current usage had been taking ART for ≥6 months, although their median CD4 cell count was only 96 cells/µL (IQR 32-319). HIV viral load results were available for 97/125 patients on ART for ≥6 months; 48 (49.5%) had >1000 copies/mL (median 557,000 copies/mL), highly suggestive of ART failure.

TB characteristics

TB diagnostic results are outlined in Table 2. Most (242/322, 75.2%) patients could provide sputum for Xpert testing. Disseminated urinary TB was common (78.0%, 251/322). When restricted to patients in the trial intervention arm, 181/212 (85.4%) patients had disseminated TB. One-third (34.2%, 86/251) of disseminated urinary TB patients were positive on both urine TB-LAM and Xpert assays.

Of 197 patients undergoing chest radiography, 107 (54.3%) were interpreted by clinicians as consistent with TB. Only four patients (8.9% of those with CSF results) were diagnosed with TB meningitis, of whom all had positive urine TB tests (3 Xpert positive, 1 TB-LAM positive).

Patients with disseminated TB were less likely to report a cough or to be clinically suspected of having TB. They were predominantly male and had more functional impairment (bedbound, unable to perform usual activities, and lower Karnofsky score); worse nutritional status (lower BMI and MUAC); were more likely to have WHO danger signs, sepsis and severe anaemia at presentation; and had lower CD4 cell counts (Table 1).

Eleven patients died before TB treatment initiation, while for those treated, median time from admission to treatment was 2 days (IQR 1 day). Four (1%) patients stopped TB treatment during hospitalisation due to treatment side-effects. Eleven patients were diagnosed with rifampicin-resistant TB: six from sputum Xpert only, four from urine Xpert only, and one on both urine and sputum Xpert.

Mortality

Overall, 99 (30.7%) patients died by 56-days. Six patients were lost to follow-up after discharge. Mortality in HIV/TB patients did not differ by STAMP trial arm (p=0.30), consistent with mortality benefit in the trial being restricted to patients with missed TB diagnoses (and therefore not included in this analysis) [11]. Median time to death was 12 days (IQR 5-27), and 71.7% (71/99) occurred during admission, with 9 (9.1%) within 48 hours and 32 (32.3%) within 7 days of admission (Supplementary Figure 1).

Mortality was lowest in patients with negative urine TB tests (19.7% by 56-day), compared to disseminated urinary TB with one (30.5%) or two (40.7%) positive urine tests (p=0.018). Reduced functional ability (lower Karnofsky score, self-reported reductions in mobility, self-care and usual activities) and poor nutritional status (MUAC and BMI) were strongly associated with mortality (Table 3). Mortality was also associated with lower CD4, haemoglobin and renal impairment, although not with WHO danger signs.

In the multivariable model (n=320, Table 3), mortality was independently associated with advancing age, male gender, lower MUAC, lower haemoglobin and higher urine TB score. CD4 cell count was not independently associated with mortality.

Not taking ART at admission was associated with a lower mortality than taking ART at admission in an unadjusted model (HR 0.6, p=0.035, Supplementary Figure 2), despite those taking ART having a lower median CD4 count (39 cells/µL [IQR 13-122] compared to 84 cells/µL [IQR 29-244]). Although unadjusted mortality was 9.3% lower in patients from the South African site, in an adjusted model mortality was similar to those patients from Malawi (adjusted hazard ratio [HR] 0.9, p=0.729, supplementary table).

Clinical Phenotype

Cluster analysis identified four distinct groups of patients based on correlation of clinical features at admission. Although not informed by outcome data, mortality differed substantially between these groups (Figure 1, HR 2.4 for group 2, 4.5 for group 3 and 6.7 for group 4 compared to group 1, p<0.001). Group 1 (lowest mortality risk, 9.8% [5/51]) were more likely to be ART naïve, have better

functional status and nutrition (higher MUAC and BMI), less severe anaemia and higher CD4 cell count. Patients in group 2 (moderate mortality risk, 22.6% [23/102]) were characterised by a longer time on ART and almost half reporting normal physical function.

Groups 3 and 4 (highest mortality risks, 37.1% [39/105] and 52.5% [31/59] respectively) patients all reported problems with usual activities, most had WHO danger signs and severe anaemia, and men predominated. Median CD4 counts were 78 and 38 cells/μl respectively. Clinical phenotype was also strongly associated with disseminated TB: groups 3 and 4 had the highest proportion of urine-positive patients (83% and 86% respectively compared to 55% in group 1, p<0.001).

Non-TB management

Broad-spectrum antibiotics (ceftriaxone, amoxicillin-clavulanic acid or co-trimoxazole) were given to 86.0% (277/322) of patients, with median duration 6 days (IQR 4-7 days). 45.1% (125/277) received two or more different antibiotics. 10.6% (10/94) of patients tested were cryptococcal antigen positive. Median duration of hospital stay was 10 days (IQR 5-15 days). Of the ART naïve patients surviving to discharge, 65.3% (49/75) commenced ART during the study, with median time to starting ART being 19 days (IQR 9-29). ART was started in 66.7% (14/21) of those who had discontinued ART, and 8.3% (1/12) ART naïve patients who died during admission.

14.8% (37/250) of patients discharged were readmitted to hospital during the 56-day follow-up, with readmission associated with higher mortality (24% vs 9%, p=0.006). Outpatient attendance was also common, with patients discharged having a median of 2 (IQR 1-4) clinic attendances by 56 days. Patients dying after discharge were less likely to attend outpatient clinics (median 0 attendances [IQR 0-1] compared to 3 [IQR 1-4] for survivors, p<0.001).

Discussion

The main findings were that two-month mortality in patients with HIV-associated TB was substantial (31%) despite good ART coverage, TB screening and prompt TB treatment. Urine diagnostic tests (likely defining disseminated TB) were positive in 78.0% of TB patients, and were associated with higher mortality. Despite most patients being established on ART, advanced immunosuppression and poor virologic control were common, and we report higher mortality in patients taking ART at TB diagnosis. Hierarchical cluster analysis defined four distinct clinical phenotypes with highly variable mortality (9.8% to 52.5%), suggesting that baseline risk-profiles could be used to prioritise patients for intensified care.

Our observed early mortality is close to that estimated for HIV-associated TB from other studies [3,15], and was high in both South Africa (25.5%) and Malawi (34.8%). This 9.3% unadjusted risk difference indicates the magnitude of effect that could be attributed to the better resources in South Africa (upper middle income) compared to Malawi (low income). Irrespective of cause of admission, HIV-positive inpatients do badly, with early mortality risks of 20-30% reported consistently for sub-Saharan Africa [16]. However, patients with disseminated TB do consistently worse than others. In the STAMP trial, for instance, HIV-positive inpatients without confirmed TB had 2-month mortality of 16.5%, below that of urine-positive TB, although similar to TB diagnosed only through sputum [11].

In this context, TB-LAM or urine Xpert positivity was associated with a severely ill clinical phenotype. This was also observed in a South African cohort, where markers of TB dissemination were associated with increased immune activation, which may contribute to mortality through tissue damage and organ dysfunction [15]. If we assume that positive urine results provide more rapid, less costly, and more sensitive equivalent of mycobacteraemia [15,17,18], then these simple prognostic markers could be used to target additional interventions to reduce mortality, as well as being used for TB diagnosis.

TB patients taking ART ≥6 months had median CD4 count of only 96 cells/μL, with half having high viral loads (median 557,000 copies/mL). This strong relationship between disseminated TB and immunosuppression in patients taking ART prior to admission suggests that urine-positive TB could be an indicator of ART treatment failure. With successful scale-up of HIV-diagnosis and ART, the case-mix of inpatients has changed from predominantly ART-naïve [19] to that reported here: 80% with a known HIV-diagnosis taking ART. Interesting, this corresponds with a reversal in the prognostic value of ART prior to TB diagnosis, from beneficial [20,21] to a risk-factor for mortality [22]. Therefore, patients with TB should be immediately evaluated and managed for virological failure. However, facilities for rapid viral load testing are not universally available in inpatient

settings [23]. Also, the impending roll-out of Dolutegravir in the region may impact the degree of ART failure seen amongst inpatients [24].

Using both regression and cluster analysis, we found more severe functional impairment, worse nutritional status and severe anaemia being associated with both higher mortality and disseminated HIV/TB. Our findings support those reported in seriously ill HIV-positive inpatients with cough, where functional impairment (but not all WHO danger signs) were associated with poor outcomes [22]. The remarkably high mortality (50%) in those reporting severe functional impairment highlights the importance of upstream interventions to prevent TB, support early diagnosis, and improve recognition of critically-ill patients in community settings. Most patients reached their critically-ill state despite attending HIV-care services: empowering patients to promptly seek care could contribute to better outcomes.

Intervening to avert mortality in HIV/TB patients after admission maybe challenging (table 4). However, only one-third of deaths occurred within 1 week, suggesting a potential window of opportunity. The best strategy for supportive care in African hospitals with high HIV and TB-prevalence remains unclear, with early fluid resuscitation leading to increased mortality in patients with sepsis [25]. Although provision of broad-spectrum antibiotics in our cohort was almost universal, resistance to first-line antibiotics in study hospitals is now commonplace, especially in *Enterobacteriaceae* through extended spectrum β-lactamases [26]. Although Schutz et al [15] found TB, rather than bacterial coinfection, as the major cause of mortality in HIV-positive inpatients, empirical antimicrobial agents have been associated with lower mortality in advanced HIV [27]. Future strategies should account for antimicrobial resistance, and also target TB related mortality, for instance trialling high-dose rifampicin and/or host-directed therapies [28,29].

Cryptococcal meningitis is also a common cause of death in advanced HIV, and may be associated with HIV/TB [30,31]. Despite exclusion of patients with altered conscious level, CrAg positivity was over 10%, supporting screening and treatment of cryptococcal infection in this population. Anaemia has previously been associated with poor outcomes in HIV/TB [32], and this was also shown in this study. There are currently no normative guidelines on managing anaemia or blood transfusion in HIV/TB, and further research is needed before recommendations can be made [33].

Almost one-third of deaths occurred after discharge, and those who died were less likely to attend outpatient clinics for follow-up. One-third of ART-naïve patients discharged alive had not commenced ART by 2-months, despite guidelines advocating early ART. This supports more intensive follow-up and support at discharge as a possible intervention to reduce mortality. Weekly follow-up

was part of an intervention which reduced mortality in patients with low CD4 counts starting ART, and warrants evaluation in HIV/TB [34].

The strengths of this study include its being nested within a TB screening trial, that management was undertaken by routine health services, and that these data reflect the high ART coverage for the Southern Africa region. Limitations include suboptimal sensitivity of the TB screening algorithms, notably for the sputum-only arm of the parent trial. Our definition of confirmed TB included some patients who were only TB-LAM positive, and we cannot exclude a small number of false positives [35,36]. Sputum induction, which has been shown to increase the yield of sputum Xpert, was not available in this study [37]. Finally, we do not have post-mortem data.

In summary, we have shown high mortality in hospitalised patients with HIV-associated TB despite current public health interventions. Urine diagnostics provide useful prognostic and well as diagnostic information, and could be used to guide the development and targeting of intensified inpatient management strategies. HIV/TB inpatients in this region now predominantly affects patients established on ART with advanced immunosuppression likely to indicate ART failure. This population will be important to meet both EndTB and UNAIDS 2020 and 2025 targets for reducing TB deaths. Early diagnosis and management of ART failure is one of several potential interventions that could improve survival of patients hospitalised with TB. Implementation is needed in parallel with further research and upstream public health interventions.

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Conflicts of Interest

J.J.v.O. reports grants from London School of Tropical Medicine and Hygiene. All other authors have no potential conflicts to disclose.

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Table 1: Baseline characteristics in laboratory confirmed HIV/TB patients, overall and stratified by disseminated urinary TB.

		All HIV/TB (n=322)		Disseminated TB				p-value[b]
				Yes (n=251)		No (n=71)		
		n	%[a]	n	%[a]	n	%[a]	
Age	Mean	37.2	10.5	36.8	10.3	38.7	11.3	0.175
Gender	Male	175	54.3%	131	52.2%	44	62.0%	0.144
	Female	147	45.7%	120	47.8%	27	38.0%	
Site	Malawi	155	48.1%	131	52.2%	24	33.8%	0.006
	South Africa	167	51.9%	120	47.8%	47	66.2%	
Smoking	Current	35	10.9%	26	10.4%	9	12.7%	0.009
	Former	77	23.9%	51	20.3%	26	36.6%	
Co-morbidity	Yes	65	20.2%	49	19.5%	16	22.5%	0.577
New diagnosis of HIV	Yes	55	17.1%	43	17.1%	12	16.9%	0.964
ART status[d]	Naïve	34	12.7%	25	12.0%	9	15.3%	
	Current	214	80.1%	165	79.3%	49	83.1%	0.167
	Interrupted	19	7.1%	18	8.7%	1	1.7%	
Time on ART (years)[e]	Median	1.5	5.0	0.9	4.2	1.6	5.2	0.962
Second-line ART [e]	Yes	6	2.8%	2	2.5%	4	4.1%	0.547
Cough	Yes	234	72.7%	175	69.7%	59	83.1%	0.026
Fever	Yes	228	70.8%	182	72.5%	46	64.8%	0.206
Night Sweats	Yes	170	52.8%	136	54.2%	34	47.9%	0.348
Weight Loss	Yes	293	91.0%	227	90.4%	66	93.0%	0.513
≥1 WHO TB symptom	positive	317	98.4%	247	98.4%	70	98.6%	0.911
Duration of illness (days)	Median	14	21	14	21	14	21	0.873
Previous TB Treatment	Yes	73	22.7%	53	21.1%	20	28.2%	0.21
EQ5D mobility	Some problems	163	50.6%	129	51.4%	34	47.9%	0.067
	Confined to bed	77	23.9%	65	25.9%	12	16.9%	
EQ5D self-care	Some problems	129	40.1%	107	42.6%	22	31.0%	<0.001
	Unable to wash/ dress	86	26.7%	75	29.9%	11	15.5%	
EQ5D usual activities	Some problems	91	28.3%	72	28.7%	19	26.8%	0.002
	Unable to perform	165	51.2%	138	55.0%	27	38.0%	
EQ5D health score	Mean	52.1	13.6	48.0	14.2	54.0	11.4	<0.001
BMI	Median	18.2	5.0	18.0	4.6	19.4	6.2	0.049
MUAC	Median	20	5.5	20	4.5	21	6.5	0.039
Karnofsky score	Median	50	10	50	20	60	20	0.001
	≤40	74	23.0%	65	25.9%	9	12.7%	0.019
Blood pressure	Median SBP	102		101		106		0.009
	Median DBP	67		66		70		0.060
Heart Rate	Mean	104.7	20.8	105.5	21.1	101.8	19.5	0.189

Respiratory rate	Mean	23.3		22.8		23.4		0.265
Oxygen saturations (%)	Median	96	4	96	4	96	4	0.991
WHO danger sign	Yes	139	43.2%	117	46.6%	22	31.0%	0.019
Sepsis	Yes	77	23.9%	69	27.5%	8	11.3%	0.005
Haemoglobin (g/dl)	Mean	8.8	27.7	8.4	26.1	10.2	28.9	<0.001
Anaemia	Severe	133	41.3%	115	45.8%	18	25.4%	
	Moderate	117	36.5%	91	77.8%	26	22.2%	0.001
	Mild	42	13.1%	27	64.3%	15	35.7%	
CD4 count	Median	74.5	182	61	157	129	295	0.002
	<100	188	58.4%	155	61.8%	33	46.5%	0.017
C- reactive protein	Median	138	112	141.5	106	117	136	0.619
WHO stage	1 or 2	35	10.9%	28	11.2%	7	9.9%	
	3	111	34.5%	78	31.1%	33	46.5%	0.052
	4	176	54.7%	145	57.8%	31	43.7%	
Clinically suspected TB	Yes	205	63.7%	147	58.6%	58	81.7%	<0.001

Data are numbers and % unless otherwise stated. [a] If variable is median represents interquartile range, if variable is mean represents standard deviation. [b] Comparing disseminated TB yes/no, calculated using Chi-squared for proportions, t-test for means and Wilcoxon rank sum for medians. [d] restricted to patients with known HIV diagnosis. [e] restricted to patients reporting current ART use. Missing data: 1 missing haemoglobin, 2 missing second-line ART regimen, 93 missing C-reactive protein. ART is antiretroviral therapy, WHO World Health Organization, EQ5D EurQol 5 Dimension, BMI Body Mass Index, MUAC mid-upper arm circumference, SBP systolic blood pressure, DBP diastolic blood pressure. Heart rate and respiratory rate are measured per minute.

Table 2: TB investigations and results

TB investigation	n=322	%
Sputum		
Sample sent for TB testing	242	75.2
Xpert positive	168	52.2
Urine		
Sample sent for TB testing	321	99.7
TB-LAM positive	209	66.1
Xpert positive	128	40.5
Any urine TB test positive	251	78.0
Urine TB score		
0	71	22.0
1	165	51.2
2	86	26.7
Chest radiography		
Underwent chest radiography	197	61.2
Clinicians report as "consistent with TB"	107	33.2
Cerebrospinal Fluid (CSF)[a]		
Tested	45	14.0
Consistent with TB	4	1.2
Rifampicin resistant TB		
Xpert rifampicin result available (sputum or urine)	223	69.3
Rifampicin resistance detected	11	4.9

% are based on all patients (n=322) as the denominator. Sputum includes study TB screening and routine clinical samples. [a]CSF testing consistent with TB includes lymphocytes with raised protein or positive Xpert. One patient missing data for CSF testing. CSF is cerebrospinal fluid, Xpert is Xpert MTB/RIF assay, TB-LAM is Determine TB-LAM Ag assay. TB score calculated based on the number of positive urine TB tests (TB-LAM or Xpert, possible values 0-2).

Table 3: Factors associated with time to death over 56 days

Characteristic		Deaths (n=99)	Mortality risk (%)	Univariable				Multivariable			
				HR	Lower CI	Upper CI	p-value	HR	Lower CI	Upper CI	p-value
Age				1.02	1.00	1.03	0.073	1.03	1.01	1.05	0.003
Sex	Female	35	23.8	1				1			
	Male	64	36.8	1.74	1.15	2.63	0.007	1.77	1.01	2.70	0.008
Site	Malawi	54	34.8	1				-			
	South Africa	44	25.5	0.78	0.53	1.16	0.217				
ART	Currently taking	80	34.3	1				*			
	Not currently taking	19	21.6	0.60	0.36	0.99	0.035				
Duration of illness											
	<7 days	28	22.6	1				*			
	>7days	71	36.2	1.77	1.14	2.74	0.008				
EQ5D mobility[#]											
	No problems	9	11.0	1				-			
	Some problems	51	31.5	3.21	1.58	6.52	<0.001				
	Confined to bed	99	50.7	6.26	3.03	12.93					
EQ5D self-care[#]											
	No problems	10	9.4	1				-			
	Some problems	47	36.4	4.63	2.34	9.17	<0.001				
	Unable to wash/dress	42	48.8	6.86	3.44	13.68					
EQ5D usual activities[#]											
	No problems	5	7.6	1				-			
	Some problems	29	32.2	5.05	1.96	13.06	<0.001				
	Unable to perform	65	39.4	6.30	2.54	15.65					
EQ5D health score[#]				0.97	0.96	0.99	<0.001	-			
BMI				0.96	0.91	1.01	0.086	-			
MUAC				0.87	0.82	0.92	<0.001	0.89	0.83	0.94	<0.001
Karnofsky[#]				0.96	0.95	0.98	<0.001	-			
WHO danger sign											
	No	51	27.9	1				-			
	Yes	48	34.8	1.34	0.90	1.99	0.146				
Haemoglobin[$] **(g/dL)**				0.86	0.80	0.93	<0.001	0.88	0.81	0.95	0.002
CD4 count (cells/µL)				0.93	0.88	0.99	0.022	*			
eGFR[$]	≥60ml/min	17	25.0	1				-			
	<60ml/min	15	51.7	2.45	1.23	4.93	0.013				
C-reactive protein[$] **(mg/L)**				1.01	1.00	1.01	0.043	-			
WHO clinical stage											
	1 or 2	7	20.0	1				-			
	3	28	25.5	1.36	0.60	3.12	0.031				
	4	64	36.4	2.14	0.98	4.66					
Able to produce sputum											
	No	32	40.0	1							

Yes	67	27.8	0.66	0.43	1.0	0.061	*			
TB-LAM										
Negative	29	25.9	1				-			
Positive	70	33.5	1.72	1.00	2.95	0.044				
Urine Xpert positive										
Negative	49	25.3					-			
Positive	50	39.4	1.91	1.28	2.87	0.002				
Urine TB score			1.84	1.05	3.24	0.024	1.41	1.03	1.91	0.025

Hazard ratios (HR) calculated using Cox proportional hazards models. Continuous variables were all modelled as linear after checking for departures from linearity. For continuous variables, HR is for every unit increase in the variable, except for CD4 count where HR is for every 50 cells/µL increase. Urine TB score was modelled as a continuous linear variable. All p-values calculated using likelihood ratio testing. [$]Missing data: 1 missing haemoglobin, 93 missing C-reactive protein, 225 missing eGFR. [#]Variable excluded from multivariable model as distal on causal pathway to death. CRP and eGFR were excluded from the multivariable model due to >25% missing data. The following variables were excluded due to collinearity: BMI was colinear with weight; WHO stage was colinear with CD4 count; TB-LAM and urine Xpert were colinear with urine TB score. All other variables with p>0.1 in univariable analysis were entered into the multivariable model using backwards stepwise elimination (variables exited the model if P>0.1), n=321. *Variables eliminated from the multivariable model. ART is antiretroviral therapy, BMI Body Mass Index, CI confidence interval, eGFR estimated glomerular filtration rate, EQ5D EurQol 5 Dimension, HR Hazard Ratio, MUAC mid-upper arm circumference, WHO World Health Organization.

Table 4: Implications and potential interventions to reduce HIV/TB mortality

Issue	Evidence for association with HIV/TB mortality	Possible interventions	Further research/ unanswered questions
ART failure	• Higher mortality in ART experienced patients • Low median CD4 counts and high viral loads in patients taking ART >6 months	• Rapid screening for virological failure at admission (eg using point-of-care HIV viral load assay) • Adherence interventions or switch to second-line ART • Integrase inhibitors (few drug-drug interactions with TB medication)	• Prevalence of HIV drug resistance • Timing of ART switch in HIV/TB patients failing ART • Optimal regimen for switching
TB during early ART	• One-fifth of HIV/TB patients were within 3 months of ART initiation • High mortality	• Improved TB screening at ART initiation • Better implementation of TB preventative therapy	• Best approach for TB screening in ART naïve patients (eg TB-LAM, Xpert and/or chest radiography) • Implementation research for TB preventative therapy
Supportive care and co-morbidities	• WHO danger signs and sepsis are common • 10% cryptococcal antigenemia • Life-threatening anaemia has high mortality • 28% of deaths after discharge	• Screening, treatment and/or prophylaxis for co-infection • Improved supportive care • More intensive follow-up post discharge from hospital	• Prevalence of bacterial co-infection and AMR • Evidence for safety and efficacy of supportive care (eg IV fluids and/or blood transfusion) • Impact of enhanced follow-up on outcomes, and frequency of visits
Identification of high risk patients	• Clinical phenotype associated with high mortality • Urine diagnostics associated with higher mortality	• Predictive tools to identify patients at higher risk of mortality who may benefit from interventions (eg clinical risk score)	• Derivation and validation of prognostic score • Use of score(s) for implementation of interventions aimed at mortality

ART is antiretroviral therapy, TB is tuberculosis, AMR is antimicrobial resistance.

Figure Legends

Figure 1: Cluster analysis clinical phenotypes of HIV/TB patients and their mortality risk

A is a heat map comparing characteristics of clinical phenotype groups (from cluster analysis) to the overall population. Overall n=317, group 1 n=51, group 2 n=102, group 3 n=105, group 4 n=59. For continuous variables (marked with *), colours represent a ratio of mean or median values for the group compared to the overall mean or median. For categorical variables, the ratio is the group proportion compared to the overall proportion. Dark purple ( ) represents a ratio >1.6, and white ( ) represents a ratio <0.4. Missing data: 1 missing haemoglobin, 2 missing second-line ART regimen, 93 missing C-reactive protein, 222 missing HIV viral load. EQ5D variables are the proportion reporting 'no problem'. Time on ART and second-line ART are restricted to patients reporting current ART use.

B Kaplan-Meier plot of time to death by clinical phenotype group. Grey dashed vertical line represents median length of hospital stay (10 days). Hazard ratio (HR) compared to group 1 is 2.4 (95%CI 0.9-6.3) for group 2, 4.5 (95%CI 1.8-11.4) for group 3 and 6.7 (95%CI 2.6-17.3) for groups, p<0.001.

Figure 1