

Early empirical TB treatment in HIV-positive patients admitted to hospital in South Africa: an observational cohort study

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Summary:

Early empirical TB treatment in HIV-positive inpatients is common, with patients having similar characteristics but higher mortality than those with microbiological confirmation of TB. This group may benefit from rapid TB diagnostics improve confirmation of TB disease and reduce over-treatment.

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Abstract

Background: Empirical TB treatment in HIV-positive inpatients is common and may undermine the impact of new diagnostics. We sought to describe empirical TB treatment and compare characteristics and outcomes with patients treated for TB after screening.

Methods: Retrospective observational cohort study of HIV-positive inpatients treated empirically for TB prior to TB screening. Data on clinical characteristics, investigations and outcomes were collected from medical records. Comparison cohorts with microbiologically-confirmed or empirical TB treatment after TB screening with Xpert MTB/RIF and urine lipoarabinomannan assays were taken from South African STAMP trial site. In-hospital mortality was compared using a competing-risks analysis adjusted for age, sex and CD4 count.

Results: Between January 2016 and September 2017, 100 patients excluded from STAMP were treated for TB empirically prior to TB screening. After enrolment in STAMP and TB screening, 240/1177 (20.4%) patients received TB treatment, of whom 123 had positive TB tests and 117 were treated empirically. Characteristics were similar among early empirically treated patients and those treated after TB screening. 50% of early empirical TB treatment was based on radiological investigations, 22% on cerebrospinal or pleural fluid testing, and 28% on clinical features alone. Only 11/100 empirically treated patients had subsequent microbiological confirmation. In-hospital mortality was lower in patients with microbiologically-confirmed TB compared to those treated empirically (adjusted sub-distribution HR 0.5, 95% CI 0.3-0.9).

Conclusions: Empirical TB treatment remains common in severely ill HIV-positive inpatients. These patients may benefit from TB screening using existing rapid diagnostics, both to improve confirmation of TB disease and reduce over-treatment for TB.

Keywords:

Tuberculosis, HIV, hospital, empirical treatment, mortality

Introduction

Tuberculosis (TB) remains an important cause of admission to hospital and mortality in HIV-positive people living in sub Saharan Africa (SSA) [1], with post-mortem studies suggesting almost half of patients who died with TB in health facilities were undiagnosed and untreated at the time of death. Sub-optimal diagnostics still drive this scenario despite substantial investment over the last two decades to improve diagnosis of HIV-associated TB, with development and implementation of Xpert MTB/RIF assay (Xpert), Xpert Ultra and urinary lipoarabinomannan antigen (LAM) testing [2].

Sputum Xpert and urine LAM testing can increase TB diagnosis and treatment in hospitalised patients, with randomised clinical trial evidence for mortality impact in patients with more advanced disease [3,4]. However, these trials excluded patients who were treated for TB within hours of their hospital admission, before screening and enrolment into the study was conducted. Given that HIV-associated TB often presents atypically, and even the best currently available diagnostics will not diagnose all patients with TB, 'empirical' treatment (prior to testing or in the absence of a positive test) is a common and potentially life-saving approach. Indeed it could be argued that requesting TB diagnostics is not warranted for patients for whom the decision to give TB treatment has already been made on the grounds of high pre-test probability [5].

However, empirical TB treatment has adverse consequences, including high cost to both patient and health system, missing other diagnoses, drug toxicity and polypharmacy, delaying antiretroviral therapy (ART) initiation, and resource implications. Empirical TB treatment may also undermine the impact of new TB diagnostics [6]. Although World Health Organization (WHO) and national algorithms for TB diagnosis include empirical TB treatment, this should follow initial diagnostic testing for TB [7].

Few data exist describing HIV-positive patients receiving early empirical TB treatment during hospitalisation. We therefore sought to describe the proportion of HIV-positive patients receiving empirical TB treatment early during hospital admission, their clinical characteristics, diagnostic modalities undertaken and outcomes, and compare to HIV-positive patients receiving TB treatment following TB screening as part of a trial and those not receiving TB treatment.

Methods

Study design and procedures

This retrospective cohort study was conducted alongside the rapid urine-based Screening for Tuberculosis to reduce AIDS-related Mortality in hospitalized Patients in Africa (STAMP) trial, Edendale hospital site in Kwazulu-Natal, South Africa. Edendale Hospital is a regional, peri-urban hospital serving a population with high HIV and TB burden. The trial design has been described in detail elsewhere [3,8]. In brief, HIV-positive adults (≥ 18 years old) admitted to medical wards were enrolled, irrespective of clinical presentation or symptoms, and randomised to one of two TB screening strategies (screening with sputum Xpert alone, or sputum Xpert plus urine LAM and Xpert testing). Patients were usually screened for trial enrolment on the day of admission (admission >48 hours prior to screening was an exclusion criteria).

Patients were excluded from STAMP if they had received TB treatment within the preceding 12 months, including TB treatment started after admission but prior to screening for the trial. TB screening was done within 24 hours of admission, and results were fed back to hospital clinicians. Clinical events during hospital admission were recorded, and the primary outcome of STAMP was mortality at 2-months. Routine diagnostics available to hospital clinicians included Xpert (sputum and non-respiratory samples, on-site), chest radiography, ultrasound and computerised tomography (CT) scanning. Mycobacterial culture was available, but samples had to be sent off-site, and was not done routinely. Urine LAM testing was not available outside the STAMP trial during the study period, although clinicians could request urine Xpert. Non-TB diagnostics included HIV viral load and cryptococcal antigen testing.

Patients were eligible for this study if they were excluded from the STAMP trial at screening due to TB treatment being commenced after admission but prior to trial screening procedures. Patients aged <18 years or HIV-negative were excluded. Patients were also excluded if TB treatment was commenced due to positive microbiological tests (ie results available prior to TB treatment). Eligible patients were identified from STAMP screening databases from 1st January 2016 to 30th September 2017. Data on demographics, clinical characteristics, routine haematological and biochemical tests, TB diagnostic modalities, TB treatment and vital status at discharge were extracted using custom designed case report forms by retrospective review of medical records, prescription charts, and

National Health Laboratory Service (NHLS) records. Patients for whom complete individual-level data linkage was not possible were excluded.

Patients enrolled in the STAMP trial between 1st January 2016 and 30th September 2017 at the Edendale hospital site were also included as a comparison group. This STAMP patient group was further subdivided based on TB treatment: (i) patients not treated for TB during hospital admission, (ii) confirmation of TB (eg positive Xpert or urine LAM) and TB treatment started, and (iii) no positive TB tests but TB treatment started empirically prior to hospital discharge.

Patient consent statement

The study was approved by the research ethics committee of the London School of Hygiene & Tropical Medicine (UK), and by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (South Africa). Patients in the STAMP trial provided written informed consent. A waiver of informed consent was granted for the early empirical TB cohort as only anonymised routinely collected data were used, and due to the retrospective nature of the study.

Statistical methods and definitions

Study entry was defined as first documented encounter with inpatient services, time of TB treatment was decision to initiate, or initiation of, anti-TB therapy (whichever was sooner). Data on the main basis of TB treatment was based on medical records. TB diagnostic results were as documented in the medical records and/or NHLS record. Broad spectrum antibiotics included at least 3 days of either ceftriaxone, co-trimoxazole (trimethoprim/sulfamethoxazole) at treatment dose, co-amoxiclav (amoxicillin-clavulanate potassium), azithromycin, piperacillin-tazobactam, imipenem or cefotaxime. A positive WHO TB symptom screen was defined as one or more of cough, fever, weight loss or night sweats. WHO danger signs were one or more of respiratory rate >30 breaths/minute, temperature >39°C, pulse >120/minute or unable to walk unaided. Microbiologically confirmed TB was defined as any positive mycobacterial culture, Xpert or urinary LAM test. Mortality is reported during hospital admission (in-hospital mortality).

Proportions were compared using chi-squared tests, means using t-tests and medians using Wilcoxon rank sum as appropriate. In-hospital mortality risk was calculated from hospital admission, and compared between different groups receiving TB treatment (early empirical TB and those enrolled in the STAMP trial and started on TB treatment) using a competing risks model, with discharge alive from hospital as a competing risk, as this has been suggested as a more appropriate method of analysing in-hospital mortality [9,10]. Models were adjusted for age, sex and CD4 cell count at admission *a priori*, and sub-distribution hazard ratios (SHR) reported to describe associations with cumulative incidence accounting for competing risks [11]. To better understand associations with in-hospital mortality, patients were divided into three groups: (i) early empirical TB treatment (excluded from the STAMP trial), (ii) enrolled in STAMP, started on TB treatment empirically with no positive TB tests, and (iii) enrolled in STAMP with confirmation of TB (ie positive Xpert or urine LAM) and started on TB treatment. Sensitivity analyses were also conducted by including those undergoing early empirical TB treatment but with subsequent microbiological confirmation in group (iii) instead of group (i). Analyses used Stata version 16, and complied fully with STROBE and RECORD guidance [12].

Results

Between January 1st 2016 and September 30th 2017, 127 (5.1%) of 2,484 HIV-positive patients admitted to medical wards received early presumptive TB treatment, and were therefore excluded from the STAMP trial (figure 1). Of 113/127 (89.0%) with medical records available, 100 started TB treatment on criteria other than positive TB microbiological tests, and were therefore included in the main analysis. During the same period, 240 (20.4%) patients enrolled in the STAMP trial were started on TB treatment during hospital admission, of whom, 123 (51.3%) had positive TB tests.

Baseline characteristics

Patients receiving early empirical TB treatment were predominantly male. At least 94.0% had a positive WHO TB symptom screen and 39.0% had at least one WHO danger sign. Median C-reactive protein (CRP) was 133mg/L and patients had advanced immunosuppression at presentation (median CD4 count 97 cells/ μ L). Baseline characteristics were similar to STAMP trial patients started on TB treatment after TB screening (both with and without positive TB tests), but more severely immunosuppressed and more likely to have danger signs than STAMP trial patients not treated for TB (median CD4 count 282 cells/ μ L and 11.6% with WHO danger signs; table 1).

TB diagnosis and treatment

In the early empirical group (n=100), TB treatment was initiated within 6 hours for 35 (35.0%) patients, and within 24 hours in 73 (73.0%) patients. Median time to TB treatment was 15 hours (IQR 5-25). In comparison, only 50/240 (20.8%) patients in the STAMP trial received TB treatment within 24 hours of admission, and median time to TB treatment was 24 hours (IQR 24-72 hours).

The basis for starting early empirical TB treatment was results of radiology in 50 (50.0%), other investigations (CSF or pleural/ascitic fluid) in 22 (22.0%) of patients, and clinical features alone in 28 (28.0%) (table 2). In total, 72/100 (72.0%) of patients had a chest radiograph interpreted by clinicians as consistent with TB, of whom 42 (58.3%) were started on TB treatment based on this. Abnormal CSF protein and/or cell counts were the reason for starting TB treatment in 19.0% of patients. 24.0% were treated for pulmonary TB, 25.0% for TB meningitis, and the remaining 51% were treated for extra-pulmonary or disseminated TB (without meningitis). The decision to start TB treatment was made by senior clinicians for 66% of patients. Among patients screened for TB in the STAMP trial, TB treatment based only on clinical features or CSF was uncommon (8.3% and 4.6% respectively, table 2).

Microbiological investigations for TB

Among patients with early empirical TB treatment, only 34 (34.0%) had sputum samples and 32 (32.0%) had non-respiratory samples tested with Xpert (table 2). 42% of patients had no microbiological TB tests performed. 11 (11.0%) had subsequent microbiological confirmation of TB; eight patients had positive sputum Xpert, one had a positive non-respiratory (lymph node aspirate) Xpert, one patient had both positive sputum and pleural fluid Xpert, and one patient subsequently had a positive non-respiratory TB culture. 23 patients had Xpert on CSF, all were negative. One patient was diagnosed with rifampicin resistance based on Xpert.

Management and outcomes

80% of early empirical TB patients received broad spectrum antibiotics during admission. Additional opportunistic infections or HIV-associated conditions were diagnosed in 60/100 patients; 27 were diagnosed with concurrent bacterial infection, eight with *Pneumocystis jirovecii* pneumonia, ten with

renal failure, six with toxoplasmosis and four with cryptococcal meningitis (all cryptococcal antigen positive from CSF). Four (4.0%) patients had positive blood cultures, three isolated *Klebsiella pneumoniae* and one *Acinetobacter baumannii*. TB was the final diagnosis at discharge or death for 97/100 patients, with only three (3%) patients having TB treatment discontinued by clinicians due to alternative diagnoses. Of the 50 patients not taking ART at admission, 38 were recorded as starting ART, of whom 14 (36.8%) started within two weeks of admission, and 22 (57.9%) started within eight weeks. Median CD4 count for those not initiating ART was 60 (IQR 38-120, n=9), and was similar to those initiating ART.

26/100 (26.0%, 95% CI 18.2-35.6) patients undergoing early empirical TB treatment died during hospital admission compared to 29/117 (24.8%, 95% CI 17.7-33.5%) of STAMP trial patients treated for TB with positive tests, 18/122 (14.8%, 95% CI 9.4-22.1%) and 68/936 (7.3%, 95% CI 5.8-9.1%) not treated for TB (table 1). Median time to in-hospital death was 6 days (IQR 3-11) in the early empirical group, and 9 days (IQR 4-14) in the STAMP trial group, with few patients dying in the first 48 hours of admission (3.0% [3/100] and 3.8% [9/239] in the early empirical and STAMP trial groups respectively). In models adjusted for age, sex and CD4 cell count, in-hospital mortality was greater for patients treated for TB compared to those not treated for TB (adjusted SHR 2.4, 95% CI 1.6-3.4), and those undergoing early empirical TB treatment compared to all STAMP trial patients treated for TB (adjusted SHR 1.4, 95% CI 0.9-2.4). Mortality was lower for patients with microbiological confirmation of TB than for patients treated empirically for TB in both the early empirical treatment group and STAMP trial patients (adjusted SHR 0.5, 95% CI 0.3-0.9, figure 2). In-hospital mortality was similar in the early empirical treatment and empirically treated STAMP trial patients (adjusted SHR 1.1, 95% CI 0.6-1.9, figure 2). Sensitivity analyses including patients undergoing early empirical TB treatment but with subsequent microbiological confirmation of TB in the 'microbiologically confirmed' group gave similar results (adjusted SHR 0.5, 95% 0.3-0.9).

Discussion

Our main findings are that early empirical TB treatment in HIV-positive patients admitted to hospital is common, and that baseline characteristics and outcomes were broadly similar to patients started on TB treatment empirically following TB screening in the STAMP trial. In this study, few patients treated empirically went on to have microbiological confirmation of TB disease, very few patients had TB treatment discontinued, and the risk of death during hospital admission was extremely high at 26%. Before and after adjusting for age, sex and CD4 cell count, in-hospital mortality was

substantially higher in empirically treated patients than those with microbiologically confirmed TB disease. Patients not receiving TB treatment had the lowest mortality.

Of all HIV-positive admissions, 5% received early empirical TB treatment, and of all patients started on TB treatment, approximately one-third underwent early empirical treatment prior to or without TB screening. This is a similar proportion to those starting TB treatment based on positive TB microbiological test results, demonstrating how common this practice is, and the high potential to impact on evaluation of new rapid, more sensitive TB diagnostics [6]. The main drivers for early empirical TB treatment were clinical features (including patients being critically unwell, and failure to respond to antibiotics) and radiology, both of which have poor specificity for TB [13–16]. Suspected TB meningitis was also common in this cohort, although none were confirmed by Xpert or culture. Xpert Ultra on CSF and urine diagnostics (LAM and Xpert Ultra) seem to have diagnostic utility in this group [17–19]. Even following TB screening, clinicians still chose to treat for TB without microbiological confirmation in half of treated cases, highlighting that diagnostics still need improvement.

Data on empirical TB treatment in hospitalised HIV-positive patients undergoing routine clinical care are scarce. Two observational studies from sub-Saharan Africa suggested that empirical TB treatment may reduce mortality in smear-negative inpatients, however these were both conducted prior to the availability of Xpert [20,21]. An Ethiopian study of Xpert-negative hospitalised patients (21% HIV-positive) found substantial overtreatment but no differences in survival [22]. Data from outpatients have also reported widespread empirical TB treatment despite good availability of Xpert, but similar clinical outcomes, including mortality, between empirically treated and microbiologically confirmed TB patients [23,24]. Furthermore, randomised trials have demonstrated that for outpatients, empirical TB treatment in advanced HIV is not superior to isoniazid preventive therapy, has no survival benefit compared to intensive TB screening, and results in significantly more adverse drug reactions [25–28].

Whilst two randomised trials have demonstrated increased diagnosis and treatment of TB and mortality reductions with urine-based TB screening, patients undergoing empirical TB treatment very early during admission were excluded [3,4]. We found only 11% of early empirical treatment patients had microbiological confirmation of disease, and almost half did not have any Xpert or

culture testing. Clinicians may not want to invest time in investigations that will not affect their management. However, this patient group would likely benefit from TB screening, for example with sputum Xpert and urine LAM assays (+/- urine Xpert), as it would increase the proportion of patients with TB microbiologically confirmed, including diagnosis of drug resistant TB. TB screening may also prevent the unnecessary prescription of TB treatment by providing more confidence in negative results. Empirical TB treatment without definitive diagnosis can cause significant harms beyond toxic effects of the drugs themselves, including economic costs to healthcare systems and to patients, missed drug resistance, delayed ART initiation and increased morbidity and mortality from other diagnoses being missed [29].

In this study, 60% of patients were diagnosed with concurrent HIV-associated diagnoses. Our finding of higher mortality in empirically treated patients than those with microbiologically confirmed TB may be partially explained by higher prevalence of TB meningitis, untreated opportunistic infections (particularly central nervous system infections given high prevalence of abnormal CSF results), comorbidities or HIV drug resistance [30]. This population could also benefit from enhanced diagnostics beyond TB co-infection alone. The early empirical TB treatment group also had a shorter median duration on ART, raising the higher risk of immune reconstitution inflammatory syndrome (IRIS) in this group. We also found delayed initiation of ART in patients undergoing early empirical treatment, with only 37% of those not already taking ART started within 2 weeks.

One argument to support empirical TB treatment is rapid treatment initiation, which has been hypothesised to potentially impact outcomes [31]. However, median time to TB treatment was similar in patients undergoing early empirical treatment and STAMP trial TB screening (15 hours versus 1 day respectively), and few deaths occurred in the first 48 hours, suggesting time gained by empirical TB treatment is likely to be negligible in the context of rapid diagnostics. However, it should be noted that neither Xpert nor culture are perfect reference standards, and the proportion of patients undergoing TB treatment without microbiological confirmation is broadly unchanged in the last decade [32]. Therefore, without more sensitive diagnostics, empirical TB treatment, especially in patients perceived to have the highest mortality risk, will continue. To improve empirical TB treatment decision-making we need a better understanding of the factors contributing to treatment thresholds, such as the local prevalence of TB, severity of illness and perceptions of performance of diagnostics [33]. Other non-microbiological tools to help guide TB treatment

decisions may be useful, for example host response signatures [34]. It is also unclear if a lack of definitive microbiological TB diagnosis has an impact on TB treatment adherence.

The strengths of this study are being nested in a large clinical trial of TB screening, which ensured all HIV-positive medical admissions were screened and accounted for, reducing the risk of bias, and providing a comparator group of patients with and without TB diagnoses. The study also reports routine clinical practice. There are also several limitations, including those inherent of the retrospective observational design. We were unable to locate medical records for 11% of patients, potentially introducing bias. There was also some missing data with regards to CD4 cell count data, and non-TB diagnoses were not confirmed beyond clinician diagnosis. Comparison groups between TB patients included and excluded from STAMP are not entirely consistent, as some patients undergoing early empirical TB treatment had subsequent microbiological confirmation, potentially resulting in bias. However, sensitivity analyses for mortality which grouped these patients with 'microbiologically-confirmed' TB following TB screening in STAMP gave almost identical results. Inherent differences between patients deemed to be too unwell or not suitable for TB screening prior to treatment may be hard to disentangle or adjust for, and data on patients overall clinical status was not available. Inpatients enrolled onto the STAMP trial were screened for TB by dedicated research nurses and outcomes in this group may be different to patients screened during routine clinical care. There was no follow-up beyond discharge, so early post-discharge deaths would be unaccounted for. The study is also a single site study. However, it does provide important data and insight into empirical TB treatment.

In conclusion, we show that early empirical TB treatment is common in severely ill HIV-positive patients presenting to hospital in a high HIV and TB burden setting. These patients may well benefit from TB screening using newer, rapid and sensitive diagnostics such as urine LAM assays or Xpert Ultra, both to improve confirmation of TB disease and reduce over-treatment for TB. A better understanding of TB treatment decision making, including the impact of diagnostics, is warranted. This population is also a priority for better diagnostics for advanced HIV, which could potentially impact their high mortality risk.

Author contribution statement

DW, KF, ELC and AGW conceived the study; CB, DW, KF, FDG, JP and AGW designed the study. CB, FDG and JP contributed to data collection; CB, AGW and DG contributed to data analysis. CB and AGW wrote the first draft, all authors contributed to revising the manuscript for intellectual content.

Data availability statement

Data are not publicly available, but are available on reasonable request to the authors subject to relevant regulatory and ethical approval

Financial support

The Screening for TB to Reduce AIDS Related Mortality in Hospitalised Patients (STAMP) trial was funded by the Joint Global Health Trials Scheme of the UK Department of Health and Social Care, the Department for International Development, the Global Challenges Research Fund, the Medical Research Council and Wellcome Trust (number MR/M007375/1). AGW has received a Royal College of Physicians London James Maxwell Grant Prohit Fellowship, and ELC has received a Wellcome Trust Fellowship (number WT200901/Z/16/Z)

Conflict of Interest

The authors have no conflicts of interest to declare

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Table 1: Baseline characteristics and outcomes

Variable		Early empirical TB treatment	Enrolled in STAMP trial and screened for TB		
			Treated for TB without positive test (empirical)	Treated for TB with positive TB tests	Not treated for TB
Number of patients		100	117	123	937
Age, mean years (SD)		36.5 (9.8) (n=100)	38.3 (10.4) (n=117)	35.7 (10.3) (n=123)	39.7 (12.0) (n=937)
Sex	Male	61 (61.0%)	67 (57.3%)	75 (61.0%)	450 (48.0%)
	Female	39 (39.0%)	50 (42.7%)	48 (39.0%)	487 (52.0%)
HIV diagnosis	New during admission	15 (15.0%)	17 (14.5%)	26 (21.1%)	147 (15.7%)
	Diagnosed prior to admission	85 (85.0%)	100 (85.5%)	97 (78.9%)	790 (84.3%)
ART status	Naive	37 (37.0%)	30 (25.6%)	43 (35.0%)	253 (27.0%)
	Currently Taking	50 (50.0%)	77 (65.8%)	68 (55.3%)	647 (69.1%)
	Interrupted/stopped	13 (13.0%)	10 (8.5%)	12 (9.8%)	37 (3.9%)
Duration on ART, median years		0.4 (0.1, 1.3) (n=40)	0.9 (0.1, 5.7) (n=73)	0.9 (0.1, 4.6) (n=66)	2.7 (0.9, 5.9) (n=627)
Previous History of TB		20 (20.0%)	44 (37.6%)	36 (29.3%)	335 (35.8%)
Cough		61 (64%)	87 (74.4%)	99 (80.5%)	489 (52.2%)
Fever		44 (46%)	84 (71.8%)	88 (71.5%)	509 (54.3%)
Night Sweats		41 (43%)	67 (57.3%)	71 (57.7%)	373 (39.9%)
Weight Loss		68 (71%)	96 (82.1%)	118 (95.9%)	638 (68.2%)

Any WHO TB symptom		90 (94%)	114 (97.4%)	123 (100.0%)	814 (86.9%)
Any WHO Danger Sign		39 (39.0%)	38 (32.5%)	53 (43.1%)	109 (11.6%)
Haemoglobin, median g/L (IQR)		102 (81, 126)	99.0 (79.5, 114.5) (n=116)	88.0 (70.0, 112.0) (n=123)	117 (95, 134) (n=933)
CD4 Count, median cells/ μ L(IQR)		97 (32, 265) (n=85)	95.0 (29.0, 250.0) (n=117)	56.0 (18.0, 171.0) (n=123)	282 (113, 489) (n=932)
CRP, median mg/L (IQR)		132.5 (54.0, 228.0) (n=72)	120.5 (50.0, 232.5) (n=112)	141.0 (84.0, 201.0) (n=119)	105.0 (72.0, 174.0) (n=25)
Creatinine, median mmol/L (IQR)		85.0 (64.0, 114.0) (n=98)	83.0 (69.0, 113.0) (n=74)	101.0 (65.0, 183.0) (n=73)	82.5 (61.0, 137.0) (n=18)
TB treatment discontinued		3 (3.0%)	2 (1.7%)	0	-
Outcome at discharge	Discharged Alive	74 (74.0%)	88 (75.2%)	104 (85.2%)	868 (92.7%)
	In-hospital death	26 (26.0%)	29 (24.8%)	18 (14.8%)	68 (7.3%)

Data represent absolute numbers unless otherwise stated. Where data are missing, the numbers of included participants are shown in the table in parenthesis. All variables are recorded at hospital admission. WHO TB symptoms are cough (of any duration), fever, night sweats or weight loss. WHO danger signs are any of respiratory rate >30/minute, heart rate of over 120/minute, temperature over 39°C or being unable to walk unaided. 2 patients are missing data on outcome (1 from the 'treated for TB with positive test' group, and one from the 'not treated for TB' group). ART antiretroviral therapy, CRP C-reactive protein, IQR interquartile range, WHO World Health Organization.

Table 2: Basis for starting TB treatment and TB test results

		Early empirical TB treatment		Enrolled in STAMP trial and screened for TB			
				Treated for TB without positive test (empirical)		Treated for TB with positive test	
		N=100	%	123	%	117	%
Basis for starting TB treatment							
Radiology		42	42.0	3	2.4	76	65.0
	Plain radiograph	19	19.0	2	1.6	49	41.9
	Ultrasound scan	3	3.0	1	0.8	19	16.2
	CT scan	5	5.0	-	-	8	6.8
Microbiological TB test		0	-	120	97.6	-	-
Lumbar puncture and CSF		19	19.0	-	-	11	9.4
Pleural or ascitic fluid		3	3.0	-	-	10	8.5
Clinical features alone		28	28.0	-	-	20	17.1
TB test results^a							
Sputum Xpert	Negative	25	73.5	30	27.8	82	100.0
	Positive	9	26.5	78	72.2	-	-
Sputum mycobacterial culture	Negative	8	88.9	11	91.7	5	100.0
	Positive	1	11.1	1	8.3	-	-
Non-respiratory Xpert ^b	Negative	30	93.8	51	53.1	62	100.0
	Positive	2	6.3	45	46.9	-	-
Non-respiratory mycobacterial culture	Negative	1	50.0	8	88.9	5	100.0
	Positive	1	50.0	1	11.1	-	-
Urine LAM ^c	Negative	-	-	27	33.3	53	100.0
	Positive	-	-	54	66.7	-	-

Data on basis for starting TB treatment are based on those reported by clinicians initiating TB treatment.

^a % denominator for TB test results is the number of patients for whom a test is performed. Test results available after decision to treat for TB in early empirical TB group. Patients may have more than TB test. ^b

Non-respiratory Xpert included CSF Xpert. ^c Urine LAM was not available for the early empirical TB treatment group. CSF cerebrospinal fluid, CT computerised tomography, LAM lipoarabinomannan, Xpert is Xpert MTB/RIF assay.

Figure 1. Flow of participants through study

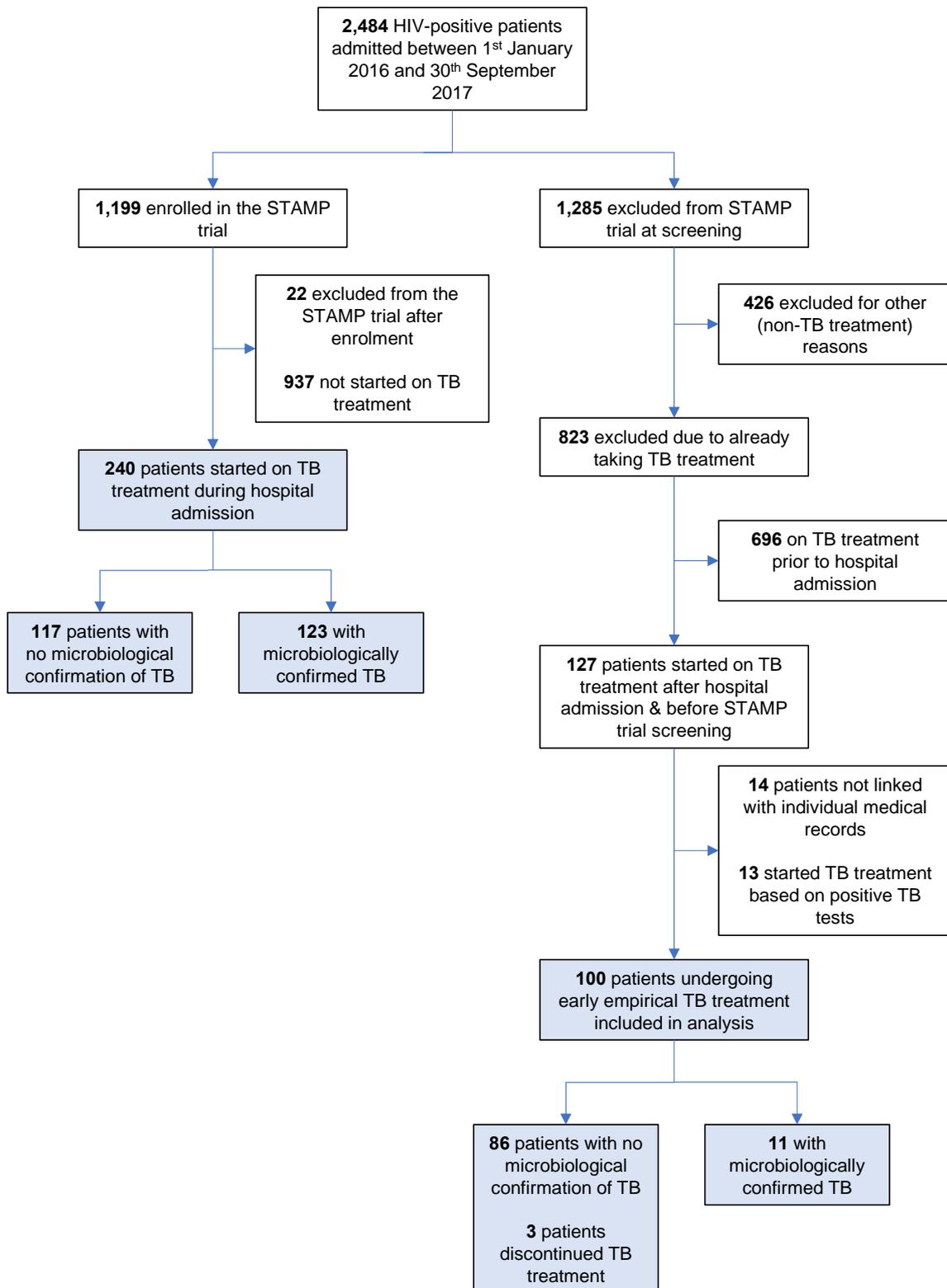
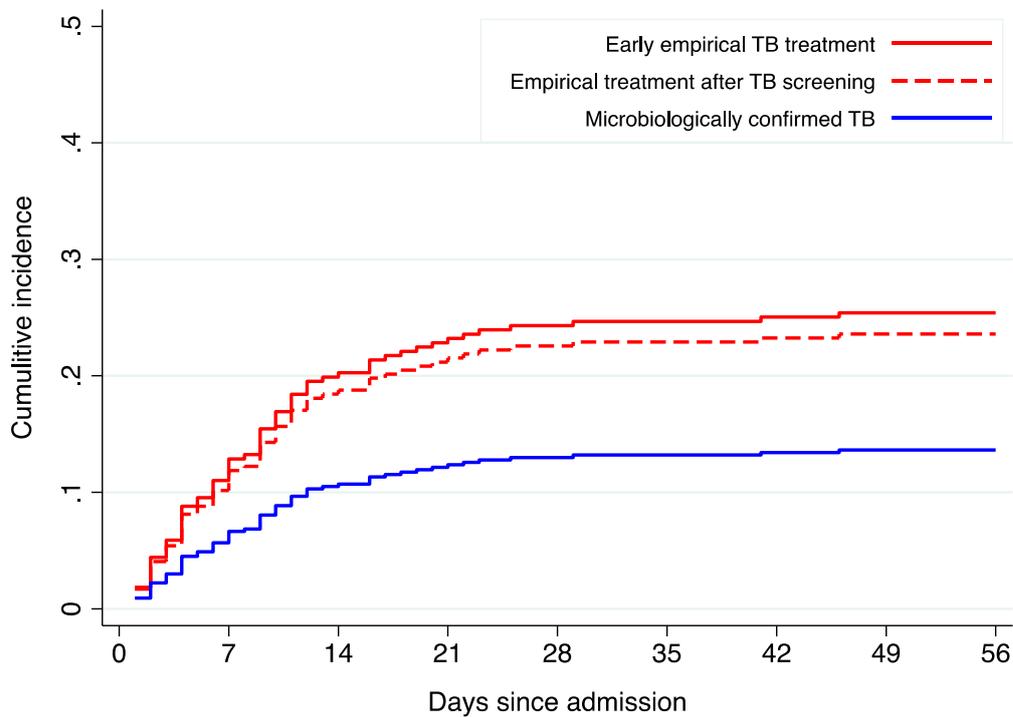


Figure 2. Cumulative incidence of in-hospital death by TB diagnosis type



Data represent cumulative incidence frequency of in-hospital death by TB treatment group, with hospital discharge as a competing risk. Model was adjusted for age, sex and CD4 count at admission to hospital (n=325). The empirical treatment after TB screening, and microbiologically confirmed groups are both patients enrolled in the STAMP trial. The early empirical TB treatment group were excluded from STAMP trial due to their having already started TB treatment. In the model, sub-distribution hazard ratio (SHR) for early empirical TB treatment is 1.09 (95% CI 0.61-1.9, ie comparing the two red line), and for microbiological confirmation is 0.52 (95% CI 0.30-0.91, p=0.02, ie comparing blue line with both red lines).