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Predictors and short-term outcomes of recurrent pulmonary tuberculosis, Uganda: a cohort study

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Abstract

Introduction—Recurrent tuberculosis (TB) occurring >2 years after completing treatment for a prior TB episode is most often due to reinfection with a new strain of *M. tuberculosis*.

Objectives—We determined the prevalence and outcome of late recurrent TB among hospitalized patients in Kampala, Uganda.

Methods—We conducted a retrospective analysis of patients admitted to Mulago Hospital who had cough of >2 weeks' duration and completed TB treatment >2 years prior to admission. All patients had mycobacterial culture performed on two sputum specimens and vital status ascertained 2-months post-enrollment. We performed logistic regression and Cox proportional hazards modelling to identify predictors of recurrent TB and survival, respectively.

Results—Among 234 patients, 84 (36%) had recurrent TB. Independent predictors included younger age (aOR=0.64, 95% CI=0.42-0.97, p=0.04), chest pain >2 weeks (aOR=3.32, 95%

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Author Contributions

Conceived and designed the experiments: NK WW AK AI JLD SDY LH AC.
Performed the experiments: SK EM PB AA.
Analyzed the data: NK DG AC JLD LH.
Contributed reagents/materials/analysis tools: LH AC JLD
Wrote the paper: NK DG KL SDY LH JLD WW AC.
Enrolled and cared for the patients included in this study: KW, NK, ZJ, SI.

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CI=1.38-8.02, p=0.007), severe weight loss ≥5 kilograms (aOR=4.88, 95% CI=1.66-14.29, p=0.004) and presence of ≥1 WHO danger sign of severe illness (aOR=3.55, 95% CI=1.36-9.29, p=0.01). Two-month mortality was 17.8% (95% CI=10.5-29.2%), and was higher among patients who were not initiated on TB treatment (aHR=16.67, 95% CI=1.18-200, p=0.04), those who were HIV-positive and not on antiretroviral treatment (aHR=16.99, 95% CI=1.17-246.47, p=0.04) and those with a history of smoking (aHR=1.20, 95% CI=1.03-1.40, p=0.02).

Conclusion—The high prevalence of late recurrent TB likely reflects high levels of TB transmission in Kampala. Increased use of empiric TB treatment and early ART treatment initiation if HIV-positive should be considered in patients with a prior history of TB, particularly if they are young, with weight loss ≥5kgs, chest pain >2 weeks or ≥1 WHO danger sign of severe illness.

Keywords

Recurrent TB; survival; treatment; Africa; Uganda

INTRODUCTION

Recurrence of tuberculosis (TB) following completion of treatment is an important but understudied problem in high-burden countries.[1-3] Recurrent TB can result from relapse of the original *M. tuberculosis* strain or from reinfection with a new strain.[4] Relapse usually occurs because of inadequate treatment whereas reinfection reflects high rates of ongoing TB transmission in at risk populations.[3, 5] Data show that the risk of recurrent TB due to reinfection is higher among HIV-positive than HIV-negative persons.[6] Thus, assessing the burden of recurrent TB and its causes in high TB-HIV incidence settings can help TB control programs determine whether limited additional resources should be focused on enhanced treatment monitoring and adherence to reduce relapse, or on TB case finding and treatment to interrupt transmission.

Molecular genotyping is the gold standard for assessing whether recurrent TB is due to relapse versus reinfection. Unfortunately, however, only a few studies in high TB burden settings have described the burden of recurrent pulmonary TB using molecular genotyping. These studies indicate that the length of time between completion of treatment and recurrence is indicative of whether recurrent disease is a result of re-infection or relapse. A study in southern India found that among patients who developed recurrent pulmonary TB one to two years following completion of treatment, the recurrence was due to relapse in 91% of HIV-uninfected patients, and was due to reinfection in 88% of HIV-infected patients.[7] In Uganda, relapse was determined to be the cause of recurrence in 80 of 98 (82%) patients presenting with another episode of TB one to two years following treatment of prior disease.[8] In contrast, among patients who developed recurrent TB > 2 years after treatment completion, molecular genotyping studies have shown reinfection to be the predominant cause.[9] In Cape Town, South Africa, a study in a predominantly HIV-uninfected population found that reinfection accounted for 12/16 (75%) cases of recurrent TB.[10] Similarly, another study from South Africa found that reinfection accounted for 23/66 (34%) recurrent TB episodes among patients who completed treatment within the prior two years but for 43/66 (65%) of recurrent TB episodes among patients who had completed treatment > 2

years earlier.[11] Studies from low-burden settings where re-infection is less likely to occur, have found that greater than 90% of relapses develop within two years of treatment completion, a key reason why Phase 3 trials of novel anti-TB drugs or regimens limit follow-up to 2 years.[12] Thus, assessing TB recurrence among patients who completed treatment for an episode of TB > 2 years earlier can serve as a proxy for reinfection.

Few studies have assessed the burden and outcome of reinfection in East Africa. Therefore, we assessed the prevalence of late recurrent pulmonary TB among hospitalized patients in Kampala, Uganda. In addition, we identified predictors and short-term mortality of late recurrent TB.

METHODS

Study design

We performed a secondary data analysis of data collected on a cohort of patients who were admitted with presumed pneumonia to Mulago Hospital in Kampala, Uganda from October 2008 to December 2013. The parent study, called the International HIV-associated Opportunistic Infections (IHOP) study, has been described in detail previously.[13-15] Briefly, IHOP was a prospective study of consecutive adults ≥18 years of age admitted to Mulago Hospital with a history of unexplained cough of two weeks' to six months' duration. Patients who had been on TB treatment within the last two years or had evidence of heart failure were excluded. At the time of enrollment, patients completed a questionnaire on demographics and clinical history. HIV testing was performed using the Ugandan Ministry of Health-approved sequential HIV-antibody testing algorithm that incorporates three rapid enzyme immunoassay kits, and CD4 cell counts were measured among those who were HIV seropositive. Smear microscopy and Lowenstein-Jensen culture were performed on two sputum samples (spot and early morning) for detection of TB. In addition, Xpert MTB/RIF testing was performed on sputum samples of patients enrolled after August 2009, and on banked sputum sediment for study participants enrolled between October 2008 and August 2009 before Xpert MTB/RIF testing was available. Test results were provided to ward clinicians who made all treatment decisions. Study staff scheduled patients for in-person follow-up at two weeks, one month and two months after enrollment to ascertain vital status, and to determine whether anti-TB and/or anti-retroviral treatment (ART) had been initiated. Study staff contacted patients or their nominated next of kin by phone to ascertain TB treatment and vital status if a follow-up visit was missed.

The parent study was approved by the institutional review boards of the University of California, San Francisco, Makerere University School of Medicine, and Mulago Hospital, as well as by the Uganda National Council for Science and Technology. All participants provided informed written consent.

For this study, we evaluated data on all patients who reported completing treatment for drug-susceptible TB >2 years prior to study enrolment. We also re-contacted patients or their next of kin to ascertain their vital status at 60 days, if this information was missing.

Outcome definitions

The primary study outcome was culture-confirmed late recurrent pulmonary TB. Patients were considered to have late recurrent TB if one or more sputum culture results were positive and confirmed by speciation testing to be *M. tuberculosis*. Patients who had contaminated or missing cultures were excluded from the analysis (Figure 1). The secondary study outcome was mortality at 60 days after enrollment.

Statistical analyses

We compared baseline demographic and clinical characteristics between patients with and without late recurrent TB using the chi-squared test for dichotomous variables and the Mann-Whitney rank sum test for continuous variables. We performed univariate logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of baseline patient characteristics with late recurrent TB; variables associated with the outcome at a $p<0.1$ were considered for inclusion in a multivariable model.[2, 16-18] Likelihood ratio testing (LRT) was used for model building and the goodness of fit test was used to assess the model fit. To determine cumulative 2-month mortality, we performed Kaplan-Meier survival analysis and log-rank tests of equality across strata for categorical predictors. Cox-proportional hazards modeling was used to identify clinical factors associated with two-month mortality. We included *a priori* known risk factors for TB-related mortality, including age, gender, history of smoking, World Health Organization (WHO) danger signs of severe illness (temperature > 39 degrees Celsius, a respiratory rate > 30 breaths per minute, a heart rate > 120 beats per minute, and being non-ambulatory because of illness),[19] HIV infection, ART and anti-TB treatment.[20-24] Likelihood ratio testing (LRT) was used for model building and the goodness of fit test to assess model fit. Cox proportional hazards assumptions were tested using the method of Schoenfeld residuals and determined to meet assumptions ($p>0.05$). The c-statistic was calculated as a standard summary measure of model performance.[25]

RESULTS

Study population

2,650 patients were enrolled into the parent IHOP study, of whom 260 had a previous history of TB and had completed treatment more than two years previously; 26 patients were excluded because of contaminated cultures (N=24) or lack of culture results (N=2). Thus, we present data on 234 patients (Figure 1). The median age was 36.9 yrs (IQR:30.8-44.2) and 58.6% were male (Table 1). The majority (68.8%) were HIV sero-positive among whom the median CD4 count was 119 (22-304) cells/uL; 46.6% were on ART at study enrolment. More than half (61.6%) had ≥1 WHO severe illness danger signs.

Prevalence and diagnosis of late recurrent TB

Overall, 84 (35.9%) patients had culture-confirmed late recurrent TB. Smear microscopy results were available for 226/234 (96.6%) and Xpert MTB/RIF results for 224/234 (95.7%) patients. Using culture results as the gold standard, compared to sputum smear microscopy, Xpert MTB/RIF had higher sensitivity (78.6%, 95% CI 68.3-86.8 vs. 65.8%, 95% CI

54.3-76.1; McNemar's X^2 test; p=0.0124 but similar specificifity (96.4%, 95% CI 91.9-98.8 vs. 95.9%, 95% CI 91.3-98.5. McNemar's X^2 exact test; p=1.000). Xpert MTB/RIF identified rifampin resistance in 3/84 (3.6%) patients with culture-confirmed late recurrent TB.

Demographic and clinical predictors of late recurrent TB

Compared to patients without late recurrent TB, patients with culture-confirmed late recurrent pulmonary TB were more likely to report severe weight loss ≥5 kilograms (75.3% vs. 55.7%, p=0.004), have chest pain ≥2 weeks (77.2% vs. 46.0%, p<0.001), have a lower CD4 count if HIV-positive (70 vs. 132 cells/μL, p=0.039), be non-ambulatory (56.9% vs. 35.7%, p=0.004), have tachycardia (28.6% vs. 9.3%, p<0.001) and have ≥1 WHO danger sign(s) of severe illness (70.8% vs. 56.4% p=0.044) (Table 1). In multivariable analysis, only younger age (aOR=0.64, 95% CI=0.42-0.97, p=0.04), chest pain >2 weeks (aOR=3.32, 95% CI=1.38-8.02, p=0.007), severe weight loss ≥5 kilograms (aOR=4.88, 95% CI=1.66-14.29, p=0.004) and presence of ≥1 WHO severe illness danger sign (aOR=3.55, 95% CI=1.36-9.29, p=0.010) remained independently associated with late recurrent TB. Inclusion of HIV infection, stratified or not by CD4 count, in the model did not alter the final effect estimates (Table 2).

Treatment of late recurrent TB

Among the 84 patients with culture-confirmed late recurrent TB, 72 (85.7%) were initiated on anti-TB treatment; 67 (79.8%) were initiated before hospital discharge based on smear or Xpert MTB/RIF testing (52 on Category I treatment regimen – rifampicin, isoniazid, ethambutol and pyrazinamide, and 15 on Category II treatment regimen – streptomycin plus category I regimen).[26] Five (5.9%) confirmed treatment initiation after hospital discharge but were uncertain of the regimen. For reasons that were unknown, 12 (14.3%) patients did not initiate treatment by two months following diagnosis.

Mortality of patients with late recurrent TB

Of the 84 patients with culture-confirmed late recurrent TB, 56 (66%) were alive, 15 (18%) were lost to follow-up and 13 (16%) had died 60 days following enrollment. Among the 69 patients for whom vital status could be confirmed, the cumulative incidence of 2-month mortality was 17.8% (95% CI=10.5-29.2). Among the 13 patients who died, 69% (n=9) had initiated anti-TB treatment – 5 on category I, 3 on category II re-treatment, 1 on an unknown TB treatment regimen – and 4 received antibiotics but no anti-TB treatment. In addition, nine of the 13 (69%) patients who died were HIV sero-positive and had a median CD4 count 20 cells/uL (IQR: 9-47); only two of nine (22%) were on ART at study enrollment.

In multivariable analysis, 2-month hazard of mortality was increased among patients who had not initiated TB treatment (aHR=16.67, 95% CI=1.18-200, p=0.04), HIV co-infected patients not on ART (aHR=16.99, 95% CI=1.17-246.47, p=0.04) and patients with one pack-year history of smoking (aHR=1.20, 95% CI=1.03-1.40, p=0.02) (Table 3). Early anti-TB treatment and ART improved survival (Figs 2 and 3). Patients with ≥1 WHO severe illness danger signs (aHR=5.92, 95% CI=0.73-48.03, p=0.096) also had increased 2-month mortality, although this did not reach pre-specified statisitical significance.

Discussion

We found that among Ugandan patients who were hospitalised with symptoms of pneumonia and who had completed TB treatment at least 2 years earlier, 36% had culture-confirmed late recurrent TB. Xpert testing was ~10% more sensitive than smear microscopy but missed ~20% of patients with culture-confirmed late recurrent TB. Patients with late recurrent TB had high short-term mortality (17.8%); the mortality rate was increased among those who had not initiated anti-TB treatment and, if HIV-infected, were not on ART. These findings highlight the high transmission rate of TB and support empirical TB treatment initiation (and early ART, if HIV positive) in patients with a remote history of prior TB and recurrent TB symptoms.

Our findings are similar to previous cohort studies from East Africa assessing the prevalence of late recurrent TB. In a large population-based cohort study of TB patients actively followed up between 1996 and 2010 in northern rural Malawi, recurrent TB developed in 41 (42%) of 98 participants who had completed TB treatment >2 years earlier.[9] In a Phase 3 vaccine trial that enrolled and prospectively followed up HIV-infected adults in Tanzania for > 5 years, TB (defined as one or more positive smear or culture results) was diagnosed in 11 of 80 participants (13.8%), at a median of 108.3 months after prior active TB.[27] A molecular genotyping study attributed 76% of recurrent episodes to reinfection.[28] As other studies have shown that the majority of recurrent TB occurring two or more years after prior treatment completion is due to reinfection,[4, 9] we can assume that the majority of cases in our study were a result of acquiring a new *M. tuberculosis* strain, even though molecular genotyping was not performed. The recent National Tuberculosis Prevalence Survey, which found that TB prevalence was nearly 2-fold higher than previously reported, indicates that TB transmission remains high in Uganda.[29] Thus, our findings support the recently revised Uganda National Strategic Plan's emphasis on enhancing case detection, through systematic screening of high-risk groups, improved utilization of current diagnostic tools, addressing key barriers in health seeking behavior, enhanced involvement of the private sector, and stepping up community engagement.[30]

More accurate diagnostics are essential to enhanced case finding. Xpert had higher sensitivity than smear microscopy, 78.6% (95% CI 68.3-86.8) vs. 65.8% (95% CI 54.3-76.1) . However, of 66 patients who received Xpert testing in real-time and had positive results, initiation of same-day treatment was missed for 7 (11%); 4 (6%) initiated TB treatment after hospital discharge and 3 (5%) did not initiate treatment during the two-month follow-up period. Xpert specificity (96.5%) in this study was lower than that reported in a large meta-analysis,[31] but is consistent with more recent studies of Xpert testing in populations with a prior history of TB,[32] Nonetheless, the positive predictive value was high (93.0%, 95% CI, 84.3%, 97.7%) given the high prevalence of recurrent TB in our population. Only 3% of our patients had RIF resistance identified by Xpert testing, which further supports reinfection, rather than relapse, as the reason for recurrent TB in the majority of patients.

Our data support the increased use of empirical treatment among hospitalised patients with a remote history of TB and symptoms suggesting recurrent TB disease, particularly when they

are HIV positive and diagnostics such as Xpert are not available. To help clinicians prioritize which patients should be treated empirically, we explored clinical characteristics associated with culture-confirmed late recurrent TB. We found that patients who had severe weight loss, chest pain for two or more weeks, and or at least one of the WHO severe illness danger signs were more likely to have late recurrent disease. It was noteworthy that these findings were consistent with a WHO recommendation regarding empirical TB treatment in patients with ≥1 WHO severe illness danger signs. Increased use of empiric treatment is particularly important given our finding that mortality was high in hospitalized patients with late recurrent TB, and earlier initiation of TB treatment appeared to reduce mortality.

A key strength of our study is that recurrent TB diagnosis was based on culture results rather than smear microscopy or Xpert MTB/RIF, which are both known to yield false-positive results due to identification of dead bacilli. Our study also had several potential limitations. Prevalence estimates from patients hospitalized at a referral facility are always likely to be higher than in the general population. Even so, our findings are similar to those reported from cohort studies in Malawi and Tanzania.[9, 27] Because our study was based on a secondary data analysis, we were limited to the data that had already been collected. As a result, we did not have information on factors that have been shown to predict recurrence, such as residual cavitary lesions, or information on drug adherence or anti-TB regimen taken during the prior episode of disease.

Conclusions and implications

Late recurrent TB was common among hospitalized patients in Uganda but was often missed by currently available rapid diagnostics. Short-term mortality was high, but reduced among those who initiated anti-TB treatment promptly, or who started ART if HIV infected. These data support early empiric treatment when Xpert testing is not available or is negative, particularly in HIV-infected patients with severe weight loss >5 kilograms, chest pain >2 weeks, ≥1 WHO severe illness danger signs. Future studies should compare outcomes of patients with presumed recurrent TB when empiric treatment is provided based on the algorithm proposed here vs. routine care.

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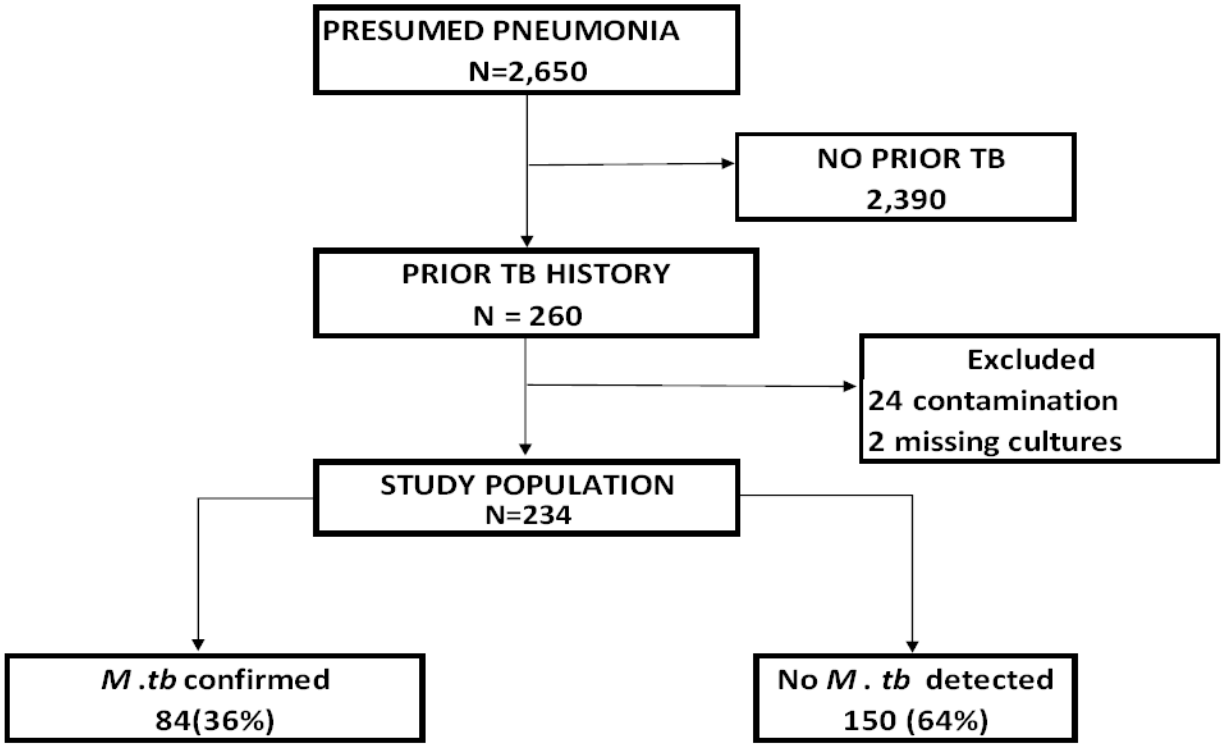

Figure 1.
STUDY POPULATION FLOW CHART

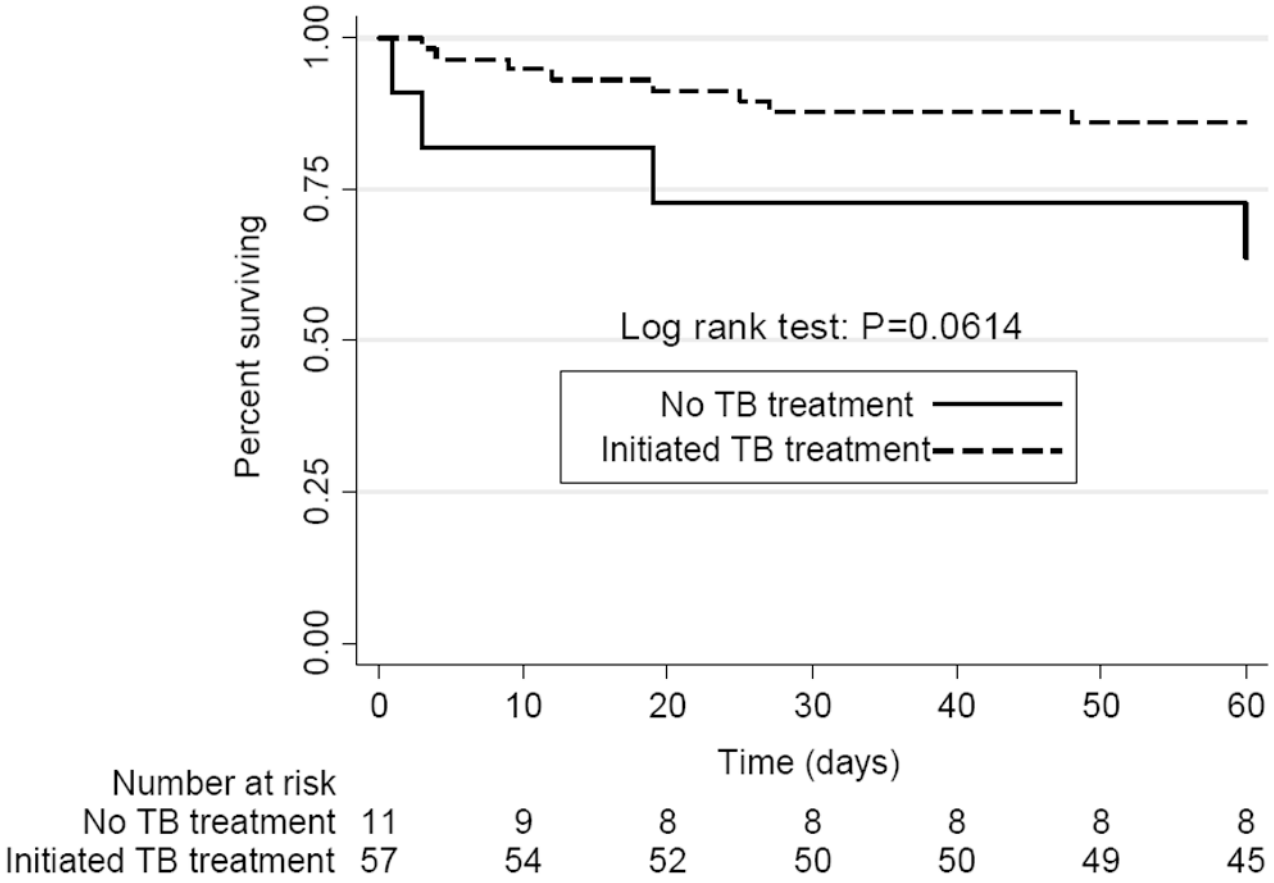

Figure 2.
Kaplan Meier log-rank survival curve by TB treatment initiation

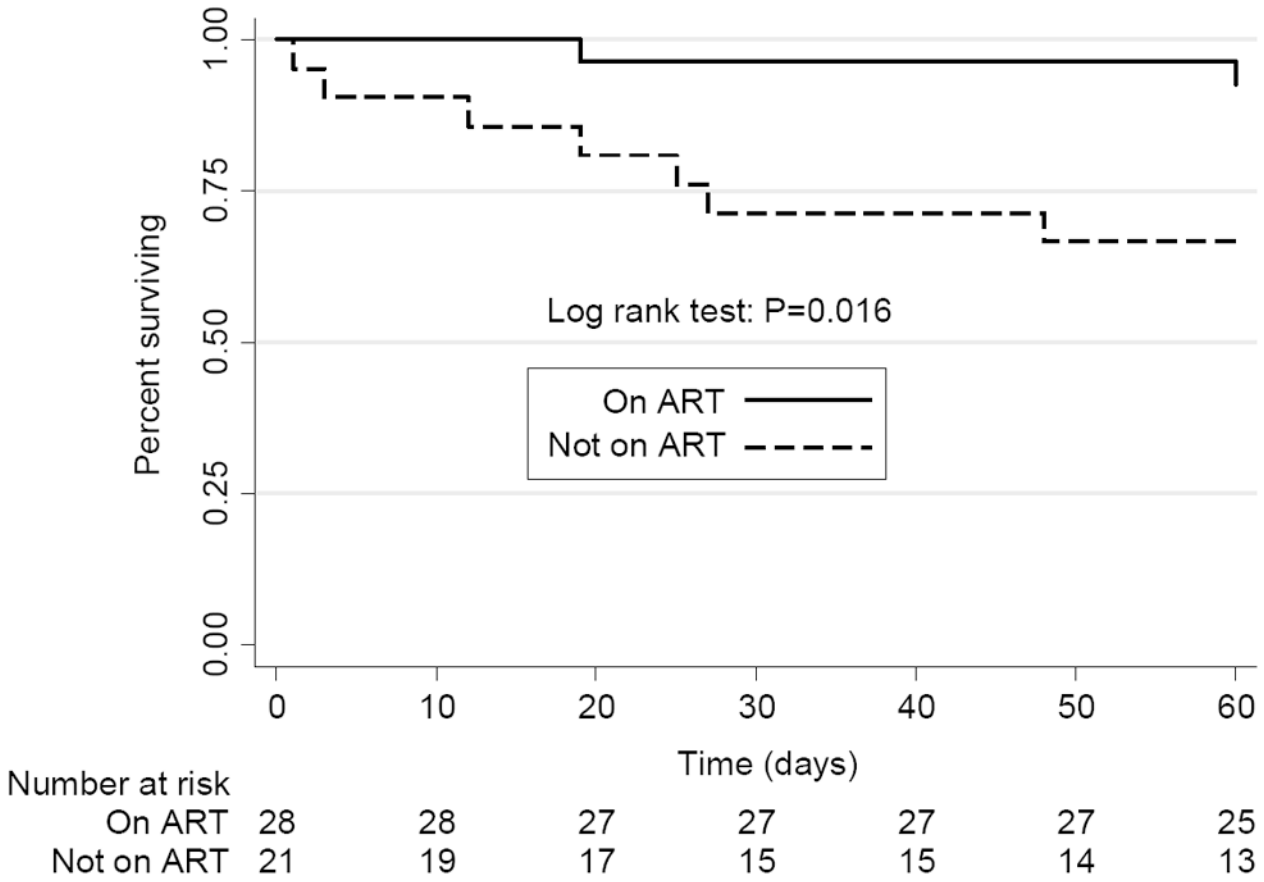

Figure 3.
Kaplan Meier log-rank survival curve by ART initiation

Table 1

Baseline characteristics of the study population and association with recurrent pulmonary tuberculosis, Uganda (2008-2013)

Characteristics	All N=234	No Recurrent TB N=150 (64%)	Recurrent TB N=84 (36%)	
	n (%)	n (%)	n (%)	p-value
Age, years, median (IQR)	36.9 (30.8-44.2)	38.1 (31.9-46.2)	34.4 (29.5-39.9)	0.083
Male	137 (58.6)	85 (56.7)	52 (61.9)	0.435
Smoking (≥ 100 cigarettes, lifetime)	77 (32.9)	48 (32.0)	29 (34.5)	0.693
Among ever smoked, pack yrs, median (IQR)	3.9 (1.5-8.4)	4.1 (1.5-8.4)	3.8 (1.2-6.4)	0.660
HIV sero-positive	161 (68.8)	102 (68.0)	59 (70.2)	0.723
Median CD4 count cells/uL (IQR)	119 (22-304)	132 (23-308)	70 (20-295)	0.039
On ART at admission (N=161)	75 (46.6)	50 (49.0)	25 (42.4)	0.415
Median years on ART (IQR)	3.2 (0.8-5.1)	3.7(0.9-5.7)	1.7(0.5-4.3)	0.191
Weight loss ≥ 5kgs (N=212) *	134 (63.2)	73 (55.7)	61 (75.3)	0.004
Chest pain >2 weeks (N=170) *	96 (56.5)	52 (46.0)	44 (77.2)	< 0.001
WHO danger signs				
Non-ambulatory, (N=198) *	86 (43.4)	45 (35.7)	41 (56.9)	0.004
Temperature > 39° Celsius	9 (3.9)	4 (2.7)	5 (6.0)	0.210
Respiratory rate >30 breaths/min	100 (42.7)	63 (42.0)	37 (44.1)	0.761
Heart rate, > 120 beats/min	38 (16.2)	14 (9.3)	24 (28.6)	< 0.001
WHO danger signs	N=198	(N=140)	N=76	
0	76 (38.4)	55 (43.7)	21 (29.2)	
≥ 1	122 (61.6)	71 (56.4)	51 (70.8)	0.044

* Missing data

Table 2

Predictors of recurrent pulmonary TB among patients admitted with suspected pneumonia

Characteristic	Unadjusted OR (95% CI) N= 234		p-value	Adjusted OR (95% CI) N=133		p-value
Age, decades	0.70	(0.54-0.92)	0.011	0.64	(0.42-0.97)	0.035
HIV sero-positive	1.11	(0.62-1.98)	0.723			
Chest pain, >2 weeks (N=170) *	3.97	(1.93-8.16)	< 0.001	3.32	(1.38-8.02)	0.007
Weight loss ≥ 5kg (N=212) *	2.42	(1.31-4.47)	0.005	4.88	(1.66-14.3)	0.004
WHO danger signs						
Non-ambulatory (N=198) *	2.38	(1.32-4.30)	0.004			
Temperature > 39 C	2.31	(0.60-8.85)	0.222			
Respiratory rate > 30	1.09	(0.63-1.86)	0.761			
Heart rate > 120	3.89	(1.88-8.03)	< 0.001			
WHO danger signs						
0	Ref			Ref		
≥1-4	1.88	(1.01-3.49)	0.045	3.55	(1.36-9.29)	0.010

* Missing data

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Table 3

Factors associated with two-month mortality among patients with recurrent pulmonary TB[1]

Characteristic	Unadjusted HR (95% CI) N=68			Adjusted HR (95% CI) N=57		
	HR	(95% CI)	p-value	aHR	(95% CI)	p-value
Age, years	0.99	(0.95-1.05)	0.982			
Male	1.91	(0.52-7.04)	0.334			
Packyears	1.03	(0.94-1.12)	0.576	1.20	(1.03-1.40)	0.018
Chestpain > 2 weeks (N=45)	2.13	(0.27-16.86)	0.472			
Weight loss ≥ 5kg (N=65)	1.46	(0.32-6.67)	0.624			
WHO danger sign category (N=57)						
0	Ref			Ref		
≥ 1-4	5.10	(0.64-39.95)	0.124	5.92	(0.73-48.03)	0.096
Missed TB treatment initiation	2.94	(0.89-10.00)	0.076	16.67	(1.18-200)	0.037
ART treatment initiated						
HIV uninfected	Ref			Ref		
HIV infected, on ART	0.41	(0.07-2.45)	0.327	0.25	(0.02-3.75)	0.319
HIV infected – No ART	2.22	(0.57-8.57)	0.249	16.99	(1.17-246.47)	0.038

[1]Conditional total effect of TB treatment initiation or non-initiation (primary or main exposure of interest) on 60-day mortality - the causal effect of interest in the analysis, and the controlled direct effect estimates of confounders (covariates) in final fit model, namely; cigarette smoking in packyears, HIV infection on ART versus not on ART, and presence of WHO danger signs of severe illness.