# Predictors and short-term outcomes of recurrent pulmonary tuberculosis in Kampala, Uganda: A cohort study

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**Background.** 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 *Mycobacterium tuberculosis*.
**Objectives.** We determined the prevalence and outcome of late recurrent TB among hospitalised patients in Kampala, Uganda.
**Methods.** We conducted a retrospective analysis of patients admitted to Mulago Hospital, who had a 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 enrolment. We performed logistic regression and Cox proportional hazards modelling to identify predictors of recurrent TB and of survival, respectively.
**Results.** Among 234 patients, 36% ($n$=84) had recurrent TB. Independent predictors included younger age (adjusted odds ratio (aOR) 0.64, 95% confidence interval (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 of ≥5 kg (aOR 4.88; 95% CI 1.66 - 14.29; $p$=0.004) and the 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 ≥5 kg, chest pain >2 weeks or ≥1 WHO danger sign of severe illness.

*S Afr Respir J* 2017;23(4):106-112. DOI:10.7196/SARJ.2017.v23i4.173

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 *Mycobacterium 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 owing 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 programmes to 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, 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 reinfection or relapse. A study in southern India found that among patients who developed recurrent pulmonary TB 1 to 2 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 found to be the cause of recurrence in 82% ($n$=80/98) of patients presenting with another episode of TB 1 - 2 years following treatment of prior disease.[8] In contrast, among patients who developed recurrent TB >2 years

after completion of treatment, molecular genotyping studies have shown reinfection to be the predominant cause.[9] In Cape Town, South Africa (SA), 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 SA found that reinfection accounted for 34% (*n*=23/66) recurrent TB episodes among patients who completed treatment within the prior 2 years but for 65% (*n*=43/66) of recurrent TB episodes among patients who had completed treatment >2 years earlier.[11] Studies from low-burden settings where reinfection is less likely to occur, have found that >90% of relapses develop within 2 years of completion of treatment, which is 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 more than 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 hospitalised patients in Kampala, Uganda. In addition, we identified the predictors and short-term mortality of late recurrent TB.

# Methods

## Study design

We performed a secondary 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 2 weeks' to 6 months' duration. Patients who had been on TB treatment within the last 2 years or had evidence of heart failure were excluded. At the time of enrolment, 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 2 weeks, 1 month and 2 months after enrolment to ascertain vital status, and to determine whether anti-TB and/or antiretroviral 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 (ref. no. 2006-017 SOMREC), and Mulago Hospital, as well as by the Uganda National Council for Science and Technology (ref. no. HS259). 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 to be *M. tuberculosis* by speciation testing. Patients who had contaminated or missing cultures were excluded from the analysis (Fig. 1). The secondary study outcome was mortality at 60 days after enrolment.

## Statistical analyses

We compared baseline demographic and clinical characteristics between patients with and without late recurrent TB using the $\chi^2$ 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*-value <0.1 were considered for inclusion in a multivariate 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 the cumulative 2-month mortality, we performed Kaplan-Meier survival analysis and log-rank tests of equality across strata for categorical predictors.

Cox proportional hazards modelling was used to identify clinical factors associated with 2-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°C, a respiratory rate of >30 breaths per minute, a heart rate of >120 beats per minute, and being non-ambulatory because of illness),[19] HIV infection, ART and anti-TB treatment.[20-24] 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]

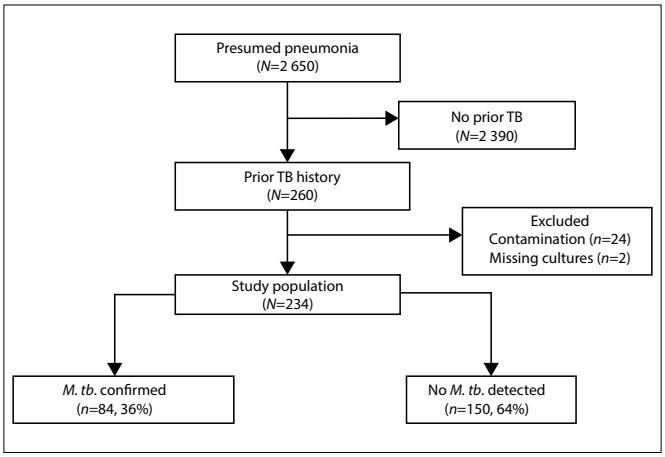


*Fig. 1. Study population flow chart.*

# Results

## Study population

A total of 2 650 patients were enrolled into the parent IHOP study, of whom 260 had a previous history of TB and had completed treatment >2 years previously; 26 patients were excluded from the study owing to contaminated cultures (*n*=24) or lack of culture results (*n*=2). Thus, we present data on 234 patients (Fig. 1). The median (interquartile range (IQR)) age was 36.9 (30.8 - 44.2) years and 58.6% were male (Table 1). The majority of the participants (68.8%) were HIV-seropositive with a median (IQR) CD4 cell count of 119 (22 - 304) cells/uL; 46.6% were on ART at enrolment into the study. More than half (61.6%) had ≥1 WHO severe illness danger signs.

## Prevalence and diagnosis of late recurrent TB

Overall, 35.9% of patients (*n*=84) had culture-confirmed late recurrent TB. Smear microscopy results were available for 96.6% (*n*=226/234) and Xpert MTB/RIF results for 95.7% (*n*=224/234) patients. Using culture results as the gold standard, Xpert MTB/RIF had higher sensitivity (78.6%; 95% CI 68.3 - 86.8 v. 65.8%; 95% CI 54.3 - 76.1; McNemar's $\chi^2$ test $p$=0.0124) but similar specificifity (96.4%; 95% CI 91.9 - 98.8 v. 95.9%; 95% CI 91.3 - 98.5; McNemar's $\chi^2$ exact test; $p$=1.000) when compared with sputum smear microscopy. Xpert MTB/RIF identified rifampicin resistance in 3.6% (*n*=3/84) of patients with culture-confirmed late recurrent TB.

## Demographic and clinical predictors of late recurrent TB

Compared with patients without late recurrent TB, patients with culture-confirmed late recurrent pulmonary TB were more likely to report severe weight loss of ≥5 kg (75.3% v. 55.7%; $p$=0.004), have chest pain ≥2 weeks (77.2% v. 46.0%; $p$<0.001), have a lower CD4 cell count if HIV-positive (70 v. 132 cells/μL; $p$=0.039), be non-ambulatory (56.9% v. 35.7%; $p$=0.004), have tachycardia (28.6% v. 9.3%; $p$<0.001) and have ≥1 WHO danger signs of severe illness (70.8% v. 56.4%; $p$=0.044) (Table 1). In multivariate 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 of ≥5 kg (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 cell 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, 85.7% (*n*=72) were initiated on anti-TB treatment; 79.8% (*n*=67) were initiated before hospital discharge based on smear or Xpert MTB/RIF testing (52 were on the category I treatment regimen – rifampicin, isoniazid, ethambutol and pyrazinamide – and 15 were on the category II treatment regimen – streptomycin plus category I regimen).[26] Five (5.9%) confirmed treatment initiation after

**Table 1. Baseline characteristics of the study population and association with recurrent pulmonary TB, Uganda (2008 - 2013)**

| Characteristics | All (*N*=234), *n* (%)* | No recurrent TB (*N*=150), *n* (%)* | Recurrent TB (*N*=84), *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 |
| 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-seropositive | 161 (68.8) | 102 (68.0) | 59 (70.2) | 0.723 |
| CD4 cell count (cells/uL), median (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 |
| Years on ART, median (IQR) | 3.2 (0.8 - 5.1) | 3.7 (0.9 - 5.7) | 1.7 (0.5 - 4.3) | 0.191 |
| Weight loss ≥5 kg (*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 °C | 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 bpm | 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 |

TB = tuberculosis; IQR = interquartile range, ART = antiretroviral therapy.
*Unless otherwise specified.
†Persons who reported smoking at least 100 cigarettes or more in a lifetime at the time of enrolment.
‡Missing data.

hospital discharge but were uncertain of the regimen. For unknown reasons, 14.3% (*n*=12) of patients did not initiate treatment at 2 months following diagnosis.

### Mortality of patients with late recurrent TB

Of the 84 patients with culture-confirmed late recurrent TB, 66% (*n*=56) were alive, 18% (*n*=15) were lost to follow-up and 16% (*n*=13) had died 60 days after enrolment. 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, 69% (*n*=9/13) of patients who died were HIV-seropositive and had a median (IQR) CD4 cell count of 20 (9 - 47) cells/uL, only 22% (*n*=2/9) were on ART at study enrolment.

In multivariate analysis, the 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 who were not on ART (aHR 16.99; 95% CI 1.17 - 246.47; *p*=0.04) and patients with 1 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 statistical 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

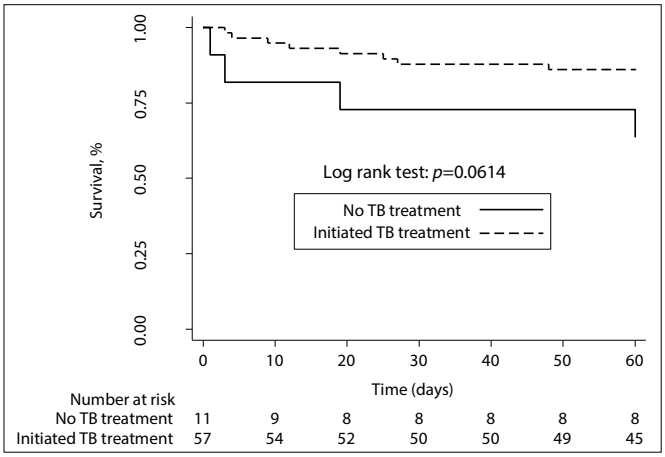


*Fig. 2. Kaplan Meier log-rank survival curve by TB treatment initiation.*

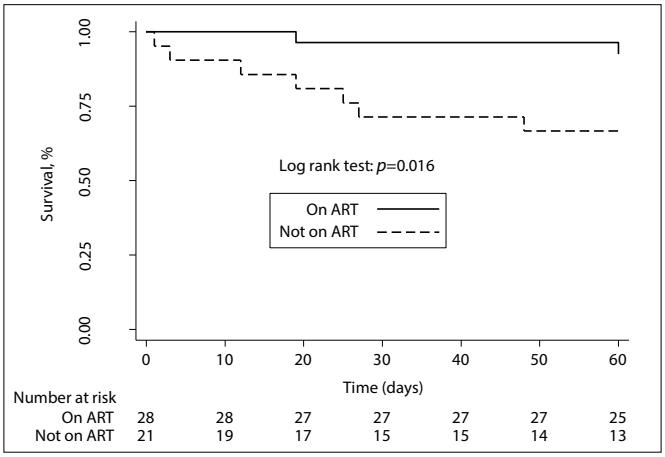


*Fig. 3. Kaplan Meier log-rank survival curve by ART initiation.*

**Table 2. Predictors of recurrent pulmonary TB among patients admitted with suspected pneumonia**

| Characteristics | OR (95% CI), (*N*=234) | *p*-value | aOR (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-seropositive | 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 ≥5 kg (*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 breaths/min | 1.09 (0.63 - 1.86) | 0.761 | | |
| Heart rate >120 bpm | 3.89 (1.88 - 8.03) | <0.001 | | |
| WHO danger signs | | | | |
| 0 | Ref | | Ref | |
| ≥1 | 1.88 (1.01 - 3.49) | 0.045 | 3.55 (1.36 - 9.29) | 0.010 |

TB = tuberculosis; OR = odds ratio; aOR = adjusted odds ratio; WHO = World Health Organization; bpm = beats per minute; Ref = 1.
*Missing data.

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 who were actively followed up between 1996 and 2010 in northern rural Malawi, recurrent TB developed in 42% (*n*=41/98) of 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 13.8% (*n*=11/80) of participants 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 ≥2 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 twofold 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 utilisation of current diagnostic tools, addressing key barriers in health-seeking behaviour, 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, i.e. 78.6% (95% CI 68.3 - 86.8) v. 65.8% (95% CI 54.3 - 76.1), respectively. However, of the 66 patients who received Xpert testing in real-time and had positive results, initiation of same-day treatment was missed for 11% (*n*=7); 6% (*n*=4) initiated TB treatment after hospital discharge and 5% (*n*=3) did not initiate treatment during the 2-month follow-up period. Xpert specificity (96.5%) in this study was lower than that reported in a large meta-analysis by Steingart *et al.*[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 prioritise 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 ≥2 weeks, and 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 empirical treatment is particularly important given our finding that mortality was high in hospitalised patients with late recurrent TB, and that earlier initiation of TB treatment appeared to reduce mortality.

### Study strengths and limitations

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 owing to identification of dead bacilli. Our study also had several

**Table 3. Factors associated with 2-month mortality among patients with recurrent pulmonary TB***

| Characteristics | HR (95% CI) (*N*=68) | *p*-value | aHR (95% CI) (*N*=57) | *p*-value |
|---|---|---|---|---|
| Age, decades | 0.99 (0.58 - 1.70) | 0.982 | | |
| Male | 1.91 (0.52 - 7.04) | 0.334 | | |
| Pack-years | 1.03 (0.94 - 1.12) | 0.576 | 1.20 (1.03 - 1.40) | 0.018 |
| Chest pain >2 weeks (*N*=45) | 2.13 (0.27 - 16.86) | 0.472 | | |
| Weight loss ≥5 kg (*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 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 |

TB = tuberculosis; HR = unadjusted hazard ratio; CI = confidence interval; aHR = adjusted hazard ratio; WHO = World Health Organization; Ref = 1; ART = antiretroviral therapy.
*Table shows the conditional total effect of TB treatment initiation (main exposure of interest) on 60-day mortality (outcome), and the adjusted direct effect estimates of of smoking, HIV infection (on ART v. not on ART), and the presence of WHO danger signs of severe illness.

potential limitations. Prevalence estimates from patients who were hospitalised 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 disease episode.

## Conclusions and implications

Late recurrent TB was common among hospitalised 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 they were HIV-infected. These data support early empirical treatment when Xpert testing is not available or is negative, particularly in HIV-infected patients with severe weight loss (>5 kg), chest pain for >2 weeks and ≥1 WHO severe illness danger signs. Future studies should compare outcomes of patients with presumed recurrent TB when empirical treatment is provided based on the algorithm proposed here v. routine care.

**Acknowledgements.** We would like to thank the Mulago Hospital administration, healthcare providers, and patients for their support and participation in the study. We also would like to thank the staff and administration of the Infectious Diseases Research Collaboration and the Uganda National TB Reference Laboratory for making this study possible. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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

**Funding.** The research was supported by the Training in Clinical Research programme at the University of California San Francisco, that was made possible by the Fogarty International Center of the National Institutes of Health under the Award Number D43 TW010037 as well as NIH K24HL087713 (LH), R01HL090335 (LH), K23HL094141 (AC), K23AI080147 (JLD), R21AI101714 (JLD), K12 HL090147-04 (NDW), and U2RTW0006879 (COHRE).

**Conflicts of interest.** None.

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*Accepted 31 August 2017.*