

## High Mortality Associated with Retreatment of Tuberculosis in a Clinic in Kampala, Uganda: A Retrospective Study

Carlos Acuña-Villaorduña, Irene Ayakaka, Scott Dryden-Peterson, Susan Nakubulwa, William Worodria, Nancy Reilly, Jennifer Hosford, Kevin P. Fennelly, Alphonse Okwera, and Edward C. Jones-López\*

*Section of Infectious Diseases, Department of Medicine, Boston Medical Center and Boston University School of Medicine, Boston, Massachusetts; Makerere University–Boston Medical Center Research Collaboration, Kampala, Uganda; Division of Infectious Diseases, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; Medical Research Council–Uganda Virus Research Institute, Uganda Research Unit on AIDS, Entebbe, Uganda; Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; Section of Infectious Diseases, Department of Medicine, New Jersey Medical School–Rutgers University, Newark, New Jersey; Division of Infectious Diseases and Global Medicine, Department of Medicine, University of Florida, Gainesville, Florida; Mulago Hospital Tuberculosis Clinic, Mulago Hospital, Kampala, Uganda*

**Abstract.** The World Health Organization recommends for tuberculosis retreatment a regimen of isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S) for 2 months, followed by H, R, E, and Z for 1 month and H, R, and E for 5 months. Using data from the National Tuberculosis and Leprosy Program registry, this study determined the long-term outcome under programmatic conditions of patients who were prescribed the retreatment regimen in Kampala, Uganda, between 1997 and 2003. Patients were traced to determine their vital status; 62% (234/377) patients were found dead. Having  $\leq 2$  treatment courses and not completing retreatment were associated with mortality in adjusted analyses.

### INTRODUCTION

Each year, 10–20% patients with tuberculosis (TB) in low- and middle-income countries present with previously treated TB and are started on therapy empirically with a standardized retreatment (Category II) regimen after failing, interrupting, or relapsing from prior treatment.<sup>1–3</sup> Following World Health Organization (WHO) guidelines, the National Tuberculosis and Leprosy Program (NTLP) in Uganda recommends a regimen of isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S) for 2 months, followed by H, R, E, and Z for 1 month and H, R, and E for 5 months.<sup>1</sup> Whereas the overall effectiveness of this regimen is 60–70%, there is widespread concern for amplification of resistance and suboptimal cure rates especially in settings with prevalent drug-resistant TB (DR-TB).<sup>1,4,5</sup> Most studies report outcomes at the conclusion of treatment, so very little is known about the long-term survival of TB retreatment patients.<sup>1,6</sup> As part of a larger program for management of DR-TB in Uganda,<sup>1</sup> we report here on the long-term outcomes of patients receiving TB retreatment in programmatic conditions.

### METHODS

We conducted a retrospective study of TB patients who received retreatment at the Mulago Hospital NTLP clinic, which serves as the largest treatment clinic in Kampala and the national referral center (approximately one-third of attendees are referral cases). Uganda is a high-burden country with an estimated annual TB incidence rate of 350 cases per 100,000 in 2003; 39% with human immunodeficiency virus (HIV) infection and a prevalence of multidrug-resistant TB (MDR-TB) of 4.4% in retreatment cases.<sup>7</sup> During the study period, the Mulago Hospital NLTP clinic treated

3,500–4,000 TB patients every year, of which ~65% were acid-fast bacilli (AFB) smear positive and 10% were retreatment cases. We reviewed the Mulago NTLP registry to identify patients fulfilling WHO criteria for category II treatment (relapse, treatment failure, or default)<sup>2</sup> between January 1997 and June 2003, residing within a 30-km radius of the clinic. We obtained demographic data, HIV status, and previous TB history from Mulago TB clinic medical records on eligible participants.

From August 2005 to October 2006, a team of experienced home visitors traced each patient to their home commencing with those closest to the clinic and following outward concentric rings until study completion. After signing informed consent, patients found alive were asked about TB symptoms and referred to care if symptomatic. In patients found deceased, a death certificate was reviewed. Patients not found at their residence were located by asking their neighbors and community leaders and, if within the study limits, were visited at their new address. We performed a proportional hazard Cox regression analysis with all-cause mortality as primary outcome. Univariate analysis was conducted for the following variables: age, gender, HIV status, number of previous TB episodes, retreatment category, and completion of therapy. Significant variables ( $P < 0.10$ ) were entered into a multivariate model. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated. The study was approved by the Uganda National Council for Science and Technology’s HIV/AIDS Research Committee and the Institutional Review Boards of the University of Medicine and Dentistry of New Jersey (now Rutgers University) and Boston University Medical Center.

### RESULTS

During the study period, 1,826 patients were started on TB retreatment. Of these, 970 (53%) nonduplicate patients resided in the study area and were traced. A total of 377 (39%) were successfully traced and 593 could not be located in their recorded household despite multiple attempts. There were no differences in terms of age and gender between patients

\*Address correspondence to Edward C. Jones-López, Section of Infectious Diseases, Boston University School of Medicine and Boston Medical Center, 850 Harrison Street, Dowling Room 3118, Boston, MA 02118. E-mail: edward.jones@bmc.org

TABLE 1  
Baseline characteristics associated with survival in Cox proportional hazards model

Variable	All (N = 284)	Alive (N = 50)	Deceased (N = 234)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	P value
Age (years)	39.2 (33–45)	38.9 (30–48)	39.3 (26–52)	1.00 (0.99–1.01)	–	0.87
Male gender	195 (68.9%)	37 (76%)	158 (68%)	0.93 (0.70–1.22)	–	0.59
HIV status						
Infected	109 (38.5%)	14 (28%)	85 (40.8%)	2.22 (0.97–5.08)	2.19 (0.95–5.05)	0.066
Unknown	161 (56.9%)	29 (58%)	132 (56.7%)	1.23 (0.54–2.79)	2.22 (0.97–5.06)	0.059
Treatment category						
Relapse	205 (73%)	37 (79%)	168 (72%)	1.00	1.00	–
Failure	18 (6%)	2 (4%)	16 (7%)	1.49 (0.89–2.49)	1.33 (0.76–2.32)	0.316
Defaulter	57 (20%)	8 (17%)	49 (21%)	1.04 (0.75–1.44)	0.78 (0.53–1.14)	0.192
Not completed retreatment	60/257 (23.3%)	1/50 (2%)	59/207 (28.5%)	2.07 (1.51–2.84)	2.32 (1.65–3.25)	0.0001
Previous TB episodes						
> 2	52 (18.3%)	12 (24%)	40 (17.1%)	1.00	1.00	–
≤ 2	232 (81.7%)	38 (76%)	194 (82.9%)	1.61 (1.14–2.27)	1.67 (1.16–2.41)	0.005

CI = confidence interval; HIV = human immunodeficiency virus; HR = hazards ratio; TB = tuberculosis.

Values are mean (interquartile range) or number (percentage).

\*Proportional hazards Cox regression model in step-forward fashion. Outcome: all-cause mortality, univariate analysis includes age, gender, category, HIV status, not completing TB retreatment, and previous TB episodes. Multivariate model variables included HIV, treatment episodes, category, and not completed retreatment.

found during tracing and those unable to be located. Of the 377 patients located, 59 (16%) were alive, 234 (62%) dead, and 84 (22%) had their household located but did not have vital status confirmation; nine patients that were found alive refused to participate. Therefore, this analysis includes 284 patients with a total follow-up time of 1,293 patient-years; median (interquartile range) follow-up was 3.15 (1.53–5.32) years. The median age at diagnosis was 39 years; 109 of 122 (89.3%) with known status were HIV infected and 197/257 (77%) patients completed retreatment. Of 280 patients with known treatment category, 205 (73.2%) were relapses, 18 (6.4%) treatment failures, and 57 (20.4%) defaulters. Among the 50 patients found alive, 19 were symptomatic and three had active TB by sputum smear or culture. Having  $\leq 2$  previous treatments (HR = 1.67, 95% CI = 1.16–2.41) and not completing retreatment (HR = 2.32, 95% CI = 1.65–3.25) were associated with increased mortality (Table 1). Figure 1 shows a Kaplan–Meier curve stratified by HIV status.

## DISCUSSION

We found a high long-term mortality in patients retreated for TB under programmatic conditions in Kampala. Although

the mortality rate is surprisingly high, it is consistent with previous studies in sub-Saharan Africa,<sup>6</sup> long-term projections from our parent prospective study at this site,<sup>1</sup> and a recent meta-analysis on the natural history of TB.<sup>8</sup> We suspect the high mortality observed was related to the combination of drug resistance in this heavily treated cohort,<sup>1,5</sup> and the effect of HIV infection—as antiretroviral therapy (ART) was not widely available in Uganda at the time. Importantly, almost half of the deaths occurred in the first 2 years after starting retreatment and survival within this period was similar by HIV status, suggesting that early mortality was mainly associated with TB whereas HIV infection was responsible for longer term mortality. Other factors such as health-care infrastructure deficiency, a mobile population, lack of directly observed therapy, and poor living conditions may have also contributed to poor outcomes. This study provides additional evidence that the retreatment regimen is associated with poor treatment outcomes, especially in patients with high rates of DR-TB (i.e., treatment failure).<sup>1,2,4,7,9</sup> As a result, several national TB programs have begun phasing out this regimen.<sup>10</sup>

Our study has limitations. Selection bias could have overestimated the mortality rate if patients neither traced nor located had significantly improved survival; we minimized this by comparing the demographic information available between the study and excluded populations. Also, most of the patients we were unable to trace lived further away from Mulago Hospital in semirural, more impoverished dwellings that would favor higher mortality. We were unable to obtain complete information on variables such as AFB smear status, drug resistance, and adherence to treatment, which could have significantly affected the outcomes; also, we did not ascertain cause of death. Survival bias may have occurred as certain patients (i.e., treatment failures, advanced HIV) may have died earlier. HIV prevalence may have been overestimated as infected patients were more likely to report their status. Also, self-report of HIV status may have led to exposure misclassification, which in turn could have diluted the effect of HIV in the primary outcome. Similarly, TB retreatment involves patients who fail or default treatment and recurrences, which were mostly smear positive at this site; however, it is possible that some cases were smear- or culture-negative TB and thus have worse outcomes,<sup>11,12</sup> overestimating TB-associated mortality. Finally, we included participants from a large referral center

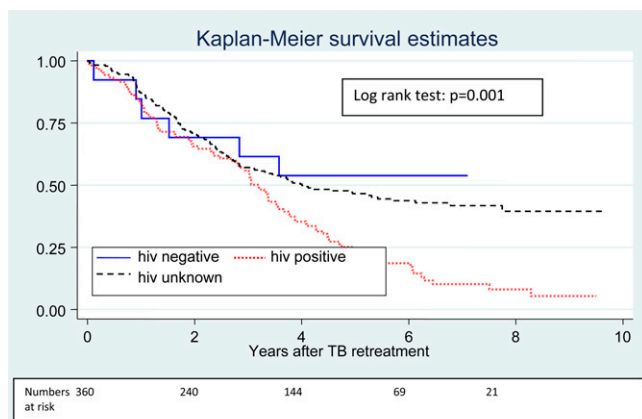


FIGURE 1. Kaplan–Meier curve of tuberculosis (TB) retreatment patients by human immunodeficiency virus (HIV) status.

and therefore our results may not be applicable to other health-care centers.

In conclusion, we found a high mortality among patients who received TB retreatment in Kampala under programmatic conditions in the preART era. The limited access to ART and use of the standard retreatment regimen, now widely regarded as suboptimal, are likely to explain these alarming results. There is an urgent need to implement measures to improve long-term outcomes in treatment-experienced TB patients.

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**Authors' addresses:** Carlos Acuña-Villaorduña and Edward C. Jones-López, Section of Infectious Diseases, Boston Medical Center, Boston, MA, E-mails: carlosvillorduna@hotmail.com and edward.jones@bmc.org. Irene Ayakaka, Makerere University–Boston Medical Center Research Collaboration, Kampala, Uganda, E-mail: ayakaka@gmail.com. Scott Dryden-Peterson, Medicine and Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, E-mail: slpeterson@partners.org. Susan Nakubulwa, Uganda Research Unit on AIDS, Medical Research Council–Uganda Virus Research Institute, Entebbe, Uganda, E-mail: susan.nakubulwa@mruganda.org. William Worodria, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, E-mail: wworo@hotmail.com. Nancy Reilly, Department of Medicine, New Jersey Medical School–Rutgers University, Newark, NJ, E-mail: reillyna@njms.rutgers.edu. Jennifer Hosford and Kevin P. Fennelly, Division of Infectious Diseases and Global Medicine, University of Florida, Gainesville, FL, E-mails: jennifer.hosford@medicine.ufl.edu and kevin.fennelly@medicine.ufl.edu. Alphonse Okwera, Tuberculosis Clinic, Mulago Hospital, Kampala, Uganda, E-mail: a\_okwera@mcuwru.edu.

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