

Risk Factors and Mortality Associated with Default from Multidrug-Resistant Tuberculosis Treatment

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Background. Completing treatment for multidrug-resistant (MDR) tuberculosis (TB) may be more challenging than completing first-line TB therapy, especially in resource-poor settings. The objectives of this study were to (1) identify risk factors for default from MDR TB therapy (defined as prolonged treatment interruption), (2) quantify mortality among patients who default from treatment, and (3) identify risk factors for death after default from treatment.

Methods. We performed a retrospective chart review to identify risk factors for default from MDR TB therapy and conducted home visits to assess mortality among patients who defaulted from such therapy.

Results. Sixty-seven (10.0%) of 671 patients defaulted from MDR TB therapy. The median time to treatment default was 438 days (interquartile range, 152–710 days), and 27 (40.3%) of the 67 patients who defaulted from treatment had culture-positive sputum at the time of default. Substance use (hazard ratio, 2.96; 95% confidence interval, 1.56–5.62; $P = .001$), substandard housing conditions (hazard ratio, 1.83; 95% confidence interval, 1.07–3.11; $P = .03$), later year of enrollment (hazard ratio, 1.62, 95% confidence interval, 1.09–2.41; $P = .02$), and health district ($P = .02$) predicted default from therapy in a multivariable analysis. Severe adverse events did not predict default from therapy. Forty-seven (70.1%) of 67 patients who defaulted from therapy were successfully traced; of these, 25 (53.2%) had died. Poor bacteriologic response, <1 year of treatment at the time of default, low education level, and diagnosis with a psychiatric disorder significantly predicted death after default in a multivariable analysis.

Conclusions. The proportion of patients who defaulted from MDR TB treatment was relatively low. The large proportion of patients who had culture-positive sputum at the time of treatment default underscores the public health importance of minimizing treatment default. Prognosis for patients who defaulted from therapy was poor. Interventions aimed at preventing treatment default may reduce TB-related mortality.

Individuals who default from tuberculosis (TB) treatment (defined as prolonged treatment interruption) have an increased risk of TB recurrence and TB-related death [1, 2]. Treatment default also poses a public health threat, because individuals who do not complete therapy are more likely to remain infectious. The consequences of default from drug-resistant TB treatment may be particularly grave, because effective therapy for patients with drug-resistant TB relies on the remaining

drugs to which the strain has in vitro susceptibility. Thus, treatment default may lead to the transmission of TB that is more difficult to cure with existing drugs.

TB cases that are multidrug resistant (MDR; defined as disease caused by a strain of *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin) constitute ~4% of the total annual TB burden. The vast majority of these cases occur in patients living in low- and middle-income regions. Although treatment for MDR TB is becoming increasingly available in these settings, up to 48% of patients who receive second-line drugs have been reported to default from treatment [3–6]. Completing MDR TB therapy is more challenging than completing first-line TB therapy for a number of reasons. The minimum recommended duration of MDR TB treatment is 18 months [7]. This long treatment course may be particularly difficult in resource-poor settings, where the need to overcome

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competing hardships, such as lack of food, inadequate water, and financial insecurities, may prevail over the need for adherence to treatment [8]. Second, the more-toxic second-line drugs used to treat MDR TB [9] often cause disruptive adverse events.

A large body of literature describes characteristics associated with default from first-line TB therapy. These include patient-related factors, such as alcoholism, drug use, treatment-related adverse events, prior treatment default, lack of social support, and low socioeconomic status [10–15], and programmatic risk factors, such as poor patient-provider communication and barriers to accessing care [16–18]. In the only study, to our knowledge, that examined risk factors specific to MDR TB treatment default, Holtz et al. [19] found that treatment default was most strongly predicted by substance use, dissatisfaction with health care worker attitudes, and indicators associated with low or unstable socioeconomic status.

In 1996, a consortium of national and international agencies, including Peru's National Tuberculosis Program, launched an ambulatory MDR TB treatment program in Lima, Peru. We identified risk factors for treatment default among patients receiving care in this program. We also estimated the proportion of deaths among patients who defaulted from treatment and identified risk factors for death after treatment default.

METHODS

Study region. Our study was conducted in metropolitan Lima, Peru, where nearly one-half of the region's 7 million inhabitants live in poverty. Although the incidence of new TB cases in Peru was estimated to be 110 cases per 100,000 persons in 2005 [20], the incidence in the densely populated shantytowns surrounding Lima has been reported to be 2–3 times higher than the national estimates [21]. The national prevalence of MDR TB among patients with TB is 3% [20].

Patient population and program characteristics. Our study included all patients with laboratory-confirmed MDR TB who initiated their first individualized treatment regimen (ITR) from February 1999 through July 2002. The treatment program included components designed to facilitate adherence. First, community health care workers directly observed treatment and provided social support on a daily basis. Second, the clinical team carefully monitored and aggressively managed adverse events. Ancillary drugs were provided free of charge. Third, patients who met financial aid criteria received individualized socioeconomic support. Fourth, psychiatric consultations and group therapy were offered to patients to address mental health needs, including depression, and to increase social support. Patients received psychiatric medications when indicated [22]. If a patient prematurely stopped treatment, the clinical team encouraged reinstitution of treatment [23].

Data collection. Peruvian clinicians retrospectively re-

viewed patient clinical charts, including standardized enrollment forms and socioeconomic assessments routinely completed for all patients. Variables abstracted included baseline clinical characteristics, radiographic findings, history of substance use, TB treatment history, socioeconomic variables, and microbiologic test results (from monthly sputum smear and culture examinations) [24]. For the subset of patients who initiated an ITR from August 2001 through July 2002, clinicians recorded data on severe adverse events during the first year of treatment. From January 2005 through March 2006, community health care workers visited the homes of the patients who defaulted from treatment to ascertain vital status and collect missing baseline socioeconomic covariates. If the patient had died, a family member was asked to complete the interview.

Exposure definitions. Patients were considered to have malnutrition or a low body mass index (calculated as the weight in kilograms divided by the square of the height in meters) at ITR initiation if they had received a clinical diagnosis of malnutrition or had a body mass index <18.5. Substance use was self-reported and, because of limited available data on frequency of use, consisted of any alcohol use at ITR initiation or a history of illegal drug use. We defined housing conditions as substandard if the dwelling demonstrated any of the following characteristics: (1) dirt floor; (2) walls made of straw matting, plastic, and/or plywood; (3) roof made of straw matting, plastic, and/or plywood; or (4) no access to water in the home. Criteria for classifying severe adverse events are shown in table 1.

To examine whether improved health status predicted treatment default, we created a time-varying variable that represented the number of consecutive months during which a negative microbiologic test result was reported. We also categorized patients who defaulted from treatment according to the duration of their ITR and bacteriologic response at default (i.e., <1 year of an ITR, at least 1 year of an ITR with adequate bacteriologic response, or at least 1 year of an ITR with poor bacteriologic response). Patients were defined as having a poor bacteriologic response at the time of treatment default if (1) they had ≥ 2 positive culture results during the last year of treatment or (2) any of the last 3 cultures performed during the final year of treatment yielded positive results. In contrast, patients were defined as having an adequate bacteriologic response at the time of treatment default if they (1) did not have a single positive culture result during the last 12 months of treatment or (2) had exactly 1 positive culture result during the previous year, but this positive culture result was followed by 3 negative culture results at least 30 days apart [25].

Outcome definitions. We used standard case definitions to define cure, treatment completion, treatment failure, and death [25]. We classified patients as having defaulted from treatment if either of the 2 following criteria were met: (1) the patient missed ≥ 30 consecutive days of treatment before physician-

Table 1. Definitions of severe adverse events for clinical chart review.

Event type	Definition
Electrolyte abnormality	Potassium concentration <3.3 mmol/L, magnesium concentration <1.5 mmol/L, calcium concentration <8.5 mmol/L
Epidermal condition	Steven-Johnson syndrome, exfoliative rash, urticaria
Hepatitis	Clinician-diagnosed hepatitis or hepatotoxicity
Hypoacusia	Severe hypoacusia diagnosed by an audiologist or clinician
Neurological event	Seizure
Psychological condition	Psychosis, psychotic syndrome, substance psychosis, or hallucinations
Renal abnormality	Creatinine clearance >1.5 mg/dL, 50% increase in creatinine clearance relative to baseline, acute renal failure, nephrotoxicity, nephropathy, protein concentration in urine >2g/day

approved treatment completion, or (2) a physician suspended treatment for a patient who was repeatedly nonadherent to treatment even after having undergone adherence counseling. Death after treatment default was defined as death due to any cause. The 2 following groups of patients were identified as having culture-positive sputum at treatment default: (1) patients who had never had at least 2 consecutive negative results of culture of specimens obtained at least 30 days apart (i.e., culture conversion) [25] and (2) patients who had experienced culture conversion but later had culture-positive sputum and, thereafter, did not experience conversion.

Statistical analysis. We compared patients who defaulted from treatment with those who died, transferred out of the program, were cured, or experienced treatment failure. Because this approach might attenuate hazard ratios for common risk factors for poor outcomes, we conducted an additional multivariable analysis in which we compared patients who defaulted from treatment with those who were cured. We imputed the median survival time after treatment default to those for whom we lacked a date of death. Because of the difficulty in distinguishing between recurring and persistent adverse events, we examined the cumulative number of months during which an adverse event was reported. We allowed this quantity to vary with time in a linear fashion.

Characteristics associated with time to treatment default or time to death after treatment default with $P \leq .20$ in Cox univariable analysis were assessed in multivariable analysis. To account for missing data, we performed multivariable Cox proportional hazards analyses on data sets that were multiply imputed using covariate and outcome data. Imputation was conducted using Markov Chain Monte Carlo methods (SAS MI procedure; SAS Institute) [26], and effect estimates were pooled across data sets. Analyses were conducted using SAS, version 9.12 (SAS Institute). Study procedures were conducted in accordance with the ethical standards of the Office for Re-

search Subject Protection of Harvard Medical School and the Research Ethics Committee at the Peruvian National Institute of Health.

RESULTS

Characteristics of the study population. During the study period, 671 patients initiated 673 ITRs for laboratory-confirmed MDR TB. For patients initiating >1 ITR, we considered only the first regimen. More than one-half of the patients (60.8%) were male, and the mean age was 31.4 years (table 2). Baseline clinical status was generally poor, and baseline psychiatric disorders (primarily depression) were common. Prior TB treatment default was reported for 17.1% of patients.

Missing data. Data were missing most frequently for low body mass index and malnutrition (14.6%), housing characteristics (13.3%), alcohol use (13.1%), and previous history of treatment default (12.7%) (table 2). Missing and incomplete intake forms and socioeconomic evaluation forms were the primary reasons for missing data.

Treatment default. Sixty-seven (10.0%) of 671 patients defaulted from therapy during the study period (figure 1). Two people continued to receive treatment and were censored at the end of follow-up (12 September 2007). The overall rate of treatment default was 4.25 cases per 1000 months of treatment. Median time to treatment default was 438 days (interquartile range, 152–710 days), and 27 (40.3%) of the 67 patients had culture-positive sputum at the time of default.

Risk factors for treatment default. Baseline alcohol use, history of drug use, high school education, substandard housing conditions, health district, and later year of enrollment were significantly associated with treatment default in univariable analysis ($P \leq .05$) (table 3). The consecutive number of months during which a patient had negative sputum culture and smear results did not predict treatment default. In the subset of pa-

Table 2. Baseline characteristics of 671 patients who received therapy for multidrug-resistant tuberculosis (TB).

Variable	Patients
Age, mean years \pm SD ^a	31.4 \pm 12.1
Female sex	263/671 (39.2)
Any alcohol use at treatment start	28/579 (4.8)
History of drug use	53/601 (8.8)
Completed high school	392/620 (63.2)
>2 prior TB treatments	468/668 (70.1)
History of treatment default	100/586 (17.1)
Substandard housing conditions	174/582 (29.9)
Psychiatric disorder	116/613 (18.9)
Health district	
A	81/670 (12.1)
B	124/670 (18.5)
C	66/670 (9.8)
D	276/670 (41.2)
E	123/670 (18.4)
Year of enrollment	
2000 or earlier	118/671 (17.6)
2001	400/671 (59.6)
2002	153/671 (22.8)
Bilateral cavitary disease	352/638 (55.2)
History of hemoptysis	264/633 (41.7)
Low BMI or malnutrition	185/573 (32.3)

NOTE. Data are proportion of patients (%), unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters).

^a Data are for 670 patients.

tients for whom adverse event data were collected ($n = 371$), severe adverse events were reported during 13 (2.9%) of 449 months contributed by patients who defaulted from treatment and during 137 (3.8%) of 3581 months contributed by patients who did not default from treatment. The number of months during which severe adverse events were reported did not predict treatment default (hazard ratio, 0.87; 95% CI, 0.36–2.08; $P = .75$).

Alcohol and drug use were collinear; therefore, we combined them into a single substance use variable. In multivariable analysis, substandard housing conditions and a history of substance use predicted a statistically significantly higher rate of treatment default. The treatment default rate also increased significantly with each subsequent year of enrollment and varied significantly among Lima's 5 health districts (table 3). When we compared patients who defaulted from treatment with those who were cured (and excluded patients who died, transferred out of the program, were censored at the end of follow-up, and experienced treatment failure), only the hazard ratio for district C changed by >10% (hazard ratio, 1.99; 95% CI, 0.49–8.14).

Survival after treatment default. Community health care workers successfully traced 47 (70.1%) of the 67 patients who defaulted from treatment; the median time from treatment de-

fault to tracing these patients was 1075 days (interquartile range, 759–1304 days) (figure 1). Interviews were not conducted for patients who moved away from Lima ($n = 6$), had an unknown address ($n = 8$), defaulted from treatment after tracing was completed ($n = 4$), were mentally unfit for interview ($n = 1$), or refused participation ($n = 1$). There were no statistically significant differences between patients who were and were not traced. Of the 47 individuals traced, 25 (53.2%) had died. Among 17 individuals for whom a date of death was obtained, median time to death after treatment default was 273 days (interquartile range, 103–503 days). In multivariable analysis, poor bacteriologic response, <1 year of an ITR, psychiatric disorder, and a high school education were all statistically significantly associated with death (table 4).

Treatment reinitiation after treatment default. Eleven (16.4%) of the 67 patients who defaulted from treatment reinitiated an ITR. Of these patients, 3 were cured, and 1 was receiving treatment at the end of the follow-up period. The other patients defaulted from treatment or died.

DISCUSSION

The proportion of patients who defaulted from treatment (10%) in this MDR TB treatment program is among the lowest reported in a low- or middle-income setting and is comparable to such proportions observed in Latvia (13%) [27], Russia

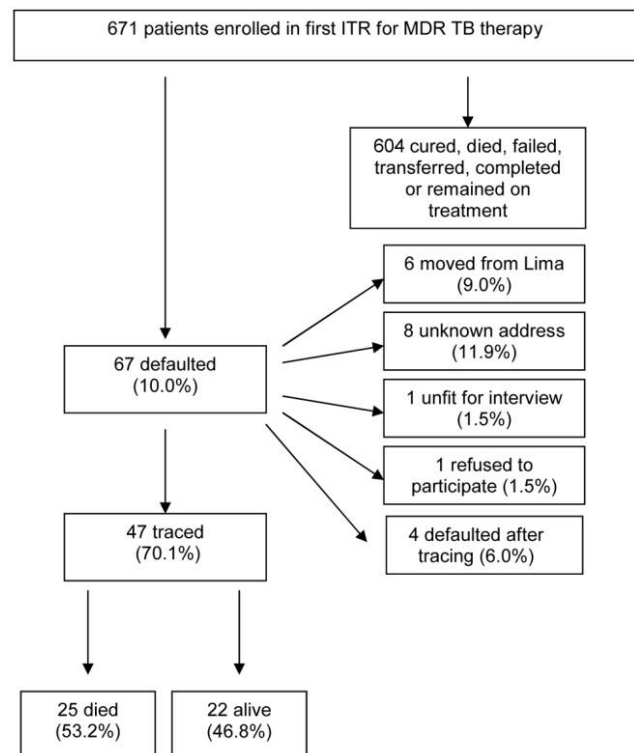


Figure 1. Follow-up for patients who initiated a first individualized treatment regimen (ITR) for multidrug-resistant (MDR) tuberculosis (TB).

Table 3. Risk factors for default from multidrug-resistant tuberculosis (TB) treatment.

Variable	Patients who defaulted treatment (n = 67)	Patients who did not default treatment (n = 604)	Univariable analysis		Multivariable analysis	
			Hazard ratio (95% CI)	P ^a	Hazard ratio (95% CI)	P ^a
Age, mean years ± SD ^b	31.9 ± 11.9	31.3 ± 12.1	1.01 (0.99–1.03)	.51	...	
Female sex	21/67 (31.3)	242/604 (40.1)	0.73 (0.44–1.22)	.23	...	
Alcohol use	9/56 (16.1)	19/523 (3.6)	4.26 (2.09–8.68)	<.001	...	
Drug use	13/62 (21.0)	40/539 (7.4)	3.11 (1.69–5.74)	<.001	...	
Substance use	16/59 (27.1)	51/524 (9.7)	3.30 (1.86–5.87)	<.001	2.96 (1.56–5.62)	.001
Completed high school	32/61 (52.5)	360/559 (64.4)	0.59 (0.35–0.97)	.04	...	
>2 previous TB treatments	49/67 (73.1)	419/601 (69.7)	1.20 (0.70–2.05)	.51	...	
History of treatment default	14/55 (25.5)	86/531 (16.2)	1.76 (0.96–3.23)	.07	...	
Substandard housing conditions	21/51 (41.2)	153/531 (28.8)	1.80 (1.03–3.14)	.04	1.83 (1.07–3.11)	.03
Psychiatric disorder	11/64 (17.2)	105/549 (19.1)	0.96 (0.50–1.83)	.90	...	
Health district						
A	12/67 (17.9)	69/603 (11.4)	3.59 (1.35–9.56)		3.34 (1.24–9.00)	
B	6/67 (8.9)	118/603 (19.6)	Referent		Referent	
C	3/67 (4.5)	63/603 (10.5)	1.08 (0.27–4.33)	.02	1.36 (0.34–5.46)	.02 ^c
D	29/67 (43.3)	247/603 (41.0)	2.43 (1.01–5.85)		2.77 (1.13–6.78)	
E	17/67 (25.4)	106/603 (17.6)	3.24 (1.28–8.21)		3.80 (1.49–9.70)	
Year of enrollment						
2000 or earlier	6/67 (9.0)	112/603 (18.5)	
2001	39/67 (58.2)	361/603 (59.8)	1.61 (1.09–2.34)	.02	1.62 (1.09–2.41)	.02
2002	22/67 (32.8)	131/603 (21.7)	
Bilateral cavitary disease	34/63 (54.0)	318/575 (55.3)	1.01 (0.62–1.66)	.96	...	
History of hemoptysis	29/64 (45.3)	235/569 (41.3)	1.18 (0.72–1.94)	.50	...	
Low BMI or malnutrition	12/54 (22.2)	173/519 (33.3)	0.73 (0.38–1.38)	.33	...	

NOTE. Data are proportion of patients (%), unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters).

^a P value for time to treatment default.

^b Data are for 670 patients, including 67 patients who defaulted treatment and 603 patients who did not default treatment.

^c Likelihood ratio P value derived from the mean test statistic from imputed data sets.

(12%) [28], Turkey (11%) [29], and a cohort of patients who received a standardized MDR TB regimen in Peru (11%) [30]. Although this proportion is lower than those observed in Taiwan (29%) [4], Argentina (20%) [5], South Korea (29%) [6], and Bolivia (48%) [3], more than one-third of the patients who defaulted from treatment had culture-positive sputum at the time of default and, therefore, were potentially infectious. This highlights the public health importance of minimizing treatment default and emphasizes the need for programmatic interventions to promote treatment completion.

Our findings support the hypothesis that program-level factors and interventions, including those designed to reduce the influence of social conditions, may greatly influence treatment default. Substance use was the strongest risk factor for treatment default and was highly concentrated among men (91.0%). The association between substance use and treatment default and other poor TB outcomes, including drug resistance [31, 32], has been reported previously [15, 28, 33]. These data suggest that a means of further improving treatment outcomes may be

to integrate screening and treatment for substance use into TB treatment efforts.

Substandard housing conditions—an indicator of poverty—predicted treatment default, despite the provision of individualized socioeconomic support to disadvantaged patients. The hazard ratio for this association (1.83; 95% CI, 1.07–3.11) is less than other reported estimates of the effect of low socioeconomic status on treatment default [11, 19]—a finding that may reflect differences in the socioeconomic indicators selected, random variation, or regional differences. It is also possible that any underlying association between poverty and treatment default in this cohort was attenuated by aggressive programmatic efforts to alleviate socioeconomic barriers to care. Several descriptive and observational reports have demonstrated that elimination of treatment barriers or provision of incentives improves adherence to long-term therapies [34–36]. Elucidating the ways in which poverty impairs a person's ability to complete long-term TB therapy, despite socioeconomic sup-

Table 4. Risk factors for death after default from multidrug-resistant tuberculosis (TB) therapy.

Variable	Patients who died (n = 25)	Patients who were alive at the home visit (n = 22)	Univariable P ^a	Multivariable analysis	
				Hazard ratio (95% CI)	P ^a
Age, mean years ± SD	30.4 ± 13.3	33.8 ± 12.5	.36	...	
Female sex	11/25 (44.0)	5/22 (22.7)	.008	2.13 (0.95– 4.76)	.07
Substance use	5/21 (23.8)	6/21 (28.6)	.40	...	
Completed high school	9/23 (39.1)	14/20 (70.0)	.02	0.39 (0.16– 0.94)	.03
>2 previous TB treatments	20/25 (80.0)	11/22 (50.0)	.04	...	
History of treatment default	6/20 (30.0)	3/18 (16.7)	.33	...	
Substandard housing conditions	9/19 (47.4)	5/17 (29.4)	.43	...	
Psychiatric disorder	6/22 (27.3)	2/22 (9.1)	.004	3.42 (1.30– 9.01)	.01
Cavitary and bilateral disease	16/24 (66.7)	8/21 (38.1)	.02	...	
History of hemoptysis	10/24 (41.7)	7/21 (33.3)	.43	...	
Low BMI or malnutrition	6/21 (28.6)	3/16 (18.7)	.009	...	
Reinitiated therapy after default	3/25 (12.0)	5/22 (22.7)	.10	...	
Treatment status at default					
Adequate bacteriologic response	3/25 (12.0)	13/22 (59.1)		Referent	
Poor bacteriologic response ^b	7/25 (28.0)	1/22 (4.5)	.002	9.94 (2.54– 38.8)	.001
>1 years of treatment ^b	15/25 (36.4)	8/22 (60.0)	.06	4.11 (1.19– 14.3)	.03

NOTE. Data are proportion of patients (%), unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters).

^a P value for time to treatment default.

^b Reference group represented by patients who had an adequate response to and received at least 1 year of multidrug-resistant TB treatment at the time of treatment default. Although 1 year of treatment was used as the cutoff, patients in this group received multidrug-resistant TB treatment for a median of 22.5 months (interquartile range, 15.5– 27.0 months) prior to treatment default.

port, will permit refinement of interventions to facilitate treatment completion among the poorest patients.

The heterogeneity in treatment default rates by year of enrollment may be explained by several programmatic factors. First, the study period corresponds to a time during which Peru was implementing substantial health care reform. This reform coincided with a decrease in the National Tuberculosis Program's performance, as demonstrated by a decrease in TB case detection rate and an increase in the proportion of patients who defaulted from a category-I TB treatment regimen [20]. Second, patient enrollment increased steadily during 1999–2002, the period corresponding to rapid city- and nationwide scale-up of individualized MDR TB treatment services. These changes may have resulted in decreased per-patient human and financial resources and reduced the ability to identify and closely monitor the patients at highest risk of treatment default. Despite the association between treatment default and later year of enrollment, the proportion of treatment defaults in 2002 (14.4%) was still comparatively low. The important influence of programmatic factors on treatment completion is underscored by results from a recent clinical trial that found that an intervention consisting of improved communication between health care personnel and patients, decentralization of treatment, patient choice of directly observed therapy supporter,

and reinforcement of supervision activities significantly curtailed treatment default [37]. Attention to these aspects of TB care delivery in the context of MDR TB service scale-up may minimize treatment default. Additional study of the specific ways in which treatment scale-up may influence the rate of treatment default is warranted.

Treatment default rates varied among Lima's 5 health districts, which may differ in terms of human resources, patient load, and overall quality of care. Variation in treatment default rates by district is unlikely to be explained by unmeasured confounding by socioeconomic variables, because measured socioeconomic characteristics (education level and dwelling characteristics) were similar among districts.

It is noteworthy that the occurrence of severe adverse events during the first year of treatment did not predict treatment default in this cohort. Because adverse events are often associated with second-line drugs used in MDR TB therapy, the lack of association in our study suggests that routine screening for and aggressive management of adverse events may have reduced the impact of these events on patients' ability to complete treatment.

This study demonstrated the grave health consequences associated with treatment default; more than one-half of all patients who defaulted from treatment had died before they could

be traced. The rate of death after treatment default was higher among women than among men. This finding is consistent with findings from previous studies conducted in Peru [24] and in other resource-poor settings [38] that showed that women were more likely than men to experience poor TB treatment outcomes. The association between female sex and death after treatment default was attenuated when we controlled for poor bacteriologic response at the time of treatment default, <1 year of an ITR, education level, and psychiatric disorder, suggesting that these variables may mediate the association between female sex and death after treatment default.

Depression was the predominant baseline psychiatric diagnosis in this cohort. If depression had improved over time, as was previously documented in a smaller Peruvian cohort [22], this may have explained the observed lack of association between psychiatric illness and treatment default. Among individuals who defaulted from treatment, however, a higher rate of death was seen among those with a baseline psychiatric illness. Depression has been shown to be associated with HIV-associated mortality and disease progression [39, 40]; however, potential biological mechanisms that mediate this association are poorly defined. We found no studies that have examined the relationship between depression and poor clinical outcomes among patients with TB. Further investigation regarding the relationship between psychiatric morbidity and poor TB outcomes is warranted.

Because of the retrospective nature of this study, some data were missing for most variables. We believe that data were randomly missing, conditional on other covariates. Data were more likely to be missing for patients who defaulted from treatment or died early; however, reasons for missing data were unlikely to be associated with unmeasured variables, because data were collected using forms that were universally required for patients. If, however, nonrandom, unmeasured factors contributed to missing data, the imputation methods used would not be valid and the direction of the bias would be difficult to predict. Because we restricted our analysis of adverse events to those that we considered to be severe, we were unable to draw inferences about the relationship between moderate or mild adverse events and treatment default.

The comparatively low frequency of treatment default observed among patients treated in this comprehensive MDR TB treatment program could be improved by responding to patient and programmatic characteristics associated with treatment default. The implementation of interventions designed to facilitate treatment completion for vulnerable groups is crucial to the success of programs that provide long-term therapies. Furthermore, the high mortality rate associated with treatment default and the large proportion of patients who had positive culture results at the time of treatment default emphasize the critical role that prevention of treatment default may play in

minimizing TB-related mortality and reducing the ongoing transmission of *M. tuberculosis* infection.

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