MAJOR ARTICLE

Aggressive Regimens for Multidrug-Resistant Tuberculosis Reduce Recurrence

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(See the Major Article by Porco et al on pages 761–9.)

Background. Recurrent tuberculosis disease occurs within 2 years in as few as 1% and as many as 29% of individuals successfully treated for multidrug-resistant (MDR) tuberculosis. A better understanding of treatment-related factors associated with an elevated risk of recurrent tuberculosis after cure is urgently needed to optimize MDR tuberculosis therapy.

Methods. We conducted a retrospective cohort study among adults successfully treated for MDR tuberculosis in Peru. We used multivariable Cox proportional hazards regression analysis to examine whether receipt of an aggressive MDR tuberculosis regimen for ≥18 months following sputum conversion from positive to negative was associated with a reduced rate of recurrent tuberculosis.

Results. Among 402 patients, the median duration of follow-up was 40.5 months (interquartile range, 21.2–53.4). Receipt of an aggressive MDR tuberculosis regimen for ≥18 months following sputum conversion was associated with a lower risk of recurrent tuberculosis (hazard ratio, 0.40 [95% confidence interval, 0.17–0.96]; $P = .04$). A baseline diagnosis of diabetes mellitus also predicted recurrent tuberculosis (hazard ratio, 10.47 [95% confidence interval, 2.17–50.60]; $P = .004$).

Conclusions. Individuals who received an aggressive MDR tuberculosis regimen for ≥18 months following sputum conversion experienced a lower rate of recurrence after cure. Efforts to ensure that an aggressive regimen is accessible to all patients with MDR tuberculosis, such as minimization of sequential ineffective regimens, expanded drug access, and development of new MDR tuberculosis compounds, are critical to reducing tuberculosis recurrence in this population. Patients with diabetes mellitus should be carefully managed during initial treatment and followed closely for recurrent disease.

Keywords. resistance; recurrence; relapse; Peru; regimen.

The long, complex, and toxic nature of drug regimens for multidrug-resistant MDR) tuberculosis, defined as a strain of *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin, challenges the delivery of effective treatment. Among national tuberculosis programs that have overcome these challenges and achieved good retention and cure rates in both adults and children [1, 2], recurrent tuberculosis following MDR tuberculosis cure remains an important concern. Recurrence occurs within 2 years in 1% to 29% of those successfully treated [2–7]. Effective approaches to reduce recurrence are critical because of the limited retreatment options available for this patient population and the risks they pose to close contacts.

Because recurrent tuberculosis after cure reflects, at least in part, the efficacy of the treatment regimen, a better understanding of specific treatment-related factors that influence recurrence after cure may inform initiatives to optimize therapy for drug-resistant

Received 30 July 2012; accepted 19 November 2012; electronically published 7 December 2012.

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Clinical Infectious Diseases 2013;56(6):770–6

DOI: 10.1093/cid/cis1008

tuberculosis. In Peru, we previously found that aggressive regimens for MDR tuberculosis were associated with a lower risk of death (unpublished data). In this paper, we examine whether receipt of an aggressive regimen for at least 18 months after sputum conversion was associated with a reduced rate of recurrent tuberculosis disease in a cohort of MDR tuberculosis patients who were cured by individualized and supervised MDR tuberculosis regimens.

METHODS

Study Population

The study population comprised all patients with MDR tuberculosis treated between 1 February 1999 and 31 July 2002 in Lima, Peru, who met 2 inclusion criteria: (1) the ambulatory regimen delivered during the study period was the first regimen individualized to each patient's drug susceptibility test results and treatment history; and (2) this regimen resulted in cure. Patients were excluded from analyses if we lacked data on their regimen composition or if patients did not attend any follow-up visits after treatment completion and could not be traced for a follow-up interview. Following an international consensus definition for retrospective analyses [8], we classified an individual as cured if he or she completed the full duration of the MDR tuberculosis regimen, had no more than 1 culture positive for *M. tuberculosis* within the last 12 months of the MDR tuberculosis regimen, and none in the last 3 months. We previously examined recurrent tuberculosis in this cohort and found a rate of 3.2 cases per 1000 person-months (95% confidence interval [CI], 1.8–5.4 cases per 1000 person-months) in the first 12 months after cure and 0.5 cases per 1000 person-months (CI, .1–1.9 cases per 1000 person-months) in months 13–24 after cure [3].

Ethics Statement

This study was approved by research ethics committees at Harvard Medical School and Peru's National Institute of Health.

Treatment and Monitoring

Baseline evaluation, drug susceptibility testing (DST), and treatment monitoring were performed as described previously [9]. DST to the first-line drugs (isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin) was routinely performed. In at least 75% of patients, DST was performed to all the following second-line drugs: amikacin, capreomycin, cycloserine, ethionamide, kanamycin, para-aminosalicylic acid; ciprofloxacin or ofloxacin; and either gatifloxacin, levofloxacin, or moxifloxacin. A small number of patients had isolates tested to other agents: amoxicillin-clavulanic acid, clofazimine, clarithromycin, or rifabutin. Regimens were individualized to DST according to previously described principles [10].

Outpatient treatment was directly observed, either at public health centers or in patients' homes, by community health workers or nurses. Adverse events were managed by these workers according to established algorithms [11], in consultation with physicians from the National TB Program consortium. Adjunct medical services (including thoracic surgery) and psychosocial and nutritional support were provided to patients free of charge as deemed necessary by expert providers [9, 11–14]. Following cure, the target for routine follow-up was monthly sputum specimens for smear microscopy and culture for the first 6 months after completion for MDR tuberculosis treatment and every 3 months for 18 months thereafter.

Exposure and Covariate Assessment and Definitions

All exposure and covariate data were abstracted from paper and electronic charts [15]. The exposure of interest was receipt of an aggressive regimen for at least 18 months after sputum conversion from positive to negative. The minimum 18-month duration was selected a priori and was based on existing treatment recommendations [10, 16]. Time to sputum conversion was calculated as the number of months from the start of the regimen until the date of the first of 2 consecutive negative cultures, taken at least 30 days apart (among patients who were culture positive at the start of the MDR tuberculosis regimen).

An aggressive regimen was one that contained at least 5 antituberculosis agents—including one fluoroquinolone and one of the injectable agents (streptomycin, kanamycin, capreomycin, amikacin)—that met criteria suggesting efficacy according to the individual's baseline DST and treatment history [10]. An agent was considered efficacious if either (1) all in vitro sensitivity testing prior to the start of this regimen confirmed susceptibility to the agent used; or, (2) in vitro sensitivity testing to the agent was not available and the patient had not received the agent for >1 month prior to the individualized MDR tuberculosis regimen. Treatment regimens changed occasionally by design—regimens were generally started empirically and then changed in response to availability of baseline DST results—and in response to adverse events and drug stock-outs. For this reason, we classified a patient's regimen as aggressive or not for each treatment day, because regimen adjustments during treatment could change whether or not the regimen on any day met the exposure definition. If at least 75% of regimen days in a month met the aggressive definition, then we coded the treatment month as exposed to an aggressive regimen; otherwise, the treatment month was coded as unexposed. The threshold of 75% was selected a priori. We then summed the total number of months post–sputum conversion that each person received an aggressive regimen and

created a binary variable to reflect exposure of at least or less than 18 months.

We also collected data on each patient's tuberculosis treatment experience prior to receiving the individualized MDR tuberculosis regimen, including whether she or he had received the standardized MDR tuberculosis regimen used in Peru between 1997 and 2001. This regimen consisted of 4 months of kanamycin, ethionamide, ciprofloxacin, ethambutol, and pyrazinamide, followed by 14 months of ethionamide, ciprofloxacin, ethambutol, and pyrazinamide [17]. To screen for diabetes, a single fasting glucose level was measured among patients at the start of the individualized MDR tuberculosis treatment. Final classification of diabetes was based on physician diagnosis at the start of the MDR tuberculosis regimen. Body mass index was defined as low if it was <18.5 kg/m^2 for women and <20.0 kg/m^2 for men, and malnutrition was physician-diagnosed.

Outcome Definition and Assessment

Individuals were classified as having recurrent tuberculosis if they met at least 1 of the following criteria during follow-up: (1) at least 1 culture positive for *M. tuberculosis*; or (2) initiation of a tuberculosis treatment regimen. Between June 2004 and July 2008, in addition to reviewing medical records of patients enrolled in treatment in 1999–2002, study workers conducted home visits in order to collect information on recurrent tuberculosis and vital status after cure. If the study subject had died before the home visit, the study worker invited a household member to complete the interview.

Statistical Analyses

Follow-up for each individual began on the date of cure and ended on either the date of the home visit or the date of the subject's last health center visit, whichever came later. For subjects with recurrent tuberculosis, follow-up ended on the earliest date that the case definition was met. In the absence of known recurrent tuberculosis, deaths after cure were treated as censored observations. If the date of death was unknown, we imputed it as the midpoint from the date of cure to the date the subject's family reported the death to study personnel.

We conducted Cox proportional-hazards analyses to identify univariable predictors of time to recurrent tuberculosis. Those variables that predicted the outcome at a P value ≤.20 were considered candidates for the multivariate model. We retained a candidate variable in the final model if it remained associated with time to recurrence at a P value ≤.10 or if inclusion of that variable changed the effect estimate of another variable in the model by >10%. We included age in the final multivariable model due to its strong established link to tuberculosis risk. We also adjusted for 2 additional baseline variables, a diagnosis of extensively drug-resistant (XDR) tuberculosis and resistance to ≥5 drugs, due to their potential inverse correlations with receipt of an aggressive regimen. For covariates in the final model, we evaluated the proportional hazards assumption using plots of the cumulative hazard function and Schoenfeld residuals plotted against time. To address missing data in multivariable analyses, we imputed data sets using Markov chain Monte Carlo methods (SAS MI procedure; SAS Institute) using information from all potential predictor variables [18]. Adjusted hazard ratios were estimated by pooling across data sets.

RESULTS

A total of 671 individuals initiated a first MDR tuberculosis treatment in the program during the study period. Two of these individuals lacked data on regimen composition and were excluded. Among the remaining 669 individuals, 442 met the definition of cure at the end of the MDR tuberculosis regimen. Of these, 40 individuals (9%) were excluded because they could not be assessed for recurrent tuberculosis for the following reasons: the individual had moved outside of the Metropolitan Lima area (n = 15), the study team was not able to locate the individual (n = 14), or the individual refused to be interviewed (n = 11). The final cohort consisted of 402 individuals, representing 91% of cured patients.

The median age at the initiation of the MDR tuberculosis regimen was 27.5 years (interquartile range [IQR], 22.5–36.7 years), and 158 (39%) were female (Table 1). At the start of the MDR tuberculosis regimen, individuals had received a median of 3 (IQR, 2–4) prior tuberculosis regimens; half had bilateral chest cavitation, 44% had received a prior MDR tuberculosis regimen that included second-line drugs, 69% had isolates resistant to at least 5 drugs, and 7% had isolates that met the definition of XDR tuberculosis. The median duration of postcure follow-up was 40.5 months (IQR, 21.2–53.4 months), and the maximum duration was 74 months. Baseline characteristics among the 402 individuals who were included in the analysis and the 40 who were excluded due to lack of follow-up were generally similar (Table 1); however, individuals for whom we lacked follow-up data tended to have more advanced disease at the time of MDR tuberculosis initiation and appeared less likely to have been smokers and less likely to have resistance to ≥5 drugs.

Among the 402 individuals included, 243 (60.5%) were classified as receiving an aggressive regimen for at least 18 months following sputum conversion. Among 159 people who did not meet this definition, 37 never received an aggressive regimen and 122 people received an aggressive regimen for a time <18 months after sputum conversion (median, 13.9 [IQR, 10.0–15.2]). The mean duration of treatment following sputum conversion surpassed 18 months in both groups and was slightly

Table 1. Characteristics of the Study Cohort and the Group Lost to Follow-up

Variable	Study Cohort (N = 402)		Losses to Follow-up (n = 40)	
	No. With Data	No. (%)	No. With Data	No. (%)
Age, y[a]	402	27.5 (22.5–36.7)	40	26.5 (21.2–36.1)
Female sex	402	158 (39)	40	12 (30)
Low BMI or malnutrition[b]	348	100 (29)	33	15 (46)
No. of prior tuberculosis regimens[a]	402	3 (2–4)	40	3 (2–4)
Received an aggressive regimen for ≥18 mo after sputum conversion	402	243 (60.5)	40	25 (62.5)
Bilateral chest cavitations	389	195 (50)	38	23 (61)
Alcohol or substance use	367	55 (15)	37	4 (11)
Ever smoked cigarettes	367	40 (11)	38	2 (5)
Diabetes mellitus	360	9 (3)	37	2 (5)
HIV infection	397	3 (1)	39	1 (3)
Psychiatric disorder	373	58 (16)	37	7 (19)
Resistant to ≥5 drugs	402	277 (69)	40	24 (60)
Received prior standardized MDR tuberculosis regimen	402	176 (44)	40	20 (50)
XDR tuberculosis	402	26 (7)	40	3 (8)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; MDR, multidrug resistant; XDR, extensively drug resistant.

[a] Continuous variable; median (interquartile range) presented.

[b] Body mass index <18.5 in women or <20 in men, or a clinician diagnosis of malnutrition.

Table 2. Characteristics of Study Cohort, by Regimen Type

Variable	Aggressive Regimen for ≥18 mo Postconversion (n = 243)		No Aggressive Regimen for ≥18 mo Postconversion (n = 159)	
	No. With Data	No. (%)	No. With Data	No. (%)
Age, y[a]	243	27 (21–38)	159	27 (23–36)
Female sex	243	93 (38)	159	65 (41)
Low BMI or malnutrition[b]	206	67 (33)	142	33 (23)
No. of prior tuberculosis regimens[a]	243	3 (2–4)	159	3 (2–4)
Bilateral chest cavitations	236	123 (52)	153	72 (47)
Alcohol or substance use	224	36 (16)	143	19 (13)
Ever smoked cigarettes	224	27 (12)	143	13 (9)
Diabetes mellitus	225	7 (3)	135	2 (1)
HIV infection	239	2 (1)	158	1 (1)
Psychiatric disorder	232	33 (14)	141	25 (18)
Resistant to ≥5 drugs	243	139 (57)	159	138 (87)
Received prior standardized MDR tuberculosis regimen	243	91 (37)	159	85 (53)
XDR tuberculosis	243	7 (3)	159	19 (12)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; MDR, multidrug resistant; XDR, extensively drug resistant.

[a] Continuous variable, median (interquartile range) presented.

[b] Body mass index <18.5 in women or <20 in men, or a clinician diagnosis of malnutrition.

longer among individuals who received an aggressive regimen for 18 months following sputum conversion than those who did not (25.1 and 23.7 months, respectively; $P = .002$, Wilcoxon rank sum). Table 2 shows characteristics of the study cohort, stratified by exposure status. Individuals who did not receive at least 18 months of an aggressive regimen after sputum conversion were generally similar to those who did. The first group was more likely to have a baseline isolate that either met the definition of XDR tuberculosis or demonstrated resistance to ≥5 drugs. These patients were also more likely to have had prior exposure to the standardized MDR tuberculosis regimen.

We identified 26 cases of recurrent tuberculosis during the study period. In univariable analysis, receipt of an aggressive regimen for at least 18 months following sputum conversion was associated with a 60% lower rate of recurrent tuberculosis (hazard ratio [HR], 0.40 [95% confidence Interval {CI}, .18–.88]; $P = .02$). Variables positively associated with time to recurrent tuberculosis at a P value ≤.20 were a diagnosis of diabetes mellitus (HR, 5.96 [95% CI, 1.75–20.29]; $P = .004$); a prior treatment with the standardized MDR tuberculosis regimen (HR, 2.16 [95% CI, .98–4.78]; $P = .06$); and an isolate resistant to at least 5 drugs (HR, 1.91 [95% CI, .72–5.08]; $P = .19$; Table 3).

In a multivariable analysis adjusting for baseline, resistance to at least 5 drugs, age and XDR tuberculosis diagnosis, an aggressive regimen for at least 18 months following sputum conversion was associated with a reduced risk of recurrent

Table 3. Predictors of Recurrent Tuberculosis[a]

Variable	No Recurrent Tuberculosis (n = 376), No. (%)	Recurrent Tuberculosis (n = 26)	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Age, y[b]	27.0 (22.4–36.4)	30.4 (23.7–40.4)	1.02 (.99–1.05)	.32	1.00 (.96–1.03)	.83
Female sex	150 (40)	8 (31)	0.61 (.26–1.40)	.24		
Low BMI or malnutrition (n = 348)[c]	95 (29)	5 (23)	0.68 (.25–1.87)	.45		
Number of prior tuberculosis regimens[b]	3 (2–4)	3 (3–4)	1.11 (.89–1.39)	.36		
Received an aggressive regimen for ≥18 mo after sputum conversion	233 (62)	10 (38)	0.40 (.18–.88)	.02	0.40 (.17–.96)	.04
Bilateral chest cavitations (n = 389)	183 (50)	12 (46)	0.88 (.41–1.90)	.74		
Alcohol or substance use (n = 367)	53 (15)	2 (9)	0.58 (.14–2.47)	.46		
Ever smoked cigarettes (n = 367)	38 (11)	2 (9)	1.02 (.24–4.38)	.98		
Diabetes mellitus (n = 360)	6 (2)	3 (13)	5.96 (1.75–20.29)	.004	10.47 (2.17–50.60)	.004
Psychiatric disorder (n = 373)	54 (15)	4 (16.7)	0.99 (.34–2.93)	.99		
Resistant to ≥5 drugs	256 (68)	21 (80.8)	1.91 (.72–5.08)	.19	1.54 (.31–4.56)	.43
Received prior standardized MDR tuberculosis regimen	160 (43)	16 (62)	2.16 (.98–4.78)	.06	2.22 (.98–5.03)	.06
XDR tuberculosis	23 (6)	3 (12)	1.64 (.49–5.48)	.42	1.09 (.31–3.76)	.90

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MDR, multidrug resistant; XDR, extensively drug resistant.

[a] Sample size is 402 unless otherwise specified.

[b] Continuous variable, median (interquartile range) presented.

[c] Body mass index <18.5 in women or <20 in men, or a clinician diagnosis of malnutrition.

tuberculosis (HR, 0.40 [95% CI, .17–.96]; *P* = .04; Table 3). Although diagnosed in only 3% of the cohort, diabetes mellitus also significantly predicted time to recurrent tuberculosis (HR, 10.47 [95% CI, 2.17–50.60]; *P* = .004). Individuals who had received the standardized MDR tuberculosis regimen prior to the individualized MDR tuberculosis regimen experienced a 2-fold increase in the risk of recurrent tuberculosis, which was borderline statistically significant (HR, 2.22 [95% CI, .98–5.03]; *P* = .06).

DISCUSSION

Robust evidence regarding the optimal management of patients with MDR tuberculosis is scanty [19]. Our findings indicate that receipt of aggressive regimens for at least 18 months following sputum conversion may reduce recurrent tuberculosis following MDR tuberculosis cure. Although reducing the number of drugs or the duration of the MDR tuberculosis regimen would certainly be desirable to reduce the burden on patients and programs, any efforts to minimize or shorten MDR tuberculosis therapy must be informed by a better understanding of specific treatment-related factors that may influence recurrent tuberculosis after cure. The present finding, coupled with our previous observation that an aggressive regimen for MDR tuberculosis prevents death (unpublished data), suggests that use of aggressive regimens for MDR tuberculosis may optimize treatment outcomes and be a suitable background regimen against which future MDR tuberculosis treatment strategies could be compared.

Although universally recommended, not all patients who were cured received an aggressive regimen. This is likely due to a combination of program and clinical factors, such as high levels of baseline drug resistance that limited the number of effective drugs available, delays in DST, and occasional drug stock-outs. Measures to minimize exposure to sequential ineffective regimens, rapid DST, and strong supply chains will maximize the number of patients who can access an aggressive regimen.

We identified 2 additional factors that may contribute to the burden of recurrent tuberculosis after MDR tuberculosis cure: a baseline diagnosis of diabetes mellitus and receipt of a prior MDR tuberculosis regimen. Diabetes has previously been shown to be associated with tuberculosis [20, 21] and MDR tuberculosis [22], as well as with poor outcomes for individuals receiving tuberculosis or MDR tuberculosis treatment [23]. To our knowledge, this report is among the first to identify diabetes mellitus as a risk factor for recurrent tuberculosis in individuals treated for MDR tuberculosis. There are several possible explanations for this finding, including the effects of diabetes on the immune system [24], evidence that diabetes may alter the pharmacokinetics of certain drugs [25, 26], or an increased risk of adverse events due to overweight or obesity [27]. Our finding suggests that patients

with diabetes mellitus should be identified early in MDR tuberculosis treatment, managed carefully during treatment to ensure adequate diabetes and MDR tuberculosis drug delivery, and followed closely after treatment to ensure prompt diagnosis of recurrent tuberculosis disease. A better understanding of whether optimal control of diabetes mellitus improves MDR tuberculosis treatment outcomes is critically needed to inform the clinical management of individuals with both diseases.

Although not statistically significant, patients tended to be at higher risk for recurrent tuberculosis after cure if they had received the standardized MDR tuberculosis regimen prior to the individualized MDR tuberculosis regimen. The standardized regimen, no longer part of the national policy, consisted of a combination of drugs that would not have been expected to "cover" the broad-spectrum tuberculosis resistance in this patient population [28]. It cured only 48% of those treated [29], and left >80% of those who survived treatment failure with amplified resistance [30]. Associations between suboptimal regimens, prior second-line drug exposure, and increased drug resistance have been documented previously [31–33]. Furthermore, previous treatment, resistance to all injectable agents, and resistance to a greater number of drugs were associated with increased tuberculosis recurrence risk among MDR and XDR tuberculosis patients in Estonia [34]. It is possible that these factors mediate the relationship between prior standardized MDR tuberculosis treatment and tuberculosis recurrence observed in this cohort. Elimination of suboptimal regimens will not only facilitate prompt initiation of appropriate MDR tuberculosis regimens, it will likely improve early treatment responses and may decrease the risk of recurrent tuberculosis after cure.

An important limitation of this report was that we were not able to determine whether recurrent tuberculosis episodes were due to true relapse or to reinfection, as molecular genotyping and DST were not available for the isolates from the recurrent episodes. If risk factors for recurrence and reinfection are different, we might expect that the observed associations with recurrence are attenuated and the hazard ratios underestimated. A second limitation is that appropriate therapy for diabetes was determined for each patient by an endocrinologist at the start of the MDR tuberculosis regimen and was provided free of charge for patients of low economic status. This provision of therapy, however, was not continued after the completion of the MDR tuberculosis regimen. We did not collect information as to whether patients continued diabetes therapy, if indicated, after the end of the MDR tuberculosis regimen; therefore, it is not possible to determine whether controlled or uncontrolled diabetes after cure was associated with recurrence.

In conclusion, these results provide a better understanding of the role of the MDR tuberculosis regimen's composition and its association with tuberculosis recurrence after cure. Implementing measures to ensure that aggressive regimens for MDR tuberculosis are implemented widely, early, effectively, and for sufficient duration will likely improve treatment outcomes and reduce the risk of recurrent tuberculosis.

Notes

Financial support. This work was supported by the Charles H. Hood Foundation; the David Rockefeller Center for Latin American Studies at Harvard University; the NEW AID Foundation; the von Clemm Foundation at Harvard School of Public Health; the Bill & Melinda Gates Foundation; the National Heart, Lung, and Blood Institute (K01 HL080939 to M. B. V.), the National Institute of Allergy and Infectious Diseases (K01 A1065836 to C. D. M.); and the Research Core of the Department of Global Health and Social Medicine at Harvard Medical School.

Potential conflicts of interest. C. D. M. has served as a board member of Otsuka Scientific Advisory Board. S. S. S. has received a grant from the Eli Lilly Foundation. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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