ORIGINAL ARTICLE

Community-Based Therapy for Multidrug-Resistant Tuberculosis in Lima, Peru

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ABSTRACT

BACKGROUND

Despite the prevalence of multidrug-resistant tuberculosis in nearly all low-income countries surveyed, effective therapy has been deemed too expensive and considered not to be feasible outside referral centers. We evaluated the results of community-based therapy for multidrug-resistant tuberculosis in a poor section of Lima, Peru.

METHODS

We describe the first 75 patients to receive ambulatory treatment with individualized regimens for chronic multidrug-resistant tuberculosis in northern Lima. We conducted a retrospective review of the charts of all patients enrolled in the program between August 1, 1996, and February 1, 1999, and identified predictors of poor outcomes.

RESULTS

The infecting strains of *Mycobacterium tuberculosis* were resistant to a median of six drugs. Among the 66 patients who completed four or more months of therapy, 83 percent (55) were probably cured at the completion of treatment. Five of these 66 patients (8 percent) died while receiving therapy. Only one patient continued to have positive cultures after six months of treatment. All patients in whom treatment failed or who died had extensive bilateral pulmonary disease. In a multiple Cox proportional-hazards regression model, the predictors of the time to treatment failure or death were a low hematocrit (hazard ratio, 4.09; 95 percent confidence interval, 1.35 to 12.36) and a low body-mass index (hazard ratio, 3.23; 95 percent confidence interval, 0.90 to 11.53). Inclusion of pyrazinamide and ethambutol in the regimen (when susceptibility was confirmed) was associated with a favorable outcome (hazard ratio for treatment failure or death, 0.30; 95 percent confidence interval, 0.11 to 0.83).

CONCLUSIONS

Community-based outpatient treatment of multidrug-resistant tuberculosis can yield high cure rates even in resource-poor settings. Early initiation of appropriate therapy can preserve susceptibility to first-line drugs and improve treatment outcomes.

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In Peru, multidrug-resistant tuberculosis, defined as disease caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampin, is responsible for about 3 percent[1,2] of cases among patients not previously treated for tuberculosis and about 15 percent of cases among those previously treated. It has frequently been suggested that the comprehensive "DOTS" strategy — which involves giving a short course of directly observed multidrug treatment, as well as requiring government commitment, case detection by smear microscopy, a regular supply of antituberculosis drugs, and standardized recording and reporting — can eliminate multidrug-resistant tuberculosis.[3-5] However, the short-course chemotherapy on which DOTS is based usually fails to cure multidrug-resistant tuberculosis.[6-8] Rates of cure of multidrug-resistant tuberculosis with standardized short-course chemotherapy range from 5 percent[9] to 60 percent.[10]

Therapy for multidrug-resistant tuberculosis has been virtually nonexistent in poor countries. It has been argued that drug-susceptibility testing and second-line drugs are not cost effective in these countries because of limited resources and that intensive clinical management is impossible because of lack of infrastructure.[3,11,12] There are few treatment models, and the reported rates of success of treatment of multidrug-resistant tuberculosis in middle-income countries and regions ranged in recent reports from less than 60 percent in Indonesia and Taiwan[13,14] to just over 80 percent in Hong Kong, Korea, and Turkey.[15-17] In these studies, treatment of multidrug-resistant tuberculosis was costly and was provided in referral hospitals. The few studies of the treatment of multidrug-resistant tuberculosis in outpatients all found successful outcomes in less than half of cases.[18-20]

Without treatment, multidrug-resistant strains can spread rapidly within vulnerable populations.[21-23] Because standardized short-course chemotherapy for multidrug-resistant tuberculosis has been associated with unacceptably high rates of failure and relapse,[6,10,24] new approaches to treatment in poor countries are needed.[25-27] We conducted a community-based project for the treatment of multidrug-resistant tuberculosis in a resource-poor setting. This DOTS-Plus project — which entailed the addition of second-line drugs, monitoring by sputum culture, drug-susceptibility testing, and directly observed individualized therapy[28] to the well-established Peruvian DOTS program — treated a cohort of patients with long-standing disease due to highly resistant strains of *M. tuberculosis*.[29,30] We identified risk factors associated with poor outcomes and predictors of the time to death.

METHODS

STUDY PATIENTS

Between August 1, 1996, and November 30, 1998, 731 patients were referred for evaluation for multidrug-resistant tuberculosis by Socios En Salud, a nongovernmental organization working in northern Lima, Peru, in collaboration with the Peruvian Ministry of Health and academic and nongovernmental organizations based in the United States. Seventy-five (10 percent) met the following criteria for inclusion in the study: beginning of supervised, individualized treatment for multidrug-resistant tuberculosis before February 1, 1999; residence in the government-approved catchment area in northern Lima (Carabayllo, Comas, and Independencia districts); referral by a collaborating health center after the failure of at least one course of directly observed, standardized short-course chemotherapy; laboratory-documented multidrug-resistant tuberculosis; survival until the results of drug-susceptibility testing became available; and provision of written informed consent. All 75 patients who began therapy during this period are included in this report; high-grade drug resistance, gravity of disease, and the presence of coexisting conditions were not indications for exclusion. Most patients referred did not live in the catchment area.

BACTERIOLOGIC STUDIES AND DRUG-SUSCEPTIBILITY TESTING

Sputum samples were collected for smear microscopy and culture at base line and monthly thereafter. The samples were processed and read according to international standards[31] at Sergio E. Bernales Hospital in Lima. At base line, isolates of *M. tuberculosis* were tested for susceptibility to the following drugs: isoniazid (concentrations, 0.2, 1, and 5 μg per milliliter), rifampin (1 μg per milliliter), ethambutol (5 μg per milliliter), pyrazinamide (100 μg per milliliter), streptomycin (2 and 10 μg per milliliter), kanamycin (5 μg per milliliter), capreomycin (10 μg per milliliter), ethionamide (5 μg per milliliter), cycloserine (30 μg per milliliter), and ciprofloxacin (2 μg per milliliter). Testing was performed by staff

members of the Massachusetts State Laboratory Institute, using the proportion method[32] on 7H10 agar plates and, for pyrazinamide, the BACTEC[33] method. Highly resistant isolates were tested on 7H9 agar plates for susceptibility to amikacin (2, 4, and 8 μg per milliliter), rifabutin (0.12, 0.5, and 2 μg per milliliter), and clarithromycin (2, 8, and 32 μg per milliliter) at the National Jewish Medical and Research Center in Denver.

TREATMENT AND MONITORING OF ADVERSE EVENTS

While the results of susceptibility testing were pending, most patients were treated empirically under direct observation with regimens containing at least five drugs to which their strains were deemed likely to be sensitive on the basis of previous regimens used. The definitive regimens, containing a minimum of five drugs and lasting at least 18 months, were determined on the basis of the results of drug-susceptibility tests, which were available a mean (±SD) of 62.6±32.9 days after sputum collection. First-line drugs were used preferentially even in cases in which repeated test results were inconsistent, provided that susceptibility had been documented at least once. A parenteral agent was administered for at least six months after culture conversion.[34] Treatment was terminated after 12 or more consecutive negative cultures had been recorded. Sputum samples continued to be collected and cultured at least annually after the completion of treatment. Patients received limited nutritional, financial, and social support through Socios En Salud.[35]

Treatment was given on an outpatient basis. Treatment and surveillance for adverse events were managed by a team of specially trained community health workers, nurses, and physicians under the auspices of Socios En Salud.[29,30] Each patient underwent complete clinical — including neurologic, psychiatric, and audiometric — evaluations before enrollment. Base-line laboratory analyses included a complete blood count, measurement of blood urea nitrogen and serum creatinine, tests of hepatic function (measurement of serum aminotransferases, bilirubin, and alkaline phosphatase), enzyme-linked immunosorbent assay for the human immunodeficiency virus (HIV), and a Venereal Disease Research Laboratory test at base line. Monitoring of renal and hepatic function was performed regularly during therapy; other laboratory tests were performed as indicated, on the basis of symptoms.

DEFINITIONS OF OUTCOME

Probable cure was defined by at least 12 months of consecutive negative cultures during therapy; a single intervening positive culture with fewer than 10 colonies was allowed. Treatment failure was defined by the presence of a positive culture after six months of treatment. Withdrawal from therapy was defined by one or more months of missed therapy during the first year, and two or more months missed during the second year. Death was defined as death from any cause during therapy or follow-up. Relapse was defined by two or more positive cultures after the completion of treatment among patients whose treatment outcome was probable cure.

COLLECTION OF DATA

Patients' characteristics and risk factors at base line (drawn from clinical records with the use of a structured instrument) included the following: extent of pulmonary parenchymal damage; number of previous treatments; low body-mass index (the weight in kilograms divided by the square of the height in meters), defined as less than 18.5 for women and less than 20 for men[36]; anemia, defined as a hematocrit of less than 30 percent in women or less than 36 percent in men[37]; the number of antituberculosis agents to which the infecting strain was resistant; the number of drugs in the regimen; age; sex; household size; history of homelessness, substance abuse, or institutionalization; medical history and coexisting conditions; respiratory difficulty, observed as tachypnea at rest (more than 26 breaths per minute),[38] dyspnea at rest or on exertion, or use of accessory muscles; and the time elapsed since the first diagnosis of tuberculosis and multidrug-resistant tuberculosis.

STATISTICAL ANALYSIS

Statistical analyses were performed to determine the associations between risk factors and a poor outcome (treatment failure or death) during therapy and the follow-up period, through August 31, 2002.

Clinically relevant risk factors were analyzed with the use of Kaplan–Meier estimates and Cox proportional-hazards models to generate estimates of the associations with the time to death or treatment failure. Confounding by demographic characteristics, previous treatment history, and resistance to first-line drugs was assessed by multiple Cox proportional-hazards models. Plots of the natural logarithm of the negative of the natural logarithm of

the survival curves for all levels of primary predictors were consistent with the assumption of proportionality.[39] Data on patients who withdrew from therapy were censored at the time of withdrawal, since their risk of a poor clinical outcome could no longer be assessed.[40]

Data were entered into Access97 (Microsoft). Data were missing for some patients for some risk factors; missing values for body-mass index and hematocrit were imputed as the sex-specific medians. SAS software (version 8.1) was used for all analyses. All reported P values are two-sided.

RESULTS

BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The patients were young, and most were single (Table 1), with nearly equal numbers of men and women. The household size was generally large, and often two or more patients came from a single household. More than half the patients had prior or current medical illness; four had concurrent extrapulmonary tuberculosis. One of 65 patients tested had HIV infection. A low hematocrit was recorded in 12 patients (18 percent). Nearly half the patients had an elevated resting respiratory rate, a low body-mass index, or both. Bilateral cavitary parenchymal disease was evident in 47 base-line chest radiographs (63 percent). The patients had received treatment with a median of 3 prior antituberculosis regimens (range, 0 to 8) during the nearly four years between the diagnosis of tuberculosis and the initiation of the individualized regimens described here. The patients had been previously exposed to a median of 7 antituberculosis drugs (range, 0 to 10) for at least one month each. The infecting strains of *M. tuberculosis* were resistant to a median of 6 drugs (range, 2 to 12).

OUTCOMES

The 75 patients received treatment with 58 different regimens (Fig. 1), containing a median of six drugs (range, five to nine) (Table 2) and lasting a median of 23 months (range, 0.4 to 35.9). The records of 60 patients were reviewed systematically for adverse events; 44 patients (73 percent) had such events, and all events were managed without physician-directed discontinuation of therapy.[41]

Sixty-six patients completed four or more months of therapy; conversion was evident in smears and cultures in a median of just over one month. Of these 66 patients, 55 (83 percent) had probable cures at the completion of therapy, 5 patients (8 percent) withdrew from therapy, therapy failed in 1 patient, and 5 patients (8 percent) died while receiving therapy, after having completed more than four months of therapy.

Patients were followed for a median of 40 months (range, 7 to 66) after therapy. During therapy and follow-up, 18 poor clinical outcomes occurred: 17 deaths and 1 failure of therapy. Autopsies were not performed; the causes of death, as suggested by the clinical history, are shown in Table 3.

PREDICTORS OF A POOR CLINICAL OUTCOME

In univariate analyses, a low hematocrit was found to predict a poor outcome throughout therapy and follow-up: after four months of therapy, only four patients with a normal base-line hematocrit value (6 percent) had died, whereas five patients with a low hematocrit (42 percent) had died ($P<0.001$ by the generalized Wilcoxon test). Low base-line body-mass index was also predictive of earlier death: at four months, only one patient with normal base-line body-mass index (2 percent) and eight patients with low body-mass index (25 percent) had died ($P<0.001$ by the generalized Wilcoxon test).

In the final multiple Cox proportional-hazards regression model, a low hematocrit ($P=0.01$ by the Wald χ^2 test) and resistance to pyrazinamide or ethambutol ($P=0.02$ by the Wald χ^2 test) were significantly associated with the time to a poor outcome (Table 4). Although low body-mass index was of borderline statistical significance in this model ($P=0.07$ by the Wald χ^2 test), it confounded the effect of a low hematocrit, lowering the effect estimate by more than 30 percent. After adjustment for low body-mass index and low hematocrit, nulliparous women were at greater risk for a shorter time to a poor outcome than other women ($P=0.01$ by the Wald χ^2 test).

DISCUSSION

Large-scale, standardized surveys have revealed the presence of patients with multidrug-resistant pulmonary tuberculosis in virtually every country studied, yet to date, specific therapy for this disease has been restricted to high- and middle-income countries where care is usually delivered within specialized referral centers. This project in Peru yielded more probable cures than expected in patients whose prognosis was poor because of chronic,

Table 1. Characteristics of the 75 Patients at the Initiation of Individualized Treatment Regimens.

Characteristic*	No. of Patients (%)	Median (Range)
Sex		
Male	37 (49)	
Female	38 (51)	
Age (yr)		26.8 (11.8–65.1)
Household size (no. of members)		7 (2–20)
Marital status		
Unmarried (single, widowed, separated, or divorced)	47 (66)	
Married	24 (34)	
Parity		0 (0–9)
0 live births	23 (61)	
≥1 live births	15 (39)	
Hematocrit (%)		36.5 (21–51)
Men		41 (21–48)
Women		34 (24–51)
Men with hematocrit <36%	7 (23)	
Women with hematocrit <30%	5 (14)	
Observed respiratory difficulty†		
Any	32 (49)	
None	33 (51)	
Resting respiratory rate		25 (15–40)
>26 breaths/min	13 (45)	
≤26 breaths/min	16 (55)	
Body-mass index		19.9 (12.4–29.8)
Men		20.6 (13.1–29.8)
Women		19.0 (12.4–25.2)
Men with body-mass index <20	15 (41)	
Women with body-mass index <18.5	17 (45)	
Previous or current coexisting condition‡		
Any	40 (53)	
None	35 (47)	
History of homelessness, imprisonment, other institutionalization, or addiction to drugs or alcohol	17 (23)	
Months from first diagnosis of tuberculosis to individualized treatment regimen		44.2 (2.1–383.4)
Months from first diagnosis of multidrug-resistant tuberculosis to individualized treatment regimen		8.1 (0.2–103.2)
No. of drugs to which *M. tuberculosis* strain was resistant at initiation of treatment§		
All drugs		6 (2–12)
First-line drugs		5 (2–5)
Second-line drugs		1 (0–7)
Parenteral drugs		1 (0–4)

* Data on some of the characteristics were missing for some patients. Data on household size were available for 69 patients; on marital status, for 71; on parity, for the 38 women; on hematocrit, for 68 patients; on respiratory difficulty, for 65; on respiratory rate, for 29; and on body-mass index, for 69.

† Observed respiratory difficulty was defined as dyspnea, use of accessory muscles, or elevated resting respiratory rate.

‡ Previous or current coexisting conditions included psychiatric illness (28 patients), hepatitis (3 patients), human immunodeficiency virus infection (1 patient), hypothyroidism (1 patient), diabetes (1 patient), epilepsy (1 patient), malnutrition (15 patients), anemia (12 patients), gastritis (10 patients), and aortic stenosis (1 patient).

§ The drugs tested were isoniazid, pyrazinamide, rifampin, ethambutol, streptomycin, kanamycin, capreomycin, ciprofloxacin, ethionamide, and cycloserine; when clinically indicated, amikacin, rifabutin, and clarithromycin were also tested. The first-line drugs were isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. The second-line drugs were kanamycin, capreomycin, ciprofloxacin (or other fluoroquinolones), ethionamide, cycloserine, amikacin, rifabutin, and clarithromycin. The parenteral drugs were streptomycin, kanamycin, capreomycin, and amikacin.

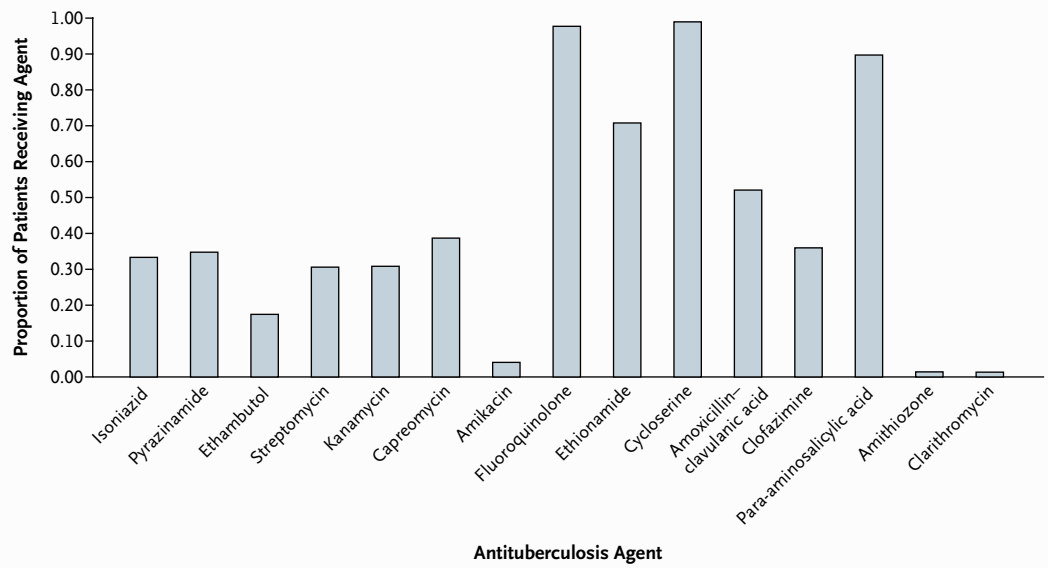

Figure 1. Frequency Distribution of Antituberculosis Agents Received by the 75 Patients as Part of Individualized Treatment Regimens.

All patients were infected with strains that were resistant to at least low-dose isoniazid (critical concentration, 0.2 μg per milliliter) and rifampin. High-dose isoniazid (900 mg twice weekly) was given to patients whose infecting strains had in vitro susceptibility to high-dose isoniazid (critical concentration, 5.0 μg per milliliter). The fluoroquinolones used were ciprofloxacin and ofloxacin.

Table 2. Characteristics of Treatment Regimens.*

Characteristic	No. (%)	Median (Range)
No. of drugs per patient in individualized treatment regimen		6 (5–9)
First-line drugs		1 (0–4)
Second-line drugs		5 (2–7)
Parenteral drugs		1 (1–2)
Receipt of regimen containing ethambutol or pyrazinamide		
Regimen containing ethambutol and pyrazinamide	6 (8)	
Regimen containing ethambutol only	7 (9)	
Regimen containing pyrazinamide only	20 (27)	
Regimen containing neither drug	42 (56)	
Time to conversion — days		
Smear		38 (14–264)
Culture		35 (23–181)
Duration of therapy — mo		23 (0.4–35.9)

* Data on time to conversion were available for the 66 patients who completed at least four months of therapy. For all other variables, data were available for all 75 patients.

highly resistant tuberculosis, extensive parenchymal damage, and previous exposure to repeated, standardized regimens that probably resulted in the amplification of drug resistance. The percentage with probable cures in our community-based, ambulatory program (83 percent) was as high as any reported in a hospital setting to date.

The seminal report on the treatment of severe multidrug-resistant tuberculosis in a referral hospital in the United States documented a favorable response in 65 percent of patients.[42] In reports from middle-income countries or regions, the percentages responding favorably ranged from 50 percent in Taiwan[14] to more than 80 percent in Hong Kong,[15] Korea,[16] and Turkey.[17] The only comparisons to date of studies among outpatients are from Florida, in which only 48 percent of patients completed treatment,[19] and Korea and Peru (a study using the Peruvian National Tuberculosis Program standardized regimen), in which 48 percent were cured.[18,20]

The encouraging outcomes in Lima are proba-

bly due to several factors, some unique to our study population and others to the treatment program. Although our patients had been sick for longer and had higher-grade resistance than those in other cohorts, they were generally younger, with fewer serious coexisting conditions. Unlike the cohorts in Korea and Florida, which had high default rates,[18,19] all patients in our cohort received directly observed therapy. Adverse effects, moreover, were carefully managed to ensure completion of treatment: only one patient withdrew from therapy because of adverse events.[41]

Therapy was more aggressive than in other studies; patients were treated with more drugs and at higher doses for longer periods.[13,41,43] It is likely that this protocol mitigated, to some degree, the effect of high-grade resistance. In other cohorts, such resistance has increased the likelihood of treatment failure.[42,44,45] Furthermore, the use of individualized regimens permitted patients to receive treatment with maximally effective drug combinations to which the strains had documented in vitro susceptibility, thus reducing the risk of further amplification of resistance.[46,47] More than 70 percent of the patients with strains resistant to all five first-line drugs had probable cures at the completion of treatment.

Our results suggest that shortening the time to the initiation of appropriate therapy will further improve outcomes and reduce costs in a number of ways. Most important, in a setting with high cure rates with first-line treatment, patients in whom directly observed, short-course regimens have failed and patients thought to have primary multidrug-resistant tuberculosis are unlikely to benefit from the standardized retreatment regimens recommended for resource-poor settings.[48] Additional courses of therapy based on isoniazid and rifampin are likely to lead to increased parenchymal damage and amplified resistance to the other first-line drugs.[6] In fact, in a preliminary analysis from a larger cohort of patients in Lima, resistance to streptomycin, pyrazinamide, and ethambutol was three times as likely in strains collected from patients who had been treated with two or more previous regimens as in those who had received no treatment or treatment with only one regimen.[49]

The treatment of patients with strains resistant to four or five first-line drugs is more difficult and more expensive than the treatment of those whose strains are sensitive to one or more of these agents. We found that patients with strains resistant to pyrazinamide and ethambutol were more likely to have poor outcomes. Moreover, the resistance pattern was the greatest determinant of the cost of therapy in this cohort, with costs per patient ranging from $504 to $32,383. At a mean of $15,681 per patient, these costs were low — approximately 10 percent of those for hospitalized patients[50,51] — but well beyond the reach of most national tuberculosis programs. Advocacy work and pooled procurement have since resulted in dramatic decreases in the costs of second-line antituberculosis drugs.[52] Now such patients can be treated for approximately half the earlier cost; preserved susceptibility to pyrazinamide and ethambutol further reduces the expense.

The association between signs of severe, protracted disease — elevated resting respiratory rate, bilateral involvement, low body-mass index, and anemia — and poor outcome is not unexpected and further underscores the importance of early referral for appropriate therapy.[53-55] Aggressive adjuvant interventions (blood transfusion, hyperalimentation, and supplemental oxygen) may be important for reducing mortality among chronically ill patients. Even if these costly therapies prove beneficial, however, referring patients to appropriate therapy before they have manifestations of chronic disease would save both lives and resources. It would also reduce rates of transmission. Inadequately treated patients often remain infectious, transmitting multidrug-resistant strains to household members and health care workers.

The poorer outcomes for women, although not fully explained by the data available for this population, are consistent with the elevated risk of progres-

Table 3. Suspected Causes of Death among Patients Who Died during or after Individualized Treatment.

Cause	During Therapy		After Completion of Therapy
	<4 mo Completed	≥4 mo Completed	
Massive hemoptysis	3	0	0
Respiratory failure	5	2	1 (14 wk after completion)
Sepsis (multisystem organ failure)	0	1	0
Relapse or reinfection with multidrug-resistant tuberculosis	0	0	1 (23 wk after completion)
Probable narcotic overdose	0	0	1 (43 wk after completion)
Unknown	1	2	

Table 4. Risk Factors Associated with the Time to a Poor Outcome during Therapy.*

Risk Factor	Patients with Poor Outcomes	Univariate Analysis		Multivariate Analysis
		Crude Hazard Ratio (95% CI)	P Value†	Adjusted Hazard Ratio (95% CI)
	no./total no.			
Sex		2.14 (0.80–5.71)	0.13	—
Female	12/38			
Male	6/37			
Age		1.40 (0.54–3.65)	0.49	—
>26.8 yr	7/37			
≤26.8 yr	11/38			
Body-mass index		5.13 (1.68–15.69)‡	0.004	3.23 (0.90–11.53)§
Low	14/32			
Normal	4/43			
Hematocrit		5.17 (2.03–13.17)‡	<0.001	4.09 (1.35–12.36)‡§
Low	8/12			
Normal	10/63			
Radiographic findings		1.77 (0.64–4.64)	0.28	—
Bilateral disease and cavitary lesions	14/50			
Bilateral disease only	4/21			
Neither bilateral disease nor cavitary lesions	0/4			
Resting respiratory rate¶		10.32 (1.27–84.04)‡	0.03	—
>26 breaths/min	1/16			
≤26 breaths/min	7/13			
Pyrazinamide and ethambutol in regimen‖		0.47 (0.19–1.18)	0.11	0.30 (0.11–0.83)‡§
Neither	13/42			
Either	5/27			
Both	0/6			
Parity**		3.87 (0.82–18.21)	0.09	7.48 (1.50–37.34)‡
0 live births	9/23			
≥1 live births	3/15			

* CI denotes confidence interval. Both univariate and multivariate analyses were Cox proportional-hazards regression analyses.
† P values were derived by the Wald χ^2 test.
‡ P<0.05 by the Wald χ^2 test.
§ The multivariate model included low hematocrit, low body-mass index, and the combined predictor for pyrazinamide and ethambutol.
¶ The resting respiratory rate was not included in the multiple logistic-regression models because of the large number of missing values.
‖ Exclusion of these drugs was predicated on definitive evidence of in vitro resistance. Inclusion in the regimen was based on at least one confirmation of susceptibility.
**Only women were included. The multivariate model was adjusted for anemia and low body-mass index.

sion from infection to disease, increased mortality, and higher incidence of extrapulmonary disease among women with tuberculosis in many parts of the world.[56-58] Our finding that young, childless women were less likely to respond to therapy may point to the important role of adult children, who often provided substantial support to their mothers. It is also possible that the long-standing disease afflicting young women in northern Lima was so debilitating as to have precluded reproduction for physiological and social reasons.

Our experience establishes that patients with chronic multidrug-resistant tuberculosis can be treated successfully as outpatients outside referral centers and in a resource-poor country. The DOTS-Plus model relies on community health workers supervised by nurses working in close collaboration with the country's successful National Tuberculosis

Program. By moving treatment into the community, it is possible, without compromising the quality of therapy, to lower costs and reduce the risk of nosocomial spread of multidrug-resistant tuberculosis.[59-61] During the past two years, we have expanded the DOTS-Plus model to cover much of Lima. The costs of therapy have continued to drop even as control over the distribution of second-line drugs has been enhanced. Successful community-based therapy for multidrug-resistant tuberculosis — and potentially for HIV[62,63] — provides hope for the tens of millions of patients who are suffering from chronic infectious diseases in settings with limited health infrastructure.

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