MAJOR ARTICLE

Clinical Outcomes of Estonian Patients with Primary Multidrug-Resistant versus Drug-Susceptible Tuberculosis

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Little is known about the clinical outcomes of patients with primary multidrug-resistant (MDR) tuberculosis. Clinical outcomes among 46 patients in Estonia with primary MDR tuberculosis and 46 patients with pansusceptible tuberculosis were compared. Patients with MDR tuberculosis were more likely than those with pansensitive tuberculosis to have treatment failure (odds ratio, 8.9; 95% confidence interval [CI], 3.0–26.3) after adjusting for medical problems and weeks of effective treatment, often with second-line drugs. Ten patients (22%) with MDR tuberculosis and 2 (4%) with susceptible tuberculosis died of tuberculosis ($P = .03$). MDR tuberculosis (hazard ratio [HR], 7.8; 95% CI, 1.6–37.4), number of medical problems (HR, 2.5; 95% CI, 1.5–4.4), and male sex (HR, 5.8; 95% CI, 1.1–29.6) were associated with death due to tuberculosis in multivariable analysis. Human immunodeficiency virus test results were negative for all 55 patients tested. These findings underscore the urgent need for increased attention to prevention and treatment of MDR tuberculosis globally.

Resistance of *Mycobacterium tuberculosis* to antituberculous drugs was first documented soon after the initiation of streptomycin use in the 1940s [1]; this resistance appears with increasing frequency globally [2]. Of considerable concern is the large number of reported outbreaks of multidrug-resistant (MDR) tuberculosis [3–13], which is defined as tuberculosis due to *M. tuberculosis* strains that are resistant to, at least, isoniazid and rifampin. A summary of antituberculosis drug resistance surveys conducted in 35 countries showed that resistance of *M. tuberculosis* to 1 or more antimycobacterial drugs is common and that the prevalence of acquired MDR tuberculosis (MDR tuberculosis in patients who have received ⩾1 month of previous antituberculosis drug therapy) and primary MDR tuberculosis (MDR tuberculosis in those who have received <1 month of prior antituberculosis therapy) varied significantly by country [14]. This global surveillance project identified Estonia as one of the "hot spots" for a high prevalence of MDR tuberculosis [14, 15].

Drug toxicities and costs associated with the treatment of MDR tuberculosis are greater than those for the treatment of drug-susceptible tuberculosis [16], but the effect of multidrug resistance on cure, relapse, and survival of patients with primary MDR tuberculosis remains unclear. Mitchison and Nunn [17] found that strains that are initially resistant to rifampin alone were associated with higher rates of treatment failure and

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relapse rates than were drug-susceptible strains or strains with other drug resistance patterns; however, none of the patients in their study were infected with MDR *M. tuberculosis* strains. Outbreaks of MDR tuberculosis among predominantly HIV-infected patients have been associated with very high mortality rates (41%–98%) [9, 12, 18–23]. In contrast, few studies (which have yielded disparate results) have addressed clinical outcomes among HIV-negative patients with MDR tuberculosis [24–26]. Goble et al. [24] reviewed the clinical courses of 171 patients who were referred for treatment of acquired MDR tuberculosis from 1973 through 1983 (and, therefore, were unlikely to have been infected with HIV). For these persons, the median duration of tuberculosis was 6 years, and they had previously received a median of 6 antituberculosis drugs; 56% were cured and remained free of disease for a mean follow-up of 51 months, and a 20% mortality rate attributable to tuberculosis was demonstrated. Telzak et al. [25] described the treatment responses of 26 HIV-negative patients who had MDR tuberculosis (18 had primary disease); 96% remained free of disease after a median of 91 weeks of follow-up.

In Estonia, a Baltic nation (population, 1.5 million) that gained independence from the former Soviet Union in 1991, the rates of infection with both primary and acquired MDR tuberculosis have been increasing [27]. During the period in which this study was conducted, treatment was very rarely directly observed; treatment was highly individualized, and second-line drugs, including amikacin, kanamycin, ciprofloxacin, cycloserine, and para-aminosalicylic acid, were used to treat MDR tuberculosis. Both privately employed and government-employed physicians treated patients with tuberculosis, regardless of the drug susceptibility pattern. A tuberculosis control program did not exist during the study period, although a tuberculosis registry was maintained and tuberculosis treatment drugs were provided for free.

In 1994, 623 tuberculosis cases were reported in Estonia. Of the isolates tested for drug susceptibility, 24 (9%) of 266 primary tuberculosis cases were MDR, whereas 5 (19%) of 26 patients with previously treated tuberculosis had MDR tuberculosis [27]. In 1995, 598 tuberculosis cases were reported, and 20 (9%) of 232 new patients with positive culture results and 11 (35%) of 31 previously treated patients had MDR tuberculosis; in 1996, 683 tuberculosis cases were reported, and 39 (12%) of 335 new patients with tuberculosis and 14 (20%) of 71 previously treated patients had MDR tuberculosis (unpublished data). Estonia has thus far enjoyed a low rate of HIV infection. Only 61 HIV-positive persons and 1 patient with HIV and *M. tuberculosis* coinfection were reported from 1988 through 1996 (Danilovitsch M, personal communication). We present the outcomes of patients enrolled in a retrospective matched cohort study conducted in Estonia that examined the treatment and clinical outcomes of patients with primary MDR tuberculosis as compared with those for new patients with tuberculosis that is drug susceptible. This is the first published report of the clinical outcomes of patients with primary MDR tuberculosis from a setting of low HIV prevalence, in which directly observed short-course therapy had not yet been systematically implemented. This information is important for the development of enhanced strategies for the treatment of patients with MDR tuberculosis and for the prioritization of public health spending.

METHODS

Tuberculosis in Estonia. The Estonian national tuberculosis registry contains the names and dates of registration of all patients with new or relapse tuberculosis in Estonia; all patients with tuberculosis are entered into this registry in either Tallinn or Tartu. Since 1992, most adult patients suspected of having pulmonary tuberculosis (with the exception of prisoners) have had sputum specimens submitted for culture for *M. tuberculosis* and have had susceptibility tests performed at the time of diagnosis and during follow-up (often at 2, 5, 7, and 11 months, and at the end of therapy). Conventional culture on solid Lowenstein-Jensen media and susceptibility tests done by use of the proportion method [28], with use of streptomycin (8.0 μg/mL), isoniazid (0.2 μg/mL), rifampin (40.0 μg/mL), and ethambutol (5.0 μg/mL), were done in Tallinn throughout the study period and in Tartu until January 1995. Susceptibility testing done by means of radiometric respirometry with the BACTEC-460 system [29], with use of streptomycin (6.0 μg/mL), isoniazid (0.1 μg/mL), rifampin (2.0 μg/mL), and ethambutol (7.5 μg/mL), was done in Tartu starting in January 1995. Susceptibility of a selection of isolates to first- and second-line drugs (both for quality control purposes) was determined, by use of the BACTEC system, at the Swedish Institute for Infectious Disease Control tuberculosis laboratory, Stockholm (the World Health Organization Supranational Reference Laboratory for the Baltic region). An *M. tuberculosis* isolate was considered to be MDR if it was resistant in vitro to, at least, isoniazid (high-level resistance) and rifampin. HIV testing was done by means of dual ELISAs.

Patient selection and data collection. The Estonian national tuberculosis registry was reviewed to obtain a list of all persons registered with a new diagnosis of tuberculosis from January 1994 through December 1996. In addition, all laboratory records for *M. tuberculosis* culture and sensitivity results from the same period were reviewed. Thus, all eligible patients who had pansensitive or MDR tuberculosis diagnosed during the study period were identified. Medical records for all eligible patients with primary MDR tuberculosis and for the selected

sample of patients with a first diagnosis of pansensitive tuberculosis were reviewed to ensure that patients met eligibility criteria. Eligible patients had to have culture-positive tuberculosis, no previous history of tuberculosis, less than 1 month's exposure to antituberculosis drugs, and either MDR or pansensitive tuberculosis, and were registered as tuberculosis patients from January 1994 through December 1996. Patients with a history of prior tuberculosis treatment were excluded by examination of both the tuberculosis registry and patient charts. Patients with *M. tuberculosis* isolated only from extrapulmonary sites were excluded because of the possibility of different clinical outcomes among these patients compared with patients with pulmonary tuberculosis, because of their small number, and because of the resultant inability to meaningfully stratify outcomes according to location of tuberculosis disease. MDR tuberculosis patients were patients whose sputum samples yielded *M. tuberculosis* isolates that had high-level isoniazid resistance and rifampin resistance documented in laboratory records as well as in patient charts. Pansensitive tuberculosis patients were patients who had *M. tuberculosis* isolates fully susceptible to all drugs tested (isoniazid, rifampin, streptomycin, and ethambutol). Patients who had MDR tuberculosis and those with pansensitive tuberculosis were matched 1:1 with one another according to month (registration within 1 month of each other) and region (Tallinn or Tartu) of registration, to control for unmeasured differences in different treatment practices. Patients who had MDR and those who had pansensitive tuberculosis were not matched by sex, because we wanted to evaluate the patient's sex as a potential risk factor for MDR tuberculosis. The ratio of eligible patients with MDR tuberculosis to those with pansensitive tuberculosis was 1:12; patients who had pansensitive tuberculosis were grouped according to the month and region of registration, and a matching patient with pansensitive tuberculosis was selected randomly for each patient who had MDR tuberculosis.

We reviewed the inpatient and outpatient medical records of all selected patients in January 1998 and conducted physician and patient interviews during the same month, when the patient could be located and had consented to an interview. The gathered data addressed potential risk factors for tuberculosis infection and disease, treatment medications and duration, patient compliance with therapy, outcome of therapy response (clinically, microbiologically, and radiographically), and medical factors (other than tuberculosis) that might affect clinical outcome. Additional information regarding the date and cause of death was extracted from death records at the Estonia Central Statistics Office. Tuberculosis was considered the probable cause of death in this analysis when it was cited as the cause of death in both the patient chart and the death records at the Estonia Central Statistics Office. None of the patients had postmortem examinations. Follow-up chest radiographs were obtained at a median of 18 months after the pretreatment chest radiograph in 96% of the patients who had MDR tuberculosis and 89% of the patients who had pansusceptible tuberculosis. Follow-up was considered to start on the date of entry in the tuberculosis registry and was considered to end at the time of death, loss to follow-up, or January 1998, whichever occurred last.

Statistical analysis. Treatment duration was considered the number of months during which the patient continued to visit health care practitioners, receive prescriptions for antituberculosis drugs, and self-report compliance with antituberculosis medications. Default was defined, in accordance with the standards of the International Union against Tuberculosis and Lung Disease, either as the failure of a patient to return for a prescription to receive antituberculosis drugs for $\geqslant$2 months or as a known break in treatment of $\geqslant$2 months [30]. Cure was said to have occurred in patients who had $\geqslant$1 sputum smear that tested negative for acid-fast bacilli at the end of the prescribed course of tuberculosis treatment; this was also the definition used for multivariable models. Treatment failure was defined as a positive sputum culture result after $\geqslant$6 months of therapy (among those with pansusceptible tuberculosis) or after $\geqslant$12 months of potentially effective therapy (among those with MDR tuberculosis). Death due to tuberculosis was also considered treatment failure. Potentially effective treatment was defined as treatment with $\geqslant$2 antituberculosis medications to which a patient's *M. tuberculosis* isolate was susceptible on the basis of results of susceptibility tests for isoniazid, rifampin, streptomycin, and ethambutol; for patients with MDR tuberculosis, potentially effective treatment was defined as the use of at least 2 second-line drugs (for which susceptibility testing was not routinely available). If the MDR isolate was susceptible to streptomycin or ethambutol, and if the patient received 1 of these medications plus at least 1 second-line drug, then treatment was also defined as potentially effective.

Continuous variables were compared by use of the Wilcoxon 2-sample test. Variables associated with treatment failure ($P <$ .2) in matched univariable analysis or possible confounding variables were included in multivariable, conditional logistic regression models. Collinear variables, such as patient age, were excluded from final models. Matched ORs, multivariable ORs, 95% CIs, and Mantel-Haenszel *P* values are presented. Kaplan-Meier survival curves and survival analysis with use of univariable and multivariable Cox proportional hazard models were done; survival time was calculated, in days, from the first day of antituberculosis treatment to the date of death or, for those who lived, the date of chart abstraction in January 1998. Patients who died of causes other than tuberculosis were censored on their date of death. All analyses were done with the use of SAS software (SAS Institute).

Table 1. Demographic and pretreatment clinical characteristics of patients in Estonia with multidrug-resistant (MDR) or pansusceptible tuberculosis.

Characteristic	Patients with MDR tuberculosis ($N = 46$)	Patients with pansusceptible tuberculosis ($N = 46$)	Matched OR (95% CI)	Matched P
Female sex	20 (44)	10 (22)	3.5 (1.1–14.6)	.02
Age, median y	44	50		.10
Other medical problems, median no.	1	1		.10
Prior hospitalizations, median no.	1	0		.03
History of heavy alcohol use	18 (39)	21 (46)	0.8 (0.3–1.9)	.50
Positive result of AFB smear prior to treatment	32 (70)	34 (74)	0.8 (0.2–2.3)	.60
Cavity on pretreatment chest radiograph	34 (74)	42 (91)	0.3 (0.1–1.0)	.03
Duration of symptoms before seeking medical attention, median weeks	4	6		.70
Did not attend school after elementary grades[a]	4 (22)	4 (29)	1.0 (0.01–79)	1.00

NOTE. Data are no. (%) of patients with characteristic, unless otherwise indicated. AFB, acid-fast bacilli.

[a] From interview; $n = 18$ for patients with MDR and $n = 14$ for patients with pansusceptible tuberculosis.

RESULTS

After all tuberculosis registry and laboratory data were reviewed, 103 patients with possible primary MDR tuberculosis were identified, compared with 83 listed in the tuberculosis registry alone. Of these 103 patients, 34 did not have conditions that met the definition of primary MDR tuberculosis, primarily because they had been receiving treatment for at least 1 month before the first isolation of MDR *M. tuberculosis.* Another 12 patients had isolates with only intermediate resistance to isoniazid or with susceptibility to rifampin. Four patients had pleural tuberculosis only. One of these 4 reportedly died of tuberculosis, 1 defaulted, 1 still tested positive (by smear) for acid-fast bacilli and was undergoing antituberculosis therapy at the time of the study, and 1 died of nontuberculosis causes. Of the 53 eligible patients who had MDR tuberculosis, 46 (87%) were enrolled in the study. The 7 eligible patients with MDR tuberculosis who were not enrolled could not be located, and their medical records could not be found; none of the 7 were listed in the Central Statistics Office death records. Forty-six matched eligible patients who had pansusceptible tuberculosis were selected randomly; the charts could not be found for only 3 (7%) of these original 46 patients, and another 3 patients who had pansusceptible tuberculosis and who were matched with the corresponding MDR tuberculosis patients were selected randomly in their stead. Eighteen patients with MDR tuberculosis and 14 patients with pansusceptible tuberculosis were located, and they all completed interviews; these interviews did not add significantly to the information gathered from other sources.

The median follow-up time for patients with MDR and pansusceptible tuberculosis was 22 and 24 months, respectively ($P = .2$; range, <1 month to 50 months, with date of death or default as time of last follow-up for patients with either of these outcomes).

Demographic and clinical data for the 46 pairs of patients with MDR and pansusceptible tuberculosis are summarized in table 1. The majority of patients in both groups were male, although more MDR tuberculosis patients (44%) than pansusceptible tuberculosis patients (22%) were female ($P = .02$). The age range was 23 to 77 years. Median age, median number of nontuberculosis medical problems, proportion of patients who were heavy alcohol drinkers, rate of positive smear results for acid-fast bacilli before treatment, and symptom duration before medical attention was sought did not differ significantly between patients with MDR tuberculosis and those with pansusceptible tuberculosis (all $P > .2$). Patients with MDR tuberculosis had a greater number of prior hospitalizations ($P = .03$) but were less likely to have cavitation on their pretreatment chest radiograph ($P = .03$) than were patients who had pansusceptible tuberculosis. Fifty-five patients (26 with MDR tuberculosis and 29 with pansusceptible tuberculosis) underwent HIV testing, and all had negative results.

Treatment characteristics and patient outcomes are summarized in table 2. The great majority of patients in both groups were hospitalized to undergo initiation of treatment, and the duration of initial hospitalization and the number of drugs started at the time of diagnosis did not differ between groups. Both patient groups received treatment for a similar number of months (10 and 11 months, respectively), but patients with pansusceptible tuberculosis were more likely than patients who had MDR tuberculosis to be treated for a longer duration with at least 2 drugs to which their isolate was susceptible ($P = .01$). A median of 6 weeks elapsed before patients with MDR tuberculosis began treatment with at least 2 second-line drugs,

Table 2. Treatment characteristics and clinical outcomes of patients with multidrug-resistant (MDR) or pansusceptible tuberculosis.

Characteristic or outcome	Patients with MDR tuberculosis (N = 46)	Patients with pansusceptible tuberculosis (N = 46)	Matched OR (95% CI)	Matched P
Received initial treatment in hospital	40 (87)	44 (96)	0.3 (0.03–1.90)	.20
Antituberculosis medications started, median no.	3	4		.40
Second-line drugs used, median no.	2	0		<.01
Significantly different regimens, median no.	4	3		.03
Proportion of case and control patients who received ⩾1 month of treatment with ⩾2 drugs to which isolate is susceptible	35 (76)	46 (100)	Undefined	<.01
Duration of treatment with ⩾2 drugs to which isolate is susceptible, median weeks	16	39		.01
Duration before treatment was begun with ⩾2 drugs to which isolate is susceptible, median weeks	6	0		<.01
Duration of treatment with standard 3- or 4-drug regimen, median weeks	8	28		<.01
Duration of total treatment, median months	10	11		.60
Duration of inpatient treatment, median months	3	3		.40
Duration of first hospitalization, median d	64	78		.90
Received standard short-course chemotherapy[a]	0	2 (4)	Undefined	.20
Underwent lung surgery	2 (4)	1 (2)	2.0 (0.1–118)	.60
Left hospital against medical advice	15 (33)	14 (30)	1.1 (0.4–3.1)	.8
Defaulted treatment[b]	16 (35)	19 (41)	0.8 (0.3–2.2)	.7
Median no. of hospitalizations after diagnosis of tuberculosis	1.5	1.0		.1
Cavitation on follow-up chest radiograph, *n/N* (%)	19/41 (46)	12/44 (27)	1.8 (0.7–4.8)	.1
Presentation on follow-up chest radiograph worse than on pretreatment radiograph, *n/N* (%)	15/41 (37)	4/44 (9)	6.5 (1.5–59)	<.01
Cure[c]	17 (37)	28 (61)	0.3 (0.1–0.9)	.02
Treatment failure,[d] *n/N* (%)	16/18 (89)	3/30 (10)	8.9 (3.0–26.3)	<.0001
Positive result on most recent AFB smear, *n/N* (%)	14/31 (45)	1/32 (3)	10.0 (1.4–434)	<.01
Died				
Of any cause	13 (28)	5 (11)	9.0 (1.3–394)	.01
Of tuberculosis	10 (22)	2 (4)		<.01

NOTE. Data are no. (%) of patients with characteristic, unless otherwise indicated. Different denominator is given when not all patients had data available. AFB, acid-fast bacilli.

[a] Short-course chemotherapy is recommended by the World Health Organization and is defined as 2 months of treatment with isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol, followed by 4 months of treatment with isoniazid and rifampin (for patients with no prior treatment of tuberculosis).

[b] World Health Organization definition: failure by patient to take or to pick up prescription for antituberculosis medications for ⩾2 consecutive months.

[c] Completed ⩾6 months of therapy and had a negative AFB smear result at end of treatment.

[d] Defined as either death due to tuberculosis or a culture result positive for *Mycobacterium tuberculosis* after ⩾6 months of therapy, for patients with pansusceptible tuberculosis, and after >12 months of therapy with ⩾2 second-line drugs, for patients with MDR tuberculosis. OR is unmatched.

whereas all patients with pansusceptible tuberculosis began effective treatment at the time of diagnosis ($P < .01$). One patient with pansusceptible tuberculosis and 2 with MDR tuberculosis underwent lung surgery in an effort to cure their tuberculosis ($P = .6$). Similarly high proportions of both groups left the hospital against medical advice (33% of patients with MDR tuberculosis vs. 30% of patients with pansusceptible tuberculosis; $P = .8$) or defaulted during treatment (35% of MDR vs. 41% of pansusceptible; $P = .7$). The median number of hospitalizations after a diagnosis of tuberculosis did not differ between patients with MDR tuberculosis (1.5) or those with pansusceptible (1.0) tuberculosis ($P = .1$).

With regard to treatment failure, of 8 patients with MDR tuberculosis who received treatment with ⩾2 second-line drugs for ⩾12 months and who had cultures of sputum samples after 12 months, 6 (75%) still tested positive by culture for *M. tuberculosis;* an additional 10 patients with MDR tuberculosis died of tuberculosis. Among the 28 patients with pansusceptible tuberculosis who received at least 6 months of therapy and who had follow-up cultures of sputum samples, only 1 (4%) still had sputum that tested positive by culture after 6 months, and 2 died of tuberculosis (unmatched OR of treatment failure among patients with MDR tuberculosis compared with those with pansusceptible tuberculosis, 8.9; 95% CI, 3.0–26.3; $P < .0001$). Three patients with MDR tuberculosis (7%) and no patient with pansusceptible tuberculosis had antituberculosis therapy discontinued while their sputum sample still tested positive for acid-fast bacilli ($P = .08$). Forty-one patients with MDR tuberculosis (89%) and 44 (96%) with pansusceptible tuberculosis had follow-up chest radiographs done. Nineteen (46%) of the patients with MDR tuberculosis and 12 (27%) of those with pansusceptible tuberculosis had cavitation on follow-up chest radiographs ($P = .1$), and the presentation on follow-up chest radiographs was described as worse in 15 (37%) of patients who had MDR tuberculosis and 4 (9%) of patients who had pansusceptible tuberculosis ($P < .01$).

Thirteen patients with MDR tuberculosis (28%) and 5 patients with pansusceptible tuberculosis (11%) died during follow-up (matched OR, 9.0; 95% CI, 1.3–394; $P = .01$). Ten patients who had MDR tuberculosis (22%) and 2 patients who had pansusceptible tuberculosis (4%) died of tuberculosis ($P < .01$). Among the 6 patients who died of causes other than tuberculosis, 4 had myocardial infarction, 1 drowned, and 1 died after a cerebrovascular accident. Figure 1 shows the Kaplan-Meier survival curves of deaths due to tuberculosis.

In multivariable analysis, our final model examining treatment failure included drug susceptibility status, number of nontuberculosis medical problems, and number of weeks of potentially effective treatment. MDR tuberculosis was the only factor associated with treatment failure (multivariable OR, 3.3; 95% CI, 1.1–10; $P = .04$). Number of weeks of potentially effective treatment ($P = .4$) and number of other medical problems ($P = .9$) were not associated with cure or treatment failure.

Our multivariable survival analysis model that examined risk factors for death due to tuberculosis included drug susceptibility, number of nontuberculosis medical problems, and sex. Patients with MDR tuberculosis were more likely to die of tuberculosis than were patients who had pansusceptible tuberculosis (hazard ratio, 7.8; 95% CI, 1.6–37.4; $P = .01$). An increase in the number of nontuberculosis medical problems (hazard ratio, 2.5; 95% CI, 1.5–4.4; $P < .01$) and male sex (hazard ratio, 5.8; 95% CI, 1.1–29.6; $P = .03$) were also associated with death due to tuberculosis. Among the 12 patients who died of tuberculosis, 10 (83%) were male (the 2 female patients who died of tuberculosis both had MDR tuberculosis). Among the patients with MDR tuberculosis, the number of weeks before potentially effective treatment was started did not differ between those who died and those who did not die (5 weeks vs. 8 weeks; $P = .8$), nor did the rate of treatment default (41% vs. 38%; $P = .6$). Median survival time of patients who died of tuberculosis was 6 months among those with MDR tuberculosis and 13 months among those with pansusceptible tuberculosis ($P = .5$).

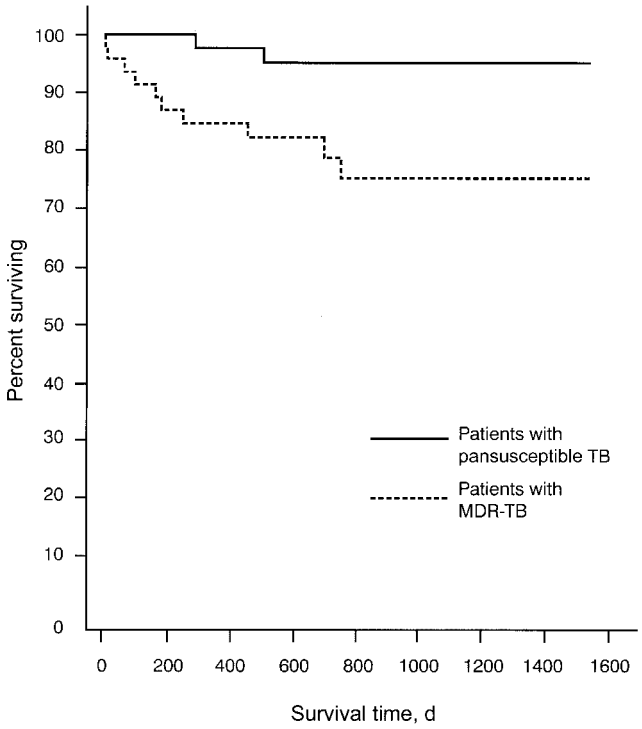

Figure 1. Kaplan-Meier survival curves of deaths due to tuberculosis (TB) for patients with multidrug-resistant (MDR) TB and patients with pansusceptible TB.

DISCUSSION

These are the first published data concerning clinical outcomes of patients with primary MDR tuberculosis in a setting of very low HIV prevalence. They suggest that HIV-negative patients with primary MDR tuberculosis are significantly more likely to have treatment failure and to die of tuberculosis than are patients with pansusceptible tuberculosis.

The patients with MDR tuberculosis and pansusceptible tuberculosis did not differ with respect to age, number of medical problems, history of alcohol abuse, or pretreatment clinical status; in fact, patients with pansusceptible tuberculosis had evidence of more-advanced tuberculosis disease on chest radiography done at the time of diagnosis, compared with those

with MDR tuberculosis. Furthermore, similar proportions of patients with MDR- and drug-susceptible tuberculosis defaulted on treatment or left the hospital against medical advice. There was, therefore, no evidence that adverse clinical outcome among patients with MDR tuberculosis was due to more severe underlying medical illness or worse compliance with antituberculosis therapy, although the latter cannot be excluded.

The majority of persons with active tuberculosis reside in countries with financial or laboratory resources that limit drug susceptibility testing of *M. tuberculosis* for purposes other than surveillance. Drug susceptibility testing on isolates from all *M. tuberculosis* culture–positive patients is, however, done in Estonia, and treatment with second-line antituberculosis drugs is initiated for persons with MDR tuberculosis.

In our study, although 77% of patients with MDR tuberculosis were treated with second-line drugs after drug susceptibility of their *M. tuberculosis* isolates was ascertained, clinical outcomes among this group were worse than among those patients with drug-susceptible tuberculosis. This may be due to the lower efficacy of second-line antituberculosis drugs compared with standard first-line therapy; primary resistance of MDR *M. tuberculosis* isolates to second-line drugs and the lack of susceptibility testing for second-line drugs to guide therapy; the median 6-week delay between diagnosis and initiation of second-line drugs among patients with MDR tuberculosis; treatment of noncompliant patients without directly observed therapy; or a genetically determined susceptibility to more-severe disease among hosts who present with primary MDR *M. tuberculosis* (which may, in most persons, have a lower propensity to cause tuberculosis disease after infection than do pansusceptible strains) [31]. It is likely that the first 4 factors (at least) contributed to the worse outcomes among patients with MDR tuberculosis in this study, although treatment delay is less likely to have contributed to adverse outcome, according to our data: patients with MDR tuberculosis who died did not wait significantly longer to start potentially effective therapy than did those with MDR tuberculosis who survived.

Our study had limitations. Seven (13%) of 53 eligible patients were not enrolled in the study (none of these patients were found in the Central Statistics Office death records). Susceptibility of *M. tuberculosis* isolates to second-line drugs was ascertained in only 9 study patients (these 9 patients are not described here because they were not representative of the patients who had MDR tuberculosis); therefore, it is impossible to determine with certainty whether patients were receiving potentially effective therapy with second-line agents.

These data are theoretically applicable to any setting in which there is low HIV prevalence and primary MDR tuberculosis exists, in particular in nations with access to second-line therapy but without the ability to directly observe therapy. There has been a general belief that the high mortality associated with MDR tuberculosis is primarily in association with HIV coinfection [9, 12, 18–23]; in this study, the 22% mortality rate among patients with MDR tuberculosis is certainly lower than the rates of 80%–90% previously noted among HIV-infected patients with MDR tuberculosis; this rate is, nevertheless, alarming. Our data also show that among patients with MDR tuberculosis who reside in a setting of very low HIV prevalence and who do not die of tuberculosis, 75% still had positive smear results after 12 months of treatment with at least 2 second-line drugs, and that even those who die of MDR tuberculosis survive for a median of 6 months after diagnosis; these patients, therefore, represent a significant potential source of ongoing transmission of MDR tuberculosis.

In summary, these data show that rates of treatment failure and death are greater among patients with primary MDR tuberculosis than among those with drug-susceptible tuberculosis, even in a setting of low HIV prevalence in which second-line drugs are used. These findings should raise the level of attention to the prevention and treatment of MDR tuberculosis.

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