Outcome of Multidrug-Resistant Tuberculosis in Human Immunodeficiency Virus–Infected Patients

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Among 324 cases of culture-proven tuberculosis from 1988 to 1996 in a hospital in Milan, Italy, 90 (27.8%) were due to *Mycobacterium tuberculosis* strains resistant to isoniazid and rifampin. Sixty-one of 69 isolates tested had identical restriction fragment length polymorphism patterns. The prevalent strain tested susceptible only to ethionamide and was also resistant to ethambutol, streptomycin, cycloserine, amikacin, kanamycin, terizodone, ofloxacin, rifabutin, rifapentin, and KRM 1648. The median survival time was 94 days. Multivariate analysis showed a trend toward better outcome in the period 1994–1996 (hazard ratio, 4.16; $P < .001$), and extrapulmonary localization of tuberculosis was the only other independent predictor of a negative outcome (hazard ratio, 2.1; $P = .019$). The delay from symptoms to beginning of therapy did not seem to be a determining factor in survival time. Standard antituberculosis therapy with four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) had a higher efficacy than did other regimens with fewer drugs but without a statistically significant difference.

From the mid-1980s, the gradual decline of tuberculosis in the developed world reversed dramatically. The resistance to antituberculosis drugs was evidenced soon after the drugs were first introduced, but multidrug resistance was not initially considered important. Recently the situation has changed [1]. The first recognized clusters of multidrug-resistant (MDR) tuberculosis among hospitalized patients with AIDS were reported to the Centers for Disease Control in 1990 [2]. The first of such clusters reported in Europe was an outbreak of six cases of nosocomial tuberculosis, originally attributed to a slow-growing *Mycobacterium bovis* observed in France between 1989 and 1991, and subsequently identified as being due to *Mycobacterium tuberculosis* [3, 4]. Afterwards, several reports from Italy [5, 6], Spain [7], and other countries [8–12] have demonstrated a large diffusion of multidrug resistance among HIV-infected persons.

MDR tuberculosis in the HIV-infected population is associated with poor treatment response, in spite of the inclusion of additional drugs to the standard treatment (isoniazid, rifampin, pyrazinamide, and/or ethambutol). Initial reports showed that 72%–89% of patients die in 4–19 weeks [1, 2]. However, more favorable rates of survival in MDR tuberculosis were subsequently observed by several authors, demonstrating that aggressive therapy can result in prolonged survival and cure, even in patients with HIV infection [13–16]. The aim of our study was to evaluate the variables influencing the span of time of survival in an HIV-positive population with tuberculosis and high levels of multiple drug resistance.

Patients and Methods

Setting. The study was conducted in the three infectious diseases divisions of the Luigi Sacco Hospital, in Milan, Italy. Luigi Sacco Hospital is a 550-bed hospital that is the largest provider of medical care to AIDS patients among the ~2 million residents of Milan and suburbs. In the three adult infectious diseases units, a total of ~800 HIV-infected patients are admitted yearly, with an additional 1,500–1,600 patients followed in day hospital and outpatient facilities.

Data collection. Patients with HIV infection and culture-proven tuberculosis were identified from the mycobacteriology laboratory log books for the dates 1 January 1988 through 31 December 1996. The microbiology records were cross-matched with the clinical records of the hospital.

The medical records of the patients with MDR tuberculosis were reviewed retrospectively. The following data were collected: demographic data; past and present medical history; date of diagnosis of AIDS; dates and results of mycobacterial smears; signs, symptoms, and roentgenographic picture of tuberculosis; treatment regimens for tuberculosis; outcome; and autopsy findings, if available.

Laboratory methods. Primary mycobacterial isolation was done by use of Lowenstein-Jensen slant cultures. The following drugs and concentrations were used for susceptibility testing: isoniazid, 1 μg/mL; ethambutol, 5 μg/mL; rifampin, 1 μg/mL; and streptomycin, 10 μg/mL. A sample of the

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multidrug-resistant *M. tuberculosis* isolates were tested again for susceptibility to pyrazinamide, cycloserine, amikacin, kanamycin, and ofloxacin (July 1993) and to rifabutin, rifapentin, terizodone, ethionamide, and KRM 1648 (June 1996).

Genomic DNA of all available MDR *M. tuberculosis* isolates was analyzed by use of DNA restriction fragment length polymorphism (RFLP) analysis done according to previously described methods [17].

Definitions of outcome-associated factors. MDR tuberculosis was defined as any active tuberculosis due to an *M. tuberculosis* isolate resistant to at least isoniazid and rifampin.

Possible factors associated with prognosis are listed in table 1. Age was dichotomized at the value of 35 years to calculate survival. Patients with a history of intravenous drug abuse were compared with patients with other risk factors for HIV infection. The history of a previous AIDS diagnosis was defined according to the modified 1987 Centers for Disease Control criteria [18]. Pulmonary tuberculosis was defined as disease with a culture positive for *M. tuberculosis* from sputum or bronchoscopic sample. Extrapulmonary tuberculosis was defined as disease with a culture positive for *M. tuberculosis* of a sample from at least one extrapulmonary site, including the isolation of *M. tuberculosis* from blood specimens. Complicated pulmonary presentation was defined as the presence of pneumothorax or pleural effusions on thoracic roentgenograms. The $CD4^+$ cell count at the time of MDR tuberculosis diagnosis was dichotomized at the value of 50 $CD4^+$ cells/μL.

A cluster of cases was defined as two or more patients whose *M. tuberculosis* isolates were identical or differed by only a single additional band, as determined by RFLP analysis. Patients with MDR tuberculosis due to an *M. tuberculosis* strain with the same RFLP pattern (epidemic strain) were compared with patients with tuberculosis due to sporadic strains. Patients diagnosed in the early phase of the epidemics (years 1991–1993) were compared with patients diagnosed in the late phase (between 1994–1996).

The therapeutic delay was calculated from the date of the appearance of the symptoms to the date of initiation of therapy. The symptoms were consistent with diagnostic standards and classification for tuberculosis of the American Thoracic Society and Centers for Disease Control [19]; they were attributed to tuberculosis after excluding other coexisting HIV-related complications (primarily bacterial infections, cytomegalovirus infection, and *Mycobacterium avium* infection). The therapeutic delay was dichotomized at the value of 30 days.

The different treatment regimens were grouped as follows: regimens initially including at least the four standard antituberculosis drugs (isoniazid, rifampin or rifabutin, ethambutol, and pyrazinamide), regimens including three of the standard drugs, and regimens including two or fewer of the standard drugs.

The date of diagnosis of MDR tuberculosis was considered as the date of collection of the first sample from which MDR *M. tuberculosis* was isolated. Survival was calculated in days from the date of diagnosis of MDR tuberculosis to the date of death or, for those who lived, to the date that the study ended (31 December 1996).

Statistical analysis. Survival analysis and identification of prognostic factors for survival were done by use of the Kaplan-Meier method and the log-rank test. Significant factors from univariate analysis ($P < .05$) were included in a Cox proportional hazards model for multivariate analysis of survival.

Table 1. Possible risk factors sought in a chart review of 90 HIV-infected patients with multidrug-resistant tuberculosis.

Type of factor	Factor
Demographic	Age
	Sex
	Risk factors for HIV infection
Medical history	Previous AIDS diagnosis
	History of previously treated tuberculosis
Examination and laboratory results	Clinical presentation (pulmonary vs. extrapulmonary disease)
	Roentgenographic picture
	$CD4^+$ cell count
	Mycobacterium tuberculosis genotype
History of present illness	Year of diagnosis of multidrug-resistant tuberculosis
	Concomitant opportunistic diseases
	Therapeutic delay
	Characteristics of treatment

Results

Study population. Between 1 January 1988 and 31 December 1996, we identified 324 cases of culture-proven tuberculosis in HIV-infected patients. The pattern of drug resistance is described in table 2: 90 patients (27.8%) had developed infection with a strain resistant to four drugs (isoniazid, rifampin, streptomycin, and ethambutol). Sixty-nine of these 90 patients had *M. tuberculosis* cultures available for RFLP analysis. A total of 9 RFLP patterns were seen among these 69 patients. Eight patients had strains of *M. tuberculosis* with unique RFLP fingerprints and 61 (88.4%) had strains whose RFLP patterns were identical, which we classified into one single cluster (figure 1). A broader susceptibility test was done on some isolates of this cluster. These isolates were found to be susceptible only to ethionamide and were resistant also to cycloserine, amikacin, kanamycin, terizodone, ofloxacin, rifabutin, rifapentin, and KRM 1648 (a rifamycin derivative). Although most of the patients received pyrazinamide as part of their antituberculosis regimen, the activity of this drug against our MDR *M. tuberculosis* strains could not be determined because of the inaccuracy of pyrazinamide susceptibility testing [17].

Clinical and radiographic findings. Table 3 shows the characteristics of 90 HIV-infected patients with MDR tuberculosis. The median age was 39 years (range, 26–49 years).

Table 2. Prevalence of patients with tuberculosis among HIV-infected subjects by year, January 1988 to December 1996 (L. Sacco Hospital).

Resistance	1988	1989	1990	1991	1992	1993	1994	1995	1996	Total
INH	1	2	—	1	1	—	1	—	—	6 (1.9%)
Rif	12	—	4	—	2	1	2	1	4	26 (8.0%)
Stm	—	4	7	2	7	3	20	1	6	50 (15.4%)
INH, Stm	—	—	—	—	—	—	2	1	3	6 (1.9%)
Stm, Rif	—	1	1	1	—	5	5	1	5	19 (5.9%)
INH, Stm, Rif, Emb	—	—	—	1	3	32	36	11	7	90 (27.8%)
Total	25	34	41	19	25	60	72	18	30	324 (100%)

NOTE. Emb = ethambutol; INH = isoniazid; Rif = rifampin; Stm = streptomycin.

Fifty-nine patients (66%) were intravenous drug users, and 64 (71%) had had previous AIDS-defining illnesses. Twenty-one patients (23%) had a history of previous tuberculosis: In at least 5 of these 21 cases, a former lack of compliance with antituberculosis medications was documented. Six of 90 patients developed MDR tuberculosis while receiving antituberculosis drugs for a susceptible organism.

All of the patients were symptomatic at the time of diagnosis, and fever was present in all cases. At the time of diagnosis of tuberculosis, 70 patients (67%) had symptoms of pulmonary disease only, 5 patients had symptoms of extrapulmonary disease only, 8 had symptoms of pulmonary and extrapulmonary disease, and 7 had fever without any apparent localization. The most commonly involved extrapulmonary sites at the time of diagnosis were the CNS, the lymph nodes, and the pericardium in five cases each. During long-term follow-up, progressive tuberculosis with disseminated disease was observed in many patients. The most common extrapulmonary sites of isolation of *M. tuberculosis* were blood (25.6%), lymph nodes (5.6%), and CSF (5.6%). Other sites of isolation were pericardial fluid, stool, urine, bone marrow, skin, and bile.

Chest roentgenograms were available for all of the patients. Fourteen patients had normal chest radiographs at admission. We observed a unifocal alveolar infiltrate in 40, multiple alveolar-interstitial infiltrates in 9, interstitial infiltrates in 19, isolated mediastinal-hilar adenopathy in 6, and isolated cardiomegaly in 2. Hilar adenopathy was described in 29% and pleural effusions in 7% of overall chest radiographs. At the onset of MDR tuberculosis, 36 patients had coexisting opportunistic diseases: The most frequent were cytomegalovirus infection (13 patients) and encephalic toxoplasmosis (7 patients). The median $CD4^+$ cell count at the time of diagnosis of MDR tuberculosis was 13 cells/μL (range, 0–252 cells/μL), and only 16 patients (18%) had >50 cells/μL.

Treatment data. For our patients, various regimens of antituberculosis therapy were used; the most frequent initial treatment consisted of isoniazid, rifampin, pyrazinamide, and ethambutol. Common alternative drugs were fluoroquinolones, streptomycin, rifabutin, amikacin, and clofazimine. Initial antimicrobial susceptibility results were available 3–6 months after receipt of specimens. Results of antibiograms showing susceptibility to ethionamide were available in the conclusive phase of the outbreak, and only one patient had initial treatment that included this drug. All but this patient received drugs to which their mycobacterial strain was resistant according to conventional testing, yet some of them responded clinically and microbiologically.

The median time from symptoms to antituberculosis treatment was 20 days. Defervescence occurred in 49 patients, but in 14 of these we observed a prompt reappearance of the symptoms within 14 days.

Survival data and autopsy findings. Eighty-four (93.3%) of 90 patients with MDR tuberculosis had died by the time of investigation, 3 were lost to follow-up, and 3 were still alive. The fatality rate was 39.1% within 10 weeks of diagnosis and 58.6% within 20 weeks. The median survival from diagnosis of MDR tuberculosis until death was 94 days. Overall, 24 HIV-infected patients with MDR tuberculosis survived for at least 6 months, but at least 7 of these patients had sputum samples persistently positive for acid-fast bacilli. Fewer than 10% survived for 12 months or more (table 4).

Autopsy results were available from 36 patients with MDR tuberculosis. In 34 cases, histopathologic evidence of tuberculosis was demonstrated. Lung involvement was present in all but three of these patients (one each with renal, meningeal, and hepatosplenic tuberculosis). Signs of disseminated tuberculosis were documented in 25 patients. In the other five patients, the involvement of lungs was accompanied by involvement of either liver, spleen, cervical lymph nodes, or meninges. In the remaining two cases without evidence of tuberculosis at autopsy, the causes of death were neurotoxoplasmosis plus disseminated cytomegalovirus infection and neurotoxoplasmosis and bacterial pneumonia.

Outcome-associated factors: univariate analysis. We evaluated all of the clinical, demographic, and laboratory variables presented in table 1 for their influence on survival. Age, risk factors for HIV infection, history of previous tuberculosis, characteristics of roentgenographic picture, *M. tuberculosis* genotype, and therapeutic delay did not significantly affect survival in the univariate analysis.

Median survival was significantly shorter in the following comparisons: men vs. women (78 days vs. 214 days; $P = .03$);

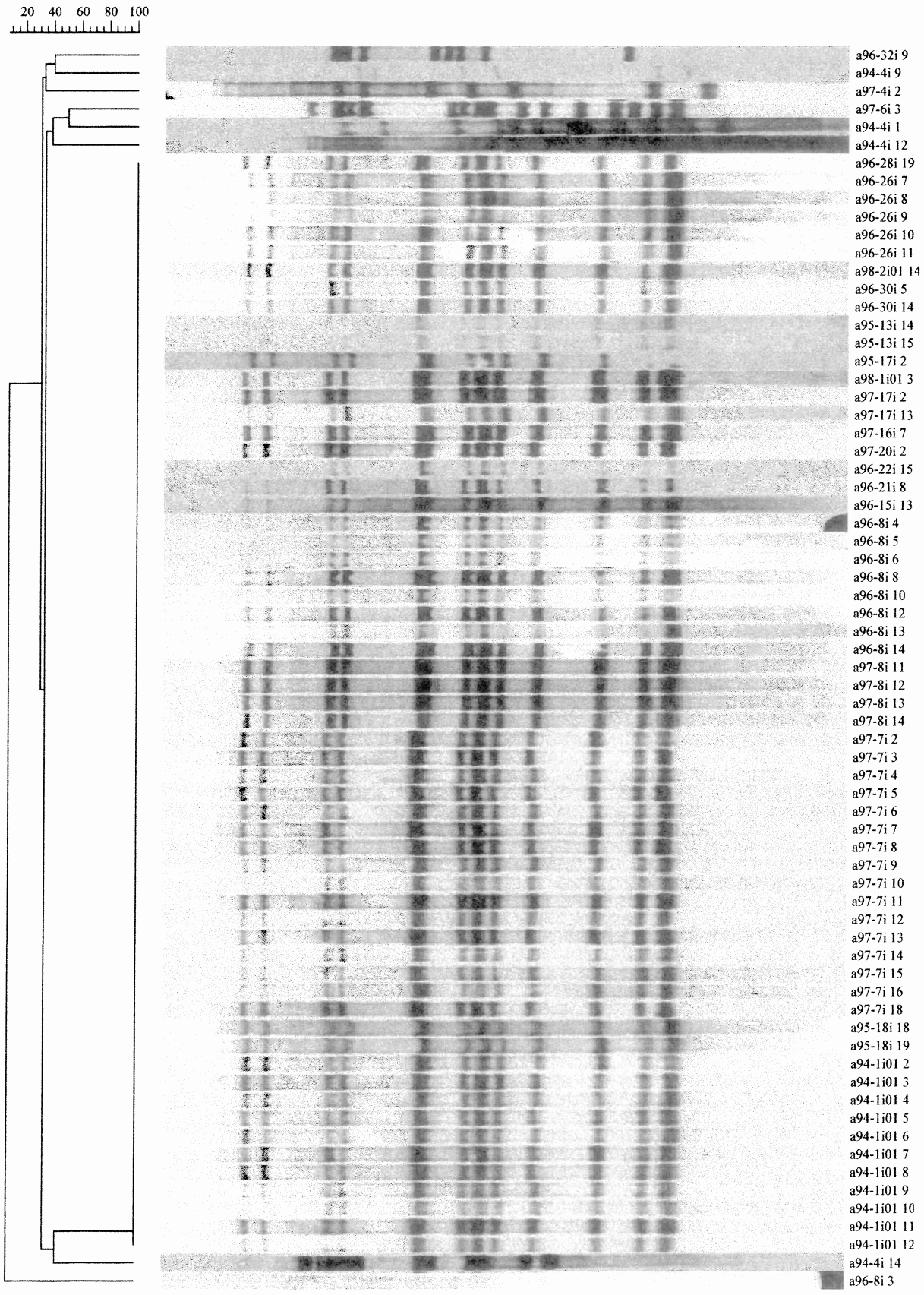

Figure 1. Dendrogram drawn by the Gel-Compare program (Applied Maths, Kortrijk, Belgium), showing the relationship of the restriction fragment length polymorphism (RFLP) patterns of 69 isolates of multidrug-resistant *Mycobacterium tuberculosis* obtained by RFLP analysis with IS*6110*. The first six lanes and the last two lanes represent sporadic strains.

Table 3. Characteristics of 90 HIV-infected patients with multidrug-resistant tuberculosis.

	No. (%) of patients with indicated characteristic
Age, y	
<35	55 (61)
≥35	35 (39)
Sex	
Male	73 (81)
Female	17 (19)
Risk factor for HIV	
Intravenous drug addiction	59 (66)
Heterosexual intercourse	21 (23)
Homosexual intercourse	9 (10)
Unknown	1 (1)
Previous tuberculosis	
Yes	21 (23)
No	69 (77)
Stage of HIV infection	
AIDS	64 (71)
Pre-AIDS	26 (29)
Tuberculosis presentation	
Pulmonary only	70 (67)
Extrapulmonary	20 (38)
$CD4^+$ cell count, cells/μL	
>25	29 (32)
>50	16 (18)
>100	9 (10)
Roentgenographic picture*	
Unifocal infiltrate	40 (51)
Multiple infiltrates	9 (12)
Interstitial infiltrates	19 (24)
Hilar adenopathy	23 (29)
Pleural effusions or pneumothorax	10 (13)
RFLP type†	
Epidemic strain	61 (88)
Sporadic strain	8 (12)
Concurrent opportunistic diseases	
Yes	36 (40)
No	54 (60)
Therapeutic delay‡	
<30 days	61 (68)
≥30 days	29 (32)
Initial treatment§	
Four or more drugs	45 (50)
Three drugs	24 (27)
Two or fewer drugs	21 (23)

* For patients with pulmonary involvement (n = 78).

† Restriction fragment length polymorphism (RFLP) analysis was done for 69 available strains.

‡ Calculated from appearance of fever to initiation of antituberculosis treatment.

§ Antituberculosis drugs in the first 2 weeks of treatment.

patients with a previous diagnosis of AIDS vs. patients without an AIDS diagnosis (79 days vs. 160 days; P = .006); patients with extrapulmonary localization at the onset vs. patients with only pulmonary involvement (40 days vs. 167 days; P < .001); patients with absolute $CD4^+$ cell counts of ≤50 cells/μL vs. patients with $CD4^+$ cell counts of >50 cells/μL (77 days vs. 166 days; P = .03); patients diagnosed in 1991–1993 vs. patients diagnosed in 1994–1996 (52 days vs. 157 days; P < .001); patients with concomitant opportunistic diseases vs. patients without opportunistic diseases (53 days vs. 135 days; P = .007); and patients receiving treatment with two drugs or fewer vs. patients receiving treatment with three drugs or with four or more drugs (38 days vs. 96 or 149 days; P < .004).

Outcome-associated factors: multivariate analysis. When the factors significantly associated with survival by univariate analysis were included in the multivariate model, only extrapulmonary presentation of tuberculosis and year of diagnosis of MDR tuberculosis remained independent predictors of poorer survival (table 5). The hazard ratio for patients with extrapulmonary tuberculosis vs. those with pulmonary tuberculosis was 2.10 (95% CI, 1.13–3.92). The hazard ratio for patients with MDR tuberculosis diagnosed in the first 3 years of the outbreak (1991–1993) vs. those diagnosed in 1994–1996 was 4.16 (95% CI, 1.89–9.17).

Discussion

The problem of MDR tuberculosis has recently received growing attention because of the increases in number and size of nosocomial outbreaks among HIV-infected patients, first in the United States [20–22] and then in the rest of the world [3–8, 12]. Approximately 8% of new cases of tuberculosis in the United States during 1996 were due to strains resistant to at least isoniazid, and 1.5% were due to strains resistant to at least isoniazid and rifampin [23]. This percentage has surely risen in large urban areas [24–26] and in defined high-risk groups, including those with HIV infection [27, 28].

Our study documents the occurrence of MDR tuberculosis between October 1991 and September 1996 among HIV-infected patients in three infectious diseases wards in a northern Italian hospital. We attribute the increase in the number of cases of tuberculosis in the period 1993–1994 to a nosocomial outbreak caused by a single strain, almost entirely responsible for the 200% excess of cases compared with 1991–1992. All but 1 of the 61 patients infected with this strain had <150 $CD4^+$ cells/μL, and the mean $CD4^+$ cell count was significantly lower than that of patients with strains susceptible to rifampin and/or isoniazid (data not shown).

It is our opinion that the main factors contributing to the spread of MDR tuberculosis in the hospital were the crowded conditions in the infectious disease wards, the low compliance of the HIV- and *M. tuberculosis*–infected drug users with isolation procedures and treatment, the fact that the patients happened to be admitted to different wards in subsequent admissions for treatment of tuberculosis, the long duration of hospitalization, and the delay in recognition of the outbreak (slow growth of the organism and delay in the results of drug susceptibility tests). Nosocomial transmission has been halted by the rigorous application of infection-control measures and, for two of the three wards, by transfer to a new wing. In recent

Table 4. Clinical, radiological, microbiological, and epidemiological findings for the 8 HIV-infected patients with multidrug-resistant tuberculosis who survived for ⩾1 year.

Patient	Year	Sex	$CD4^+$ cell count (cells/μL)	Site of tuberculosis	Treatment at 10th day	Treatment at 30th day	Treatment at 90th day	Survival (d)
11B	1994	M	2	Lung, blood	INH, Rif, Emb, PZA	INH, Rif, Emb, PZA, Stm, Cpfx	Rib, Emb, PZA, Stm, Cpfx	635
19C	1994	M	3	Lung	INH, Rif, Emb, PZA	INH, Rif, Emb, PZA	INH, Rif, Emb, PZA	487
24C	1994	F	115	Lung	INH, Rif, Emb, Cpfx, Amik	INH, Emb, Cpfx	INH, Emb, Cpfx	365
27C	1995	F	44	Lung	INH, Rif, Emb, PZA	INH, PZA, Emb, Cpfx	INH, PZA, Emb, Cpfx	749
28C	1995	F	33	Lung	INH, Rif, Emb, PZA	INH, Rif, PZA, Stm, Cpfx, Amik	Rib, Emb, PZA, Stm, Cpfx	403
29C	1995	M	134	Lung	INH, Rif, Emb, PZA	INH, Rif, Emb, PZA, Stm, Cpfx	INH, Rif, Emb, PZA, Cpfx	453
33C	1996	M	182	Lung	INH, Rif, Emb, PZA	INH, Emb, PZA	INH, Emb, PZA	367
31A	1996	M	9	Lung	Rib, Emb	Rib, Emb	INH, Rib, Emb	403

NOTE. Amik = amikacin; Cpfx = ciprofloxacin; Emb = ethambutol; F = female; INH = isoniazid; M = male; PZA = pyrazinamide; Rib = rifabutin; Rif = rifampin; Stm = streptomycin.

years, we continued monitoring, through periodic reviews of microbiological registries, the tuberculosis admissions in our wards, and we did not identify any new episode due to the MDR *M. tuberculosis* strain responsible for the outbreak [29].

The median survival time from diagnosis of MDR tuberculosis until death was 94 days, compared with 180 days for HIV-infected patients with tuberculosis due to strains susceptible to isoniazid or rifampin (data not shown). Survival data in previous studies found a much worse prognosis for HIV-infected patients with severe immune deficiency.

Table 5. Multivariate analysis of survival (Cox proportional hazards model) of outcome-associated factors—predictors of adverse outcome in 90 HIV-infected patients with multidrug-resistant tuberculosis.

	Hazard ratio (95% CI)	*P* value
Female	1	
Male	1.37 (0.72–2.56)	.335
No previous AIDS diagnosis	1	
Previous AIDS diagnosis	1.28 (0.45–1.33)	.359
Absence of opportunistic diseases	1	
Concomitant opportunistic diseases	1.41 (0.41–1.23)	.222
$CD4^+$ cell count of >50/μL	1	
$CD4^+$ cell count of ⩽50/μL	1.72 (0.86–3.45)	.125
Treatment		
Four or more drugs	1	
Three drugs	1.44 (0.73–2.83)	.289
Two or fewer drugs	1.94 (0.96–3.91)	.063
Pulmonary localization	1	
Extrapulmonary localization	2.10 (1.13–3.92)	.019
Year of diagnosis		
1994–1996	1	
1991–1993	4.16 (1.89–9.17)	.001

A low $CD4^+$ cell count [30, 31] and a prior diagnosis of AIDS were predictors of worse prognosis in patients with MDR tuberculosis [16]. We observed a negative correlation between survival and $CD4^+$ cell count of ⩽50/μL, a previous AIDS diagnosis, and the presence of concomitant opportunistic diseases, but none of these factors significantly correlated with the outcome in the multivariate analysis.

More recent reports suggest that a severe immune defect may not necessarily be responsible for the high mortality rates in MDR tuberculosis [32, 33]. Therefore, other risk factors should be taken into consideration. In the study by Goble et al. [13] of HIV-seronegative patients with MDR tuberculosis, an unfavorable response was seen among subjects who had received a high number of drugs before the current course of therapy and among male patients. In our study, the patients with previous antituberculosis treatment were not more likely to have a shorter survival time and male patients had a statistically significant reduction in survival time only in the univariate analysis.

Multivariate analysis revealed that only two variables were associated with longer survival time: the localization of tuberculosis and the year of diagnosis. Presentation with extrapulmonary tuberculosis was formerly associated with shorter survival [14, 15], and our data confirmed it. Patients diagnosed during the first phase of the outbreak had a significantly shorter survival time than did patients with diagnoses of tuberculosis in the last years of the study. In the period 1991–1993, as in early studies in the United States (1988–1992), MDR tuberculosis was not anticipated and patients subsequently found to have MDR tuberculosis rarely received effective therapy for the disease. In the US studies, the mortality varied from 72% to 89%, with a mean survival from diagnosis to death of 4–16 weeks [34]. Similarly, in the first phase of the outbreak, the mean survival time in our patients was ~13 weeks (median, 7.5

weeks), with a mortality of 83% at 6 months. In the late period of the outbreak (1994–1996), the median survival time increased from 52 days to 157 days, and the 6-month mortality decreased from 83% to 63%. Likewise, more recent US studies, referring to the years 1991–1993, showed similar figures: The median survival for HIV-infected patients varied from 95 days to 315 days [15, 16], and 82% of the 17 patients with HIV-related MDR tuberculosis survived for at least 4 months [16].

These data show that a clinical response can be obtained even when the immune deficiency is advanced and suggest that a key factor for survival in patients with MDR tuberculosis is prompt initiation of an effective regimen [14, 15, 30, 32, 33, 35]. In our patients, surprisingly, therapeutic delay did not seem to be a determining factor in survival time. This is probably because of differences in times from onset of symptoms to receipt of therapy in our study in comparison with other studies. In fact, in the first US outbreaks of nosocomial MDR tuberculosis, patients were diagnosed a median of 6 weeks after onset of symptoms. In our series, the therapeutic delay was shorter: the median time from symptoms to antituberculosis treatment was 20 days. Twenty-nine patients had a therapeutic delay of >30 days but they did not show a poorer outcome compared with that in patients who received more timely treatment.

The choice of a specific empirical regimen will necessarily depend on the local pattern of susceptibility in a given period of time. On this matter, the situation we describe is quite peculiar: one single strain was responsible for the vast majority of the MDR tuberculosis cases, and the high level of multidrug resistance (to at least 12 antituberculosis agents) seemed to preclude any "optimal" treatment regimen. On the other hand, the evidence that patients treated in the late phase of the outbreak had longer survival times seems to demonstrate that a more accurate approach to the disease could prolong the survival of the patients.

The guidelines of the American Thoracic Society and Centers for Disease Control and Prevention [36] recommend a four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin for initial treatment of newly diagnosed cases of tuberculosis in communities where the resistance to isoniazid exceeds 4%. On the basis of in vitro susceptibility testing, this recommended combination would have led to inadequate treatment of 53% of the patients in our study population in the period 1993–1995. On the other hand, the recommended regimen, including isoniazid, rifampin (or rifabutin), ethambutol, and pyrazinamide, showed higher efficacy compared with that of the other regimens by univariate analysis and warranted a survival of >1 year in at least 6 cases, with minimal variations in the treatment. Therefore, especially in a nonepidemic period, while waiting for susceptibility data, broad empirical use of more toxic second-line agents should be limited to few circumstances, such as patients with a history of previous treatments, patients believed to be an infected contact of an index case of MDR tuberculosis, and patients who do not show clinical improvement within 2 weeks of beginning standard four-drug therapy. However, clinicians must be alert for MDR tuberculosis, especially in the setting of infectious diseases wards, where the risk of tuberculosis transmission could be higher. A missed diagnosis of MDR tuberculosis and inadequate prevention of nosocomial transmission of the disease could have disastrous implications for patients and contacts.

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