Effects of HIV Status and Other Variables on the Outcome of Tuberculosis Treatment in Spain

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OBJECTIVE: To analyze the effect of human immunodeficiency virus (HIV) status and other variables on the outcome of tuberculosis treatment in Spain.

PATIENTS AND METHODS: Multicenter retrospective cohort study in 6 autonomous communities of Spain (from May 1996 to April 1997). Data on treatment outcome were collected for new cases of tuberculosis in accordance with European guidelines. Follow up of patients continued for 3 months after scheduled end of treatment.

RESULTS: Of the 4899 patients included, 3417 (69.7%) had a satisfactory outcome, 438 (8.9%) died before or during treatment, and 1044 (21.4%) had a potentially unsatisfactory outcome. On stratification by HIV status, satisfactory outcome, mortality, and potentially unsatisfactory outcome were reported for 43.4%, 21.5%, and 35.1%, respectively, of HIV-positive patients; 71%, 6.2%, and 22.8%, respectively, of HIV-negative patients; and 74.3%, 7.5%, and 18.2%, respectively, of patients with no HIV status available. HIV modified the effect of several variables on the outcome of treatment, and so separate logistic regression models for each HIV category were constructed. Among HIV-positive patients, mortality increased in patients with neoplastic disease and in users of drugs by nonintravenous routes of administration, whereas potentially unsatisfactory outcomes increased in intravenous drug users and in women.

CONCLUSIONS: In Spain, the outcome of tuberculosis treatment is much worse in HIV-positive patients. Drug use and presence of neoplastic disease substantially affect mortality.

Key words: *Outcome of tuberculosis treatment. Potentially unsatisfactory outcome. HIV status.*

Efectos del VIH y otras variables sobre el resultado del tratamiento antituberculoso en España

OBJETIVO: Analizar el efecto del virus de la inmunodeficiencia humana (VIH) y otras variables sobre el resultado del tratamiento antituberculoso en España.

PACIENTES Y MÉTODOS: Estudio multicéntrico de cohorte retrospectivo en 6 comunidades autónomas (de mayo de 1996 a abril de 1997). Se recogió información sobre el resultado del tratamiento en casos nuevos de tuberculosis siguiendo la normativa europea. Se realizó seguimiento de los casos hasta 3 meses después de la fecha prevista de finalización del tratamiento.

RESULTADOS: De los 4.899 pacientes incluidos, se observó un resultado satisfactorio en 3.417 (69,7%), 438 (8,9%) murieron antes o durante el tratamiento y 1.044 (21,4%) tuvieron un resultado potencialmente insatisfactorio. Estratificando por el estado de la infección por el VIH, las cifras fueron, respectivamente: para los que la presentaban, del 43,4, el 21,5 y el 35,1%; para los seronegativos, del 71, el 6,2 y el 22,8%, y para aquellos en quienes no constaba, del 74,3, el 7,5 y el 18,2%. El VIH modificaba el efecto de diversas variables sobre el resultado del tratamiento, por lo que se ajustaron modelos de regresión logística separados para cada categoría VIH. Entre los seropositivos, la mortalidad aumentó en enfermos con neoplasias y en usuarios de drogas por vías distintas de la parenteral, mientras que los resultados potencialmente insatisfactorios aumentaron en usuarios de drogas por vía intravenosa y en las mujeres.

CONCLUSIONES: En España, el resultado del tratamiento antituberculoso es mucho peor en enfermos infectados por el VIH. El uso de drogas y el hecho de padecer neoplasias tienen un papel importante sobre la mortalidad.

Palabras clave: *Resultados del tratamiento antituberculoso. Resultado potencialmente insatisfactorio. Estado VIH.*

Introduction

One of the priorities in the control of tuberculosis is to cure patients with the disease, given that the most effective way to prevent transmission and avoid the appearance of drug-resistant strains is to detect cases of tuberculosis early and treat them appropriately. The World Health Organization (WHO) has set a goal of

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curing at least 85% of infectious patients as part of the program to control tuberculosis. To achieve this goal, the organization recommends a directly observed treatment, short-course (DOTS) strategy, in which surveillance of the treatment outcome makes an essential contribution to the assessment of the effectiveness of control programs.[1]

In 1997, a joint working group of the WHO and the International Union Against Tuberculosis and Lung Disease drew up guidelines for monitoring the outcomes of tuberculosis treatment in the European region of the WHO.[2] Given that the overall goal is to attain satisfactory outcomes in 85% of the patients treated, and that a mortality rate of 5% is considered acceptable, an investigation should be undertaken when potentially unsatisfactory outcomes exceed 10% (treatment failure, transfer, and withdrawal from treatment).

Spain has the second highest incidence of both tuberculosis and acquired immune deficiency syndrome (AIDS) within the European Union.[3,4] Moreover, tuberculosis has consistently been the disease that has most often led to diagnosis of AIDS, with a peak in the association of the two diseases in 1994, when 41.9% of patients with AIDS had first been diagnosed with tuberculosis.[5] According to the results of the Multicenter Project on Tuberculosis Investigation (abbreviated as PMIT in Spanish), at least 18% of all patients with tuberculosis diagnosed between May 1996 and April 1997 were also infected with the human immunodeficiency virus (HIV).[6]

As noted by other authors, the overlap between populations infected by HIV and tuberculosis points to a marked interaction between these 2 diseases in Spain, and HIV infection has led to an increase in the number of patients with tuberculosis in Spain in recent decades.[7] Nevertheless, we have little information on how HIV infection affects the outcome of tuberculosis treatment in Spain in the community at large. This article analyzes this effect through the information obtained from a cohort of almost 5000 tuberculosis patients identified by the PMIT in 6 autonomous communities. The study patients came from a general population that represented 32% of the entire Spanish population.[8]

Patients and Methods

The PMIT identified a cohort of tuberculosis patients through case finding in different registers of 6 Spanish autonomous communities, namely, Asturias, Galicia, Basque Country, La Rioja, Murcia, and Catalonia. Tuberculosis cases were defined as patients with a positive sputum smear and/or culture for *Mycobacterium tuberculosis* complex, or a physician's prescription that included 2 or more tuberculosis drugs. Subjects who met the second condition but not the first were included as cases only if the prescription was maintained for 3 months, whereas those with cultures positive for *M tuberculosis* who had not received treatment, whether due to death or some other exceptional cause, were included.

Patients previously infected with tuberculosis and those in prison at diagnosis were excluded from the study for logistical reasons. Patients with no medical history available at the time of diagnosis were also excluded because this document, along with death registers, was the source of data used in this study.

Clinical and epidemiological data and data on treatment outcomes were taken from the medical history. If patients were lost to follow up, their medical history was lost, or the information on the treatment outcome in the medical history was incomplete, we searched the death registries of the autonomous communities to determine whether the patient had died.

For the purposes of the study, patients were classed as HIV positive when it was so indicated in their medical history. Otherwise, given that HIV testing is not routine in tuberculosis patients, they were classed as HIV negative when their medical history stated that the HIV test result was negative or that they were HIV negative, or as having unknown HIV status.

Treatment for the patients started between May 1996 and April 1996, and follow up lasted until 3 months after the scheduled end of treatment.

The categories for treatment outcome were defined according to European guidelines as follows[2]: *a)* satisfactory outcome, patients who completed treatment and who were discharged by the treating physician not longer than 3 months after the scheduled end of treatment; *b)* death, patients who died of any cause during the scheduled treatment period; *c)* transfer out, patients who changed center before finishing treatment and so no information on treatment outcome was available; *d)* treatment failure, patients who had not attained negative cultures or smears 5 months after starting treatment, or who had positive sputum cultures after an initial conversion to negative, and whose first-line therapy had been replaced by a second-line one; and *e)* treatment interrupted (default), patients who had interrupted treatment for more than 2 consecutive months, who had not completed therapy 3 months after the scheduled end of treatment, or who had taken less than 80% of the prescribed doses.

These categories were subsequently pooled into 3, namely: *a)* satisfactory outcome; *b)* death; and *c)* potentially unsatisfactory outcome, which included transfer to a different center, treatment failure, and treatment interruption.

For the purposes of the study, lack of information on the treatment outcome in the medical histories or missing medical histories were also classed as a potentially unsatisfactory outcome.

Statistical Analysis

Frequency distributions were calculated for the treatment outcomes by different variables and possible associations were investigated using the χ^2 test. To assess associations between different independent variables and death or potentially unsatisfactory outcome, the odds ratio (OR) and its 95% confidence interval (CI) were used. Logistic regression was used in the multivariate analysis to analyze the relationship between the treatment outcome and the variables of interest. To construct the model and verify the goodness of the fit, we used the Hosmer and Lemeshow[9] approach, in which an initial model was constructed that included all significant variables in the bivariate analysis ($P \leq .25$). By working backwards, irrelevant variables were eliminated using the likelihood ratio test to compare successive models. Epidemiological variables were added one by one to the model resulting from this process, even if they were not statistically significant, and assessed for inclusion the final model.

The statistical program used was STATA (version 6.0).[10]

Results

A total of 4899 new cases of tuberculosis met the inclusion criteria of the study. Of these, 606 (12.4%) were HIV positive, 1038 (21.2%) were HIV negative, and HIV status was unknown in 3255 (66.4%). Table 1 shows tuberculosis cases stratified by HIV status.

Sufficient information on the outcome of tuberculosis treatment was available for 4240 patients (86.6% of the total; range, 73.3% in Murcia to 89.5% in Galicia). The information on outcome was incomplete for 342 patients (7% of the total; range, 5.7% in Galicia to 16.0% in Murcia), and the medical history was missing in 317 cases (6.5% of the total; range, 3.5% in Galicia to 10.2% in Murcia).

TABLE 1
Patient Characteristics by HIV Infection Status*

Variable	Total		HIV Status					
			Positive		Negative		Not Available	
	n	%	n	%	n	%	n	%
Age group, years†								
≤14	288	5.9	3	0.5	32	3.1	253	7.8
15-24	885	18.1	24	4.0	233	22.4	628	19.3
25-34	1096	22.4	304	50.2	290	27.9	502	15.4
35-44	716	14.6	202	33.3	163	15.7	351	10.8
45-54	501	10.2	47	7.8	105	10.1	349	10.7
55-64	434	8.9	17	2.8	63	6.1	354	10.9
≥65	971	19.8	9	1.5	151	14.6	811	25.0
Not given	8	0.2	0	0.0	1	0.1	7	0.2
Sex†								
Male	3160	64.5	495	81.7	693	66.8	1972	60.6
Female	1739	35.5	111	18.3	345	33.2	1283	39.4
Nationality†								
Spanish	4735	96.7	589	97.2	969	93.3	3177	97.6
Other	164	3.3	17	2.8	69	6.7	78	2.4
IDU†								
Yes	407	8.3	355	58.6	37	3.6	15	0.5
No	4492	91.7	251	41.4	1001	96.4	3240	99.5
Drug use (nonintravenous routes of administration)†								
Yes	92	1.9	47	7.8	26	2.5	19	0.6
No	4807	98.1	559	92.2	1012	97.5	3236	99.4
Alcohol abuse†								
Yes	599	12.2	113	18.7	178	17.2	308	9.5
No	4300	87.8	493	81.3	860	82.8	2947	90.5
Other risk factors†,‡								
Yes	693	14.2	52	8.6	125	12.0	516	15.9
No	4206	85.8	554	91.4	913	88.0	2739	84.1
Site of tuberculosis infection†								
Pulmonary only	3032	61.9	252	41.5	665	64.0	2115	65.0
Pulmonary and extrapulmonary	540	11.0	167	27.6	123	11.9	250	7.7
Extrapulmonary only	1313	26.8	181	29.9	250	24.1	882	27.1
Not given	14	0.3	6	1.0	0	0.0	8	0.2
Positive culture†								
Yes	3258	66.5	405	66.8	749	72.2	2104	64.6
No	1641	33.5	201	33.2	289	27.8	1151	35.4
Positive sputum smear†								
Yes	1739	35.5	169	27.9	464	44.7	1106	34.0
No	3160	64.5	437	72.1	574	55.3	2149	66.0
Drug susceptibility testing†,§								
Yes	1010	31.0	175	43.2	259	34.6	576	27.4
No	2248	69.0	230	56.8	490	65.4	1528	72.6
No. of drugs administered†								
0‖	67	1.4	12	1.98	7	0.6	48	1.5
2	71	1.5	6	0.99	14	1.3	51	1.6
3	3592	73.3	291	48.02	786	75.7	2515	77.3
≥4	852	17.4	230	37.95	171	16.4	451	13.9
Incomplete information	317	6.5	67	11.06	60	5.7	190	5.8
Delay between symptoms and treatment in days (median)¶	43	40	45	43				
Total	4899	100.0	606	100.0	1038	100.0	3255	100.0

*HIV indicates human immunodeficiency virus; IDU, current or former intravenous drug users.
†$P<.05$.
‡Other risk factors of tuberculosis: diabetes, silicosis, chronic renal impairment, gastrectomy, corticosteroid therapy, immunosuppressive treatment, and neoplastic disease.
§Percentages calculated for a population of 3258 patients with positive culture and for a population of 4005 patients with information on delay between onset of symptoms and treatment, respectively.
‖Patients who died before started tuberculosis treatment.
¶Median calculated for 4005 patients with information on delay between onset of symptoms and treatment.

Treatment outcomes were as follows: 3417 patients (69.7%) had a satisfactory outcome; 438 (8.9%) died before or during treatment; and 1044 (21.4%) were classed as having a potentially unsatisfactory outcome. Of these last patients, 480 (9.8% of the total) had sufficient information on treatment outcome in their medical history, 288 (5.9% of the total) had incomplete information, and a medical history was not available in 276 cases (5.6% of the total), although the patients were known to still be alive. Among the cases with a potentially unsatisfactory outcome, only 16 met the definition of treatment failure and 57 were documented as having been transferred. We grouped these patients together because the percentage with treatment failure plus those transferred was low and because the European guidelines recommend pooling cases of treatment failure, transfer, and interruption of treatment in the same category (potentially unsatisfactory outcome).

On stratification of the outcomes by HIV status, large differences were found. A much lower percentage of

TABLE 2
Outcomes of Tuberculosis Treatments According to Selected Variables*

Variable	Treatment Outcome						Total	
	Satisfactory		Death		PUO			
	n	%	n	%	n	%	n	%
HIV†								
Positive	263	43.4	130	21.5	213	35.1	606	100.0
Negative	737	71.0	64	6.2	237	22.8	1038	100.0
Not given	2417	74.3	244	7.5	594	18.2	3255	100.0
Autonomous community†								
Asturias	333	69.8	58	12.2	86	18.0	477	100.0
Catalonia	1416	67.9	180	8.6	489	23.5	2085	100.0
Galicia	1002	74.1	112	8.3	239	17.6	1353	100.0
La Rioja	46	58.2	10	12.7	23	29.1	79	100.0
Murcia	112	59.9	10	5.3	65	34.8	187	100.0
Basque Country	508	70.8	68	9.5	142	19.7	718	100.0
Age group, years†								
≤14	227	78.8	3	1.0	58	20.2	288	100.0
15-24	730	82.5	6	0.7	149	16.8	885	100.0
25-34	754	68.8	65	5.9	277	25.3	1096	100.0
35-44	487	68.0	57	8.0	172	24.0	716	100.0
45-54	344	68.7	33	6.6	124	24.7	501	100.0
55-64	308	71.0	42	9.7	84	19.3	434	100.0
65-74	320	63.9	98	19.6	83	16.5	501	100.0
≥75	244	51.9	133	28.3	93	19.8	470	100.0
Nationality†								
Other	90	54.9	5	3.0	69	42.1	164	100.0
Spanish	3327	70.3	433	9.1	975	20.6	4735	100.0
IDU†								
Yes	180	44.2	77	18.9	150	36.9	407	100.0
No	3237	72.1	361	8.0	894	19.9	4492	100.0
Alcohol abuse†								
Yes	370	61.8	58	9.7	171	28.5	599	100.0
No	3047	70.9	380	8.8	873	20.3	4300	100.0
Site of tuberculosis infection†								
Pulmonary only	2173	71.7	242	8.0	617	20.3	3032	100.0
Pulmonary and extrapulmonary	322	59.6	76	14.1	142	26.3	540	100.0
Extrapulmonary only	913	69.5	116	8.8	284	21.7	1313	100.0
Not given	9	64.3	4	28.6	1	7.1	14	100.0
No. of drugs prescribed†								
0‡	0	0.0	67	100.0	0	0.0	67	100.0
2	50	70.4	8	11.3	13	18.3	71	100.0
3	2788	77.6	249	6.9	555	15.5	3592	100.0
≥4	579	68.0	73	8.6	200	23.4	852	100.0
Incomplete information	0	0.0	41	12.9	276	87.1	317	100.0
Type of center†,§								
Hospital	40	16.5	173	71.5	29	12.0	242	100.0
Tuberculosis only	805	83.9	22	2.3	132	13.8	959	100.0
General	2403	75.7	149	4.7	624	19.6	3176	100.0
Specialist	118	52.0	34	15.0	75	33	227	100.0
Other	51	69.9	3	4.1	19	26	73	100.0
Not given	0	0.0	57	25.7	165	74.3	222	100.0
Total	3417	69.7	438	8.9	1044	21.4	4899	100.0

*HIV indicates human immunodeficiency virus; PUO, potentially unsatisfactory outcome; IDU, current or former intravenous drug user.
†$P<.05$ according to χ^2 test.
‡Patients who died before starting treatment.
§Hospital indicates patients hospitalized for entire duration of treatment; tuberculosis only, clinic dedicated to tuberculosis only; general, pulmonology clinic, internal medicine clinic, or general medicine clinic not specifically dedicated to tuberculosis; specialist, clinic specialized in treatment of drug users with HIV; other, other types of clinic.

TABLE 3
Adjusted Odds Ratios (95% Confidence Intervals) From the Multivariate Analysis for Variables Associated with Mortality, According to HIV Infection Status*

Variable	HIV Status		
	Positive	Negative	Not Given
Sex, male	NS	NS	NS
Age in years	NS	1.12 (1.09-1.16)	1.08 (1.06-1.09)
No. of drugs prescribed, 3			
2	–	36.68 (1.40-964.06)	NS
≥4	NS	NS	NS
Site of tuberculosis infection, extrapulmonary			
Pulmonary only	NS	3.72 (1.36-10.22)	1.57 (1.05-2.35)
Pulmonary and extrapulmonary	NS	NS	1.87 (1.03-3.38)
Drug-sensitivity test, yes			
No	NS		
CRI, no		11.8 (3.11-44.73)	5.92 (2.53-13.87)
Corticosteroid therapy, no			2.67 (1.49-4.78)
Neoplastic disease, no	3.46 (1.35-8.82)	14.02 (4.97-39.57)	3.56 (2.26-5.60)
Drug use by nonintravenous route of administration, no	1.97 (1.01-3.99)	36.12 (5.62-232.11)	

*All models were fitted by autonomous community. The reference categories are show after the variable. Empty cells correspond to variables not included in the final model. HIV indicates human immunodeficiency virus; CRI, chronic renal impairment; NS, not significant.

tuberculosis patients with HIV coinfection had satisfactory outcomes (43.4%) than those who were HIV negative (71.0%) or than those with no HIV status available (74.3%). The lower percentage of patients with satisfactory outcomes was a consequence of both higher mortality and a higher percentage of potentially unsatisfactory outcomes (Table 2).

According to the univariate analysis, other variables besides HIV status affected treatment outcome. By autonomous community, Galicia had the highest percentage of satisfactory outcomes (74.1%), La Rioja had the highest mortality (12.7%), and Murcia had the highest percentage of missing medical histories and medical histories with incomplete information (9.1% and 15.5%, respectively). Patients over 64 years old had the lowest percentage of satisfactory results due mainly to higher mortality. Foreign-born patients had a higher percentage of potentially unsatisfactory outcomes, but mortality was lower in this group than among the autochthonous population. Patients who were or had been intravenous drug addicts also had both higher mortality and a greater percentage of potentially unsatisfactory outcomes than users of drugs by nonintravenous routes of administration. Alcoholic patients had a higher percentage of potentially unsatisfactory outcomes compared to nonalcoholic patients, but mortality was almost the same in both groups. Patients with both pulmonary and extrapulmonary infection had worse outcomes in terms of both mortality and potentially unsatisfactory outcomes compared to those with either pulmonary or extrapulmonary infection alone. Differences in outcomes were also noteworthy on stratification by the number of tuberculosis drugs prescribed and the type of center where the patients were treated (Table 2).

Separate analyses were done to investigate the factors related to mortality and potentially unsatisfactory outcomes. All patients were included in the first analysis, whereas patients who had died (n=438) were excluded from the second. Both analyses showed that HIV status strongly modified the effect of other variables on outcome of tuberculosis treatment. Therefore, we decided to fit separate logistic regression models for each of the HIV categories.

All-cause mortality was much higher in HIV-positive patients than in HIV-negative ones or those with no information on HIV status (21.5% vs 6.2%, and 7.5%, respectively) (Table 2). In the multivariate analysis, the only variables associated with mortality in patients infected with HIV were presence of neoplastic disease in addition to tuberculosis (OR=3.5; 95% CI, 1.4-8.8) and drug use by any route (not intravenous administration) (OR=2.0; 95% CI, 1.0-4.0). In addition to presence of neoplastic disease and drug use by nonintravenous routes of administration, mortality among HIV-negative patients was also positively associated with age (OR=1.1; 95% CI, 1.1-1.2), chronic renal impairment (OR=11.8; 95% CI, 3.1-44.7), and pulmonary tuberculosis (as opposed to extrapulmonary tuberculosis) (OR=3.7; 95% CI, 1.4-10.2). Among patients for whom HIV status was not available, mortality increased with age (OR=1.08; 95% CI, 1.06-1.09) and was higher in patients with pulmonary tuberculosis (OR=1.6; 95% CI, 1.1-2.6) and in those with both pulmonary and extrapulmonary tuberculosis (OR=1.9; 95% CI, 1.0-3.4) (Table 3).

The factors predictive of potentially unsatisfactory outcomes were sex—women had a higher percentage of such outcomes (OR=2.1; 95% CI, 1.2-3.5)—and intravenous drug use (OR=1.7; 95% CI, 1.1-2.8).

In individuals without HIV infection, potentially unsatisfactory outcomes were also associated with intravenous drug use (OR=3.2; 95% CI, 1.4-7.0), increased among alcoholics (OR=2.1; 95% CI, 1.3-3.3) and foreign-born patients (OR=2.4; 95% CI, 1.4-4.4), and decreased among patients treated in tuberculosis clinics (OR=0.7; 95% CI, 0.4-1.08). In patients with no HIV status available, potentially unsatisfactory outcomes were positively associated with intravenous drug use (OR=5.3; 95% CI, 1.7-16.7), foreign birth (OR=4.2; 95% CI, 2.5-

TABLE 4
Adjusted Odds Ratios (95% Confidence Intervals) From the Multivariate Analysis for the Variables Associated With a Potentially Unsatisfactory Outcome, According to HIV Infection Status*

Variable	HIV Status		Not Given
	Positive	Negative	
Sex, male	2.05 (1.19-3.54)	NS	NS
Age group in years, ≤14			
≥75	NS	NS	1.71 (1.02-2.86)
Nationality (Spanish)		2.43 (1.35-4.38)	4.21 (2.51-7.05)
Type of clinic, general†			
Hospital	NS	NS	2.46 (1.05-5.73)
Tuberculosis only	NS	0.66 (0.41-1.08)‡	0.78 (0.59-1.03)‡
Specialist	NS	–	NS
Other	–	NS	NS
No. of drugs prescribed, 3			
2	–	NS	NS
≥4	NS	1.46 (0.96-2.24)‡	1.36 (1.01-1.81)
Site of tuberculosis, pulmonary			
Pulmonary and extrapulmonary			1.78 (1.20-2.64)
Extrapulmonary			1.30 (0.97-1.75)‡
Silicosis, no			1.85 (0.96-3.57)‡
Gastrectomy, no			0.29 (0.09-1.00)
Alcohol abuse, no		2.10 (1.33-3.32)	1.36 (0.95-1.96)‡
IDU, no	1.71 (1.06-2.75)	3.15 (1.42-6.97)	5.27 (1.66-16.71)
Positive sputum smear, no			1.49 (1.14-1.96)

*All models were fitted for autonomous community. The reference categories are shown after the variable. Empty cells correspond to variables not included in the final model. Patients who died before or during treatment (n=438) were excluded from this analysis. HIV indicates human immunodeficiency virus; IDU, intravenous drug users; NS, not significant.
†Hospital indicates patients hospitalized for entire duration of treatment; tuberculosis only, clinic dedicated to treatment of tuberculosis only; general, pulmonology clinic, internal medicine clinic, or general medicine clinic not specifically dedicated to tuberculosis; specialist, clinic specialized in treatment of drug users with HIV; other, other types of clinic.
‡$P>.05$ and $\leq.10$.

7.1), age over 75 years (OR=1.7; 95% CI, 1.0-2.9), positive sputum smear (OR=1.5; 95% CI, 1.1-2.0), treatment with 4 or more drugs (OR=1.4; 95% CI, 1.0-1.8), alcoholism (OR=1.4; 95% CI, 1.0-2.0), a history of silicosis (OR=1.9; 95% CI, 1.0-3.6), and pulmonary and extrapulmonary infection (OR=1.8; 95% CI, 1.2-2.6) or extrapulmonary infection alone (as opposed to pulmonary infection) (OR=1.3; 95% CI, 1.0-1.8). Potentially unsatisfactory outcomes decreased when patients received treatment for tuberculosis in a center dedicated to treatment of tuberculosis (OR=0.8; 95% CI, 0.6-1.0) (Table 4).

Discussion

In this study of tuberculosis treatment in Spain, the percentage of satisfactory outcomes did not reach the goal of 85% proposed by the WHO, due mainly to potentially unsatisfactory outcomes, which exceeded the 10% recommended by the European Region of the WHO.[2]

The results varied markedly according to HIV status: for HIV-positive patients, the percentage of satisfactory outcomes was just 43.4%, compared to 71% for HIV-negative patients and 74.3% for those for whom HIV status was unknown. Moreover, a greater percentage of mortality and unsatisfactory outcomes were reported among tuberculosis patients infected with HIV.

To compare these results with those from other studies, differences in methodology need to be taken into account. First, in the present study, patients without medical histories or with medical histories with incomplete information on treatment outcome were classified as potentially unsatisfactory outcomes, whereas such patients were excluded from the analysis in other studies.[11,12] Arguably, it might have been more correct to exclude such patients from the present analysis, given that they may have satisfactorily completed treatment despite not having a medical history or having incomplete information. In fact, had they been excluded, the percentage of satisfactory outcomes would have increased to 53.2% for HIV-positive patients, 81.9% for HIV-negative patients, and 82.2% for patients with no HIV status available. However, we preferred to classify such cases as potentially unsatisfactory outcomes because loss of the medical history or failure to indicate the outcome in a patient who not only might not have been cured but also might be infectious is evidently not good clinical practice. In addition, this approach is in line with international organizations that consider an outcome as unsatisfactory when the final outcome of treatment is not known.[2]

Second, the outcome of tuberculosis treatment was assessed 3 months after the scheduled end of treatment. A total of 295 patients continued treatment after the scheduled end of treatment and successfully completed treatment much later. The percentage of patients who would therefore have been classed as having a satisfactory outcome if the 3-month limit had not been imposed was 53% for HIV-positive patients, 77.2% for HIV-negative patients, and 79.6% for patients with unknown HIV status.

All-cause mortality among tuberculosis patients infected with HIV in this study was lower than that

reported in Barcelona several years ago,[13] and similar to that reported in the Public Health District of Seville between 1994-1998.[14] Other local Spanish studies also observed similar differences in potentially unsatisfactory outcome according to HIV status.[14,15]

Several studies done outside Spain have found variations in the mortality rate but not in treatment interruptions among tuberculosis patients according to their HIV status.[16,17] However, like us, other international studies[18,19] have found differences in both mortality and percentage of patients who did not complete treatment. A recent review has indicated that the findings from different studies might disagree because of differences in methodology or in the study population.[20] For example, the differences between the present study and one done among South African miners,[17] particularly in the HIV-positive groups, can be explained to some extent by the "healthy worker effect," and by differences in the population. (Most HIV-positive patients in our study were intravenous drug users with high comorbidity in the community at large, whereas the miners lived in special conditions.) Importantly, the patients in the two studies received very different treatments—only 3.3% of the Spanish cases (8.7% of the patients coinfected with HIV) were attended with a directly observed treatment strategy, whereas all patients in the South African study had directly observed treatment.

It is important to determine whether the high mortality reported among patients coinfected with HIV compared to HIV-negative patients should be attributed to differences in therapeutic regimens, delays in starting treatment, or drug resistance. Differences in treatment between the 2 groups are apparent, but they are such that the regimens of HIV patients tend to last longer than recommendations of the Spanish guidelines[21] and HIV patients receive a greater number of different drugs. The median time between appearance of symptoms and treatment was lower in patients infected with HIV than in the remaining patients (40 days vs 44 days). Finally, variations in drug resistance in HIV-positive patients cannot be ruled out because, unfortunately, we were unable to obtain the findings of antimicrobial susceptibility testing. Resistance to tuberculosis drugs is nevertheless moderate in Spain[3,22] and differences related to HIV status have not been observed among new cases of tuberculosis.[23,24]

In the multivariate analysis, the only variables associated with mortality in tuberculosis patients coinfected with HIV were presence of neoplastic disease and use of drugs by nonintravenous routes of administration. The most likely explanation for the higher mortality among such patients therefore seems to be the greater severity of disease. Many HIV-positive patients were also drug users, and drug use increases the risk of dying of causes not related to tuberculosis in comparison with other tuberculosis patients of a similar age, regardless of HIV status.

The only variables associated with potentially unsatisfactory outcomes among patients coinfected with HIV were intravenous drug use and being a woman. Intravenous drug use is often associated with worse treatment outcomes in HIV-negative patients but being a woman is not. There are two possible explanations why women fare worse. First, women might be in a more disadvantaged social situation than men, and this factor can increase the likelihood of tuberculosis infection or active tuberculosis in Spain.[25] In addition, better education is inversely related to development of AIDS.[26] Social factors might therefore be expected to influence the outcome of tuberculosis treatment. Unfortunately, medical histories do not usually collect reliable information on social class and we therefore could not adjust for this variable. Alternatively, there may a gender effect in the treatment of HIV-positive women that is not present in HIV-negative women. The findings of other studies do not support such an effect, as HIV-infected women normally respond better to highly active antiretroviral therapy than men.[27] Studies with reliable information on social class would be useful as they may help clarify this aspect.

The broad scope of this study reflects experience of tuberculosis treatment in real conditions at a time when an important interaction between tuberculosis, HIV, and intravenous drug use was occurring. The study also provides an in-depth analysis of how HIV status influences other variables. Thus, the results are not only interesting for Spain, but also for other countries, such as Russia, which are in a similar situation to Spain in the 1990s.

The findings of this study suggest that tuberculosis treatment can be considered in terms of 2 clearly differentiated populations in Spain, namely, HIV-positive patients and HIV-negative patients. Although the outcome of tuberculosis treatment could be better in HIV-negative patients (particularly among immigrants, children, and alcoholics), the outcomes in patients coinfected with HIV are much worse. These patients, and intravenous drug users in particular, should undergo specific interventions to improve the outcome. Clearly, implementation of a directly observed treatment strategy, which has been shown to be effective even among intravenous drug users,[28] should be a priority. The methadone maintenance programs are a good alternative, as they have been shown to be cost-effective, even as preventative therapy,[29] and there is evidence that they are effective in Spain.[30]

Further detailed investigation is needed in women with tuberculosis and HIV to establish whether specific interventions are needed to help them to complete tuberculosis treatment.

Although widespread use of highly active antiretroviral treatment has contributed to a decrease in the incidence of cases of tuberculosis related to HIV,[5,31] availability of such drugs in itself does not improve the outcome of tuberculosis treatment. On the contrary, the increased toxicity and interactions between these antiretroviral drugs and some tuberculosis drugs increase treatment interruptions in tuberculosis patients coinfected with HIV, in turn complicating clinical management.[32]

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