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Mortality in a large tuberculosis treatment trial: modifiable and non-modifiable risk factors

T. R. Sterling,* Z. Zhao,† A. Khan,† R. E. Chaisson,‡ N. Schluger,§ B. Mangura,¶ M. Weiner,# A. Vernon† for the Tuberculosis Trials Consortium

*** Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee, † Division of TB Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, ‡ Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland, § Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York, ¶ National Tuberculosis Center, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, # Audie L Murphy Veterans Administration Hospital, San Antonio, Texas, USA**

SUMMARY

SETTING: North America.

OBJECTIVES: Tuberculosis (TB) patients in North America often have characteristics that may increase overall mortality. Identifying modifiable risk factors would allow for improvements in outcome.

DESIGN: We evaluated mortality in a large TB treatment trial conducted in the United States and Canada. Persons with culture-positive pulmonary TB were enrolled after 2 months of treatment, treated for 4 more months under direct observation, and followed for 2 years (total observation: 28 months). Cause of death was determined by death certificate, autopsy, and/or clinical observation.

RESULTS: Of 1075 participants, 71 (6.6%) died: 15/71 (21.1%) HIV-infected persons, and 56/1004 (5.6%) non-HIV-infected persons ($P < 0.001$). Only one death was attributed to TB. Cox multivariate regression analysis identified four independent risk factors for death after controlling for age: malignancy (hazard ratio [HR] 5.28, $P < 0.0001$), HIV (HR 3.89, $P < 0.0001$), daily alcohol (HR 2.94, $P < 0.0001$), and being unemployed (HR 1.99, $P = 0.01$). The risk of death increased with the number of independent risk factors present ($P < 0.0001$). Extent of disease and treatment failure/relapse were not associated with an increased risk of death.

CONCLUSIONS: Death due to TB was rare. Interventions to treat malignancy, HIV, and alcohol use in TB patients are needed to reduce mortality in this patient population.

KEY WORDS: tuberculosis; mortality; HIV; malignancy

THE INCIDENCE of tuberculosis (TB) in the United States has declined steadily over the last decade.[1] However, mortality rates among persons with TB in the US and other industrialized countries have been high,[2–4] exceeding rates among TB patients in developing countries, where TB is endemic and human immunodeficiency virus (HIV) co-infection rates are high.[5,6] This difference in mortality risk is likely related to older age and higher rates of comorbid illness among TB patients in industrialized countries.[3,4,7] It remains unclear, however, whether there are potentially modifiable risk factors that increase mortality risk.

The Tuberculosis Trials Consortium (TBTC) Study 22 was a large, randomized trial of twice-weekly isoniazid (INH) plus rifampin (RMP) vs. once-weekly INH plus rifapentine (RPT) in the 4-month continuation phase of treatment of pulmonary TB (PTB) among HIV-seronegative adults.[8] We report here mortality rates through the 2-year follow-up phase.

METHODS

The design of TBTC Study 22 has been described previously.[8] It was a randomized, open-label multicenter trial that compared two regimens in the last 4 months ('continuation phase') of 6-month treatment for PTB. All patients received INH, RMP, pyrazinamide and either ethambutol or streptomycin during the initial 2 months ('intensive phase'). The first 2 weeks of therapy were daily; thereafter, four-drug therapy could be given daily, thrice weekly or twice weekly. All intermittent and >70% of daily doses were given as directly observed therapy (DOT). Four-drug intensive phase therapy included at least 40 observed daily

Correspondence to: Dr Timothy R Sterling, Vanderbilt University Medical Center, A2209 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232, USA. Tel: (+1) 615-343-0193. Fax: (+1) 615-343-6160. e-mail: timothy.sterling@vanderbilt.edu

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doses (or equivalent intermittent doses), completed within 70 days. Patients were enrolled in 29 clinics in the US (28) and Canada (1).

Enrollment and randomization

Patients ⩾18 years of age with PTB confirmed by culture from a respiratory specimen were eligible. Patients were excluded if their isolate was resistant to 1.0 μg/ml INH or 1.0 μg/ml RMP on solid media. Other exclusion criteria included intolerance to study drugs, central nervous system (CNS) or bone/joint TB, silicosis, pregnancy or breastfeeding, Karnofsky score <60, or the following abnormal laboratory values: hemoglobin <7 g/dl, platelets <50 000/mm^3, serum aspartate aminotransferase (AST) ⩾3 times upper limit of normal (ULN), serum bilirubin ⩾2.5 times ULN, or creatinine ⩾2 times ULN. Patients were enrolled at the conclusion of the intensive phase. Computerized randomization was blocked by study site and HIV status. Enrollment of HIV-infected patients was closed after it was noted that the risk of acquired rifamycin resistance was unacceptably high among such patients in the INH plus RPT arm; 36 patients were randomized to INH plus RPT, and 35 to INH plus RMP.[9] Patients received 16 once-weekly doses of RPT 600 mg and INH 15 mg/kg (maximum 900 mg), or 32 twice-weekly doses of RMP 10 mg/kg (maximum 600 mg) and INH 15 mg/kg (maximum 900 mg), all given as DOT.

Clinical management and follow-up

Patients were seen every 4 weeks during therapy, and 3, 6, 9, 12, 18 and 24 months after completion of therapy (28 months after study entry). For this analysis, patient follow-up was censored at the 28th month after study entry.

Microbiologic methods

Cultures in liquid media (supplemented by solid media in some cases) were performed at participating sites by certified clinical laboratories. Isolates obtained at diagnosis and at the time of suspected treatment failure/relapse were sent to the Centers for Disease Control and Prevention (CDC) for confirmatory susceptibility testing using solid media and the proportional method.[10]

Definitions

Mortality was assessed during two phases: the 4-month continuation (study) phase and the 24-month follow-up phase. Failure and relapse (culture-confirmed and clinical) were defined as previously reported.[8] Cause of death was reported by local study investigators, and was based on information from the death certificate, autopsy and local hospital medical records. Deaths were attributed to TB if the most recent sputum culture was positive for *Mycobacterium tuberculosis* and the local investigator considered the death probably or possibly due to TB.

Patients were classified as having cavitation or bilateral disease if these were present on chest radiograph (CXR) at diagnosis or at the end of the intensive phase (as documented by the site radiologist or principal investigator). Patients were defined as 'underweight' if they were >10% below ideal body weight at diagnosis.[11]

Demographic factors and information pertaining to homelessness, prior incarceration, and educational and employment status were established by patient self-report at study entry. Unemployment was defined as being unemployed for >1 year during the previous 5 years. Underlying medical conditions, including malignancy, diabetes mellitus, and alcohol or injecting or non-injecting drug use were also obtained by patient self-report at study entry. Alcohol use was defined as ⩾1 drink per day during the 5 years prior to study entry. HIV infection was diagnosed by enzyme-linked immunosorbent assay (ELISA), with confirmatory Western blot. Highly active antiretroviral therapy (HAART) was defined as triple-drug antiretroviral therapy (ART).

Data management and analysis

Data analysis was performed using SAS 9 (Statistical Analysis Software Institute, Inc, Cary, NC) and Epi Info 6.04d (CDC, Atlanta, GA). Categorical variables were compared using Fisher's exact or χ^2 test. Continuous variables were compared using the *t*-test or Wilcoxon rank-sum test. Life table survival analysis was performed using the log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate risk factors for death, using stepwise selection of factors associated ($P \leqslant 0.25$) with death in univariate Cox analyses. All variables with $P \leqslant 0.05$ were retained in the final multivariate model. Pairwise correlations were performed to assess for collinearity; all were <0.4, and variance inflation factors (VIF) were <2, suggesting no collinearity among variables. Age was treated as a continuous variable for the univariate and multivariate models. For the assessment of mortality risk according to number of independent risk factors present, a dichotomous variable for age (<45 years vs. ⩾45 years) was used. National Center for Health Statistics 1997 US mortality data were used for comparison with mortality among study patients.[12] All *P* values are two-sided.

Human subjects protection

The study was approved by Institutional Review Boards at the CDC and at each site. Each participant provided informed consent. A Data and Safety Monitoring Board reviewed outcome data five times.

RESULTS

There were 1075 patients enrolled in the study between April 1995 and November 1998; enrollment of

Table 1 Demographic and clinical characteristics of study patients

Characteristic	Treatment group			HIV status		
	Once weekly (N = 538) n (%)	Twice weekly (N = 537) n (%)	P value	HIV-negative (N = 1004) n (%)	HIV-positive (N = 71) n (%)	P value
Age (mean ± SD)	44.0 ± 14.4	43.9 ± 14.7	0.69	44.1 ± 14.8	41.5 ± 10.7	0.073
Male sex	399 (74)	411 (77)	0.41	752 (75)	58 (82)	0.25
Race/ethnicity			0.90			<0.0001
White, non-Hispanic	92 (17)	92 (17)	0.99	177 (18)	7 (10)	0.10
Black, non-Hispanic	234 (43)	218 (41)	0.37	399 (40)	53 (75)	<0.0001
Hispanic	127 (24)	136 (25)	0.56	252 (25)	11 (15)	0.094
Asian	67 (12)	72 (13)	0.71	139 (14)	0 (0)	<0.0001
Native American	18 (3)	19 (4)	0.99	37 (4)	0 (0)	0.17
Birth place			0.88			0.0009
US/Canada	353 (66)	342 (64)	0.55	638 (64)	57 (80)	0.0065
Mexico	71 (13)	71 (13)	0.99	137 (14)	5 (7)	0.15
Other foreign	114 (21)	124 (23)	0.50	229 (23)	9 (13)	0.066
Education <high school graduate	302 (56)	280 (52)	0.20	557 (56)	25 (35)	0.0014
Homeless >6 months past 5 years	106 (20)	105 (20)	0.95	187 (19)	24 (34)	0.0031
Illicit drug use past 5 years	129 (24)	118 (22)	0.48	209 (21)	38 (54)	<0.0001
Daily alcohol use past 5 years	239 (44)	239 (45)	0.98	446 (44)	32 (45)	0.92
Unemployment past 5 years	241 (45)	243 (45)	0.88	434 (43)	50 (70)	<0.0001
>1 month prison past 5 years	67 (12)	61 (11)	0.65	111 (11)	17 (24)	0.0023
Diabetes	78 (15)	84 (16)	0.66	155 (15)	7 (10)	0.23
Underweight	177 (33)	153 (28)	0.13	306 (30)	24 (34)	0.65
Karnofsky score (mean ± SD)	91.7 ± 9.0	92.0 ± 9.3	0.74	91.8 ± 9.1	91.5 ± 9.9	0.99
Body weight (mean ± SD)	64.0 ± 13.3	64.3 ± 12.9	0.98	64.0 ± 13.2	65.4 ± 12.1	0.71
Cavitary chest radiograph	288/522 (55)	256/522 (49)	0.055	524/975 (54)	20/69 (29)	0.0001
Treatment failure/relapse	52 (10)	33 (6)	0.033	74 (7)	11 (15)	0.014
Malignancy	12 (2)	13 (2)	0.84	22 (2)	3 (4)	0.23
Bilateral disease	307/534 (57)	291/533 (55)	0.34	550/996 (56)	39/71 (55)	0.85
Positive sputum smear*	74/511 (14)	56/518 (11)	0.093	126/966 (13)	4/63 (6)	0.17
Positive sputum culture*	102/467 (22)	83/471 (18)	0.12	180/886 (20)	5/52 (10)	0.071

* At study enrollment.
HIV = human immunodeficiency virus; SD = standard deviation

HIV-infected patients ended in March 1997. Follow-up ended in March 2001. Baseline characteristics of study participants are shown in Table 1, stratified by treatment regimen and HIV serostatus; 537 received twice-weekly INH plus RMP and 538 received once-weekly INH plus RPT in the continuation phase of therapy. Regimens used during the intensive phase were similar in both treatment arms. Persons randomized to receive once-weekly INH plus RPT tended to be more likely to have a cavity on CXR and a positive sputum smear, and were more likely to have treatment failure/relapse. There were no other significant differences by treatment arm. Compared with HIV-seronegative participants, HIV-infected patients were more likely to be black, have been born in the US or Canada, lack a high school degree, be homeless, use illicit drugs, have a history of unemployment or incarceration, and have treatment failure/relapse; they were less likely to have a cavity on CXR.

The overall crude mortality rate among all study participants was 71/1075 (6.6%). Crude mortality rates did not differ between the two treatment groups (6.7% for twice-weekly INH and RMP vs. 6.5% for once-weekly INH and RPT, $P = 0.87$). Mortality rates were substantially higher in HIV-infected than non-HIV-infected persons (15/71; 21.1% vs. 56/1004; 5.6%; $P < 0.001$). Of the HIV-infected patients, four received concomitant HAART during anti-tuberculosis therapy, and 15 more received HAART during the follow-up phase. The mortality rate was 10.5% among the 19 patients who received HAART during the study compared to 29.6% among the 27 persons who received no ART ($P = 0.16$).

The most common cause of death was malignancy: cancer of the lung (4), prostate (4), larynx (3), and pancreas (3) were most frequently seen. Of the 7

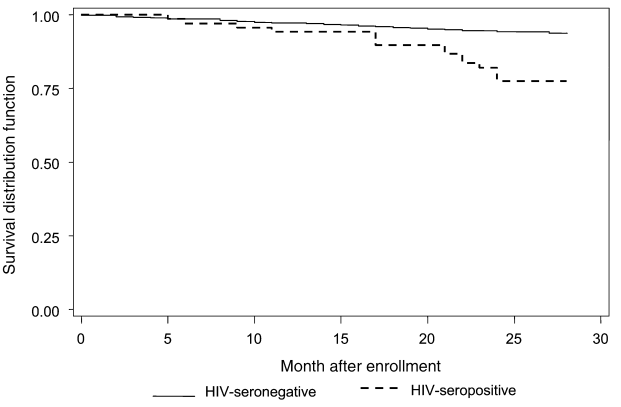

Figure Kaplan-Meier survival distribution plot, by HIV serostatus and month after enrollment. Log rank χ^2 =25.70; $P <$ 0.0001. HIV = human immunodeficiency virus.

Table 2 Univariate analysis of risk of death by clinical and demographic characteristics

Characteristic	Subjects *n*	Deaths *n* (%)	Crude HR (95%CI)	*P* value*
Treatment				
Once weekly	538	35 (6.5)	0.96 (0.60–1.53)	0.87
Twice weekly	537	36 (6.7)	1.0	
Age per 1-year increase	1075	71 (6.6)	1.04 (1.03–1.06)	<0.0001
Sex				
Male	810	62 (7.7)	2.35 (1.17–4.74)	0.016
Female	265	9 (3.4)	1.0	
Race				
White, non-Hispanic	184	19 (10.3)	1.81 (1.07–3.06)	0.027
Other	891	52 (5.8)	1.0	
Black, non-Hispanic	452	32 (7.1)	1.13 (0.71–1.80)	0.62
Other	623	39 (6.3)	1.0	
Hispanic	263	14 (5.3)	0.77 (0.43–1.38)	0.37
Other	812	57 (7.0)	1.0	
Asian	139	3 (2.2)	0.29 (0.09–0.91)	0.035
Other	936	68 (7.3)	1.0	
Native American	37	3 (8.1)	1.22 (0.38–3.88)	0.73
Other	1038	68 (6.6)	1.0	
Education†				
<High school	582	48 (8.3)	1.78 (1.08– 2.93)	0.023
⩾High school	492	23 (4.7)	1.0	
College	200	14 (7.0)	1.05 (0.59–1.89)	0.87
Not college	874	57 (6.5)	1.0	
Employment				
Unemployed	484	48 (9.9)	2.74 (1.67–4.50)	<0.0001
Employed	591	23 (3.9)	1.0	
Illicit drug use				
Yes	247	24 (9.7)	1.79 (1.09–2.92)	0.021
No	828	47 (5.7)	1.0	
Daily alcohol use				
Yes	478	46 (9.6)	2.41 (1.48–3.92)	0.0004
No	597	25 (4.2)	1.0	
Karnofsky score				
<80	57	11 (19.3)	3.55 (1.87–6.75)	0.0001
⩾80	1018	60 (5.9)	1.0	
Birth place				
US/Canada	695	56 (8.1)	2.0 (1.13–3.53)	0.017
Others	380	15 (4.0)	1.0	
Underweight				
Yes	330	28 (8.5)	1.48 (0.92–2.38)	0.11
No	745	43 (5.8)	1.0	
Homeless				
Yes	211	20 (9.5)	1.69 (1.0–2.83)	0.047
No	864	51 (5.9)	1.0	
In prison				
Yes	128	7 (5.5)	0.83 (0.38–1.82)	0.65
No	947	64 (6.8)	1.0	
Treatment failure/relapse				
Yes	85	9 (10.6)	1.74 (0.86–3.50)	0.12
No	990	62 (6.3)	1.0	
Malignancy				
Yes	25	10 (40)	8.40 (4.3–16.4)	<0.0001
No	1050	61 (5.8)	1.0	
Diabetes				
Yes	162	14 (8.6)	1.41 (0.79–2.53)	0.25
No	913	57 (6.2)	1.0	
HIV				
Yes	71	15 (21.1)	3.94 (2.23–6.96)	<0.0001
No	1004	56 (5.6)	1.0	
Cavity†				
Yes	544	29 (5.3)	0.64 (0.40–1.03)	0.065
No	500	41 (8.2)	1.0	
Sputum culture†				
Positive	185	13 (7.0)	1.29 (0.69–2.41)	0.42
Negative	753	42 (5.6)	1.0	
Sputum smear†				
Positive	130	10 (7.7)	1.26 (0.64–2.47)	0.50
Negative	899	57 (6.3)	1.0	
Bilateral disease†				
Yes	598	46 (7.7)	1.45 (0.89–2.36)	0.14
No	469	25 (5.3)	1.0	

* Univariate analysis with Cox proportional hazards model.
† Data not available for all patients.
HR = hazard ratio; CI = confidence interval; HIV = human immunodeficiency virus.

alcohol-related deaths, 2 were related to intoxication, 2 to gastrointestinal bleeding, and 2 due to cirrhosis. No deaths were attributed to anti-tuberculosis drug toxicity. Among the 71 participants who died, the last sputum culture prior to death was negative in 58, missing in 1, positive for non-tuberculous mycobacteria in 8, and positive for *M. tuberculosis* in 4. Of these 4, 1 died of trauma, 1 of central nervous system toxoplasmosis, and 1 of metastatic lung cancer. Only 1/71 (1.4%) death was attributed to TB. Among HIV-seronegative persons, 18/56 (32%) deaths were associated with malignancy, and 13 (23%) were attributed to injuries, accidents, drug overdose, or unknown cause. Other causes of death in HIV-seronegative persons included cardiac disease (6), chronic obstructive pulmonary disease (2), bacterial pneumonia (2), and cerebrovascular accident (2). Of the 15 deaths in HIV-infected persons, 11 were due to AIDS, two to malignancy, and two to drug overdose.

Deaths occurred throughout the study, during both the study and follow-up phases (Figure). There was a suggestion of increased mortality among HIV-infected persons near the end of the follow-up period. The rate of death among HIV-seronegative persons appeared stable over time (Figure).

Because there was no difference in mortality by treatment arm, all study patients were combined for analyses that assessed predictors of mortality. In univariate analyses, 12 factors were significantly associated with an increased risk of death (Table 2): age, male sex, white race, lack of a high school degree, unemployment, illicit drug use, daily alcohol use, Karnofsky score <80, birth in North America, homelessness, malignancy, and HIV infection. The presence of a cavity on CXR and Asian race/ethnicity were associated with a reduced risk of death ($P = 0.065$ and 0.035, respectively).

In a multivariate Cox proportional hazards model, factors independently associated with death were (in decreasing order of magnitude of hazard ratio) malignancy, HIV infection, alcohol use, unemployment, and age (per 1-year increase) (Table 3).

Table 3 Multivariate Cox proportional hazards model for mortality in TBTC Study 22

Factors	Adjusted HR (95%CI)	*P* value*
Malignancy	5.28 (2.55–10.93)	<0.0001
HIV infection	3.89 (2.12–7.12)	<0.0001
Alcohol use	2.94 (1.71–5.05)	<0.0001
Unemployment	1.99 (1.18–3.37)	0.0102
Age†	1.06 (1.04–1.07)	<0.0001

* Cox proportional hazards model.
† Per 1-year increase in age.
Factors eligible for inclusion in the model were: sex, race, secondary education, illicit drug use, homelessness, Karnofsky score, underweight, birth outside of the US and Canada, diabetes mellitus, cavitary pulmonary disease, bilateral pulmonary disease and treatment failure/relapse.
TBTC = Tuberculosis Trials Consortium; HR = hazard ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Table 4 Risk of death according to cumulative number of risk factors

Risk factors *n*	Deaths/in group *n/N*	Mortality rate %
0	0/229	0
1	12/339	3.5
2	30/352	8.5
3	24/142	16.9
4	5/12	41.7

Each of the five independent risk factors from the multivariate Cox proportional hazards model was assigned value = 1. Age was treated as a categorical variable (<> 45 years).

As expected, the risk of death was associated with the number of independent mortality risk factors present (test for trend: $\chi^2 = 62.9$; $P < 0.0001$) (Table 4). Among the 229 persons who had none of the five risk factors identified in the Cox model, all survived the entire study period.

Table 5 compares the mortality rates of the study population with those of the 1997 general US population, stratified by age, sex, and race. Study participants had a significantly higher risk of death than the general population in all categories except women aged 45–64 years. Using the US population in 2000 as the standard population, the age-adjusted 1997 US mortality rate was 887 per 100 000 population, while the age-adjusted rate among Study 22 participants was 7438/100 000 ($P < 0.0001$).

DISCUSSION

In this, the largest TB treatment trial ever conducted in North America, the cumulative mortality rate at the end of follow-up was substantially higher than in the general US population, even after stratifying by age, sex, and race. Of note, death was attributed to causes other than TB in all but one study patient. Although death certificates can be unreliable in determining the actual cause of death,[13–15] and therefore the proportion of deaths due to TB could have been underestimated, the increased mortality risk was likely due to underlying medical conditions (e.g., malignancy, HIV, alcohol use), and not TB. Although these underlying illnesses all predispose to the development of TB,[16] persons in this study who developed TB were at high risk of death, and TB likely did not further increase the risk of death.

Of the five risk factors independently associated with death in this study, all have been associated with an increased mortality risk in previous TB studies: malignancy,[17] HIV,[5,7,18–20] older age,[4,19–23] alcohol abuse,[19,20] and unemployment.[17] Of these, some are potentially modifiable. HAART dramatically improves the survival of HIV-infected TB patients.[24,25] In this study, the mortality rate was lower among HIV-infected persons who received HAART during the follow-up phase. The difference was not statistically significant,

Table 5 Mortality rates for selected demographic groups in TBTC Study 22 and the US population, 1997

	Study 22		US population (1997)			
Group	Death/total	Rate*	Death/total	Rate*	Rate ratio	*P* value
Men						
White,† 25–44 years	5/54	9 259	56 047/29 909 172	187	49.41	<0.0001
Black,‡ 25–44 years	8/158	5 063	20 885/4 813 967	434	11.67	<0.0001
Rate ratio		1.83				
P value		0.32				
White, 25–44 years	8/79	10 127	170 270/21 372 312	797	12.71	<0.0001
Black, 25–44 years	13/146	8 904	39 753/2 469 743	1610	5.53	<0.0001
Rate ratio		1.14				
P value		0.76				
Women						
White, 25–44 years	1/17	5 882	27 966/29 904 864	94	62.90	0.06
Black, 25–44 years	4/75	5 333	11 975/5 453 394	220	24.29	<0.0001
Rate ratio		1.10				
P value		1.0				
White, 45–64 years	0/10	0	107 861/22 251 408	485	0.0	1.0
Black, 45–64 years	1/22	4 545	27 660/3 085 671	896	5.07	0.18
Rate ratio		0.0				
P value		1.0				

* Rate on an annual basis per 100 000 population in specified group.
† White, non-Hispanic.
‡ Black, non-Hispanic.
TBTC = Tuberculosis Trials Consortium.

but power was low because of the small number of HIV-infected participants. The number of patients on HAART was low because HAART was just being introduced during the study period (1995–1998). It is unclear whether more intensive treatment of malignancy or alcohol abuse during anti-tuberculosis therapy would reduce the mortality risk. Substance abuse cessation has been associated with improved HIV treatment outcomes.[26] Comprehensive treatment programs for cancer improve survival, but we are unaware of such studies in TB patients. It is possible, however, that TB is a complication of conditions that increase the mortality risk regardless of the treatment intensity of the underlying illness. Prospective interventional studies are needed to address such questions.

The other two risk factors for death identified in this study are less modifiable. Increased age is the prime example. Unemployment is a more complex factor. It cannot easily be modified by TB control programs. It is likely a marker of low socio-economic status, and could be associated with reduced access to medical care. Delays in obtaining medical care could increase the risk of death, although such deaths usually occur shortly after initiation of therapy, and all patients in this study survived at least 2 months.[18,27] However, social support, access to health care, and employment training might be beneficial to TB patients.

Two factors not associated with increased mortality risk were TB failure/relapse and extent of disease. There were also no deaths attributed to anti-tuberculosis drug toxicity. These observations suggest that improvements in anti-tuberculosis therapy would not have substantially lowered the mortality rate in this population.

As expected, the more independent risk factors a patient had, the greater the mortality risk. Mortality risk was particularly high among persons with ⩾3 risk factors. In contrast, among patients without any of the five independent risk factors, there were no deaths during the study or follow-up phases. This identifies a group of TB patients at very low risk of death.

Patients had to survive 2 months on therapy before they could enroll in this study, and the risk of death during the first 2 months of anti-tuberculosis therapy is high.[4,18,23,28] Other TB mortality studies have included all patients who initiated anti-tuberculosis therapy, which could account for the higher mortality rates in those studies.[2,28] Additional factors may also have reduced our observed mortality rates. All study participants received DOT, which has been associated with lower mortality rates than self-administered therapy.[29,30] Study 22 inclusion criteria selected for patients with a good prognosis, so that the primary endpoint, TB failure/relapse, could be evaluated. Nonetheless, mortality rates were still significantly higher than in the general population.

This study had several strengths. It was large, prospective, all patients received DOT, and all were followed for 2 years after completion of anti-tuberculosis therapy; relapse was confirmed by DNA fingerprinting. In addition, patients were enrolled from sites throughout North America, enhancing the representativeness of the study population.

CONCLUSIONS

Among a population of TB patients selected for good survival, mortality rates were still significantly higher than in the general population. Several of the factors associated with an increased risk of death are poten-

tially modifiable (HIV, alcohol abuse, malignancy), while others are not (age, unemployment). Given the increased mortality associated with HIV infection, malignancy and alcohol abuse, prospective studies are warranted to identify interventions that reduce mortality among such TB patients.

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RÉSUMÉ

CONTEXTE : Amérique du Nord.

OBJECTIFS : Les patients tuberculeux en Amérique du Nord ont souvent des caractéristiques susceptibles d'augmenter la mortalité globale. L'identification des facteurs de risque modifiables pourrait permettre une amélioration des résultats.

SCHÉMA : Nous avons évalué la mortalité dans un grand essai du traitement de la tuberculose mené aux USA et au Canada. Les sujets atteints de tuberculose (TB) pulmonaire à culture positive ont été enrôlés après 2 mois de traitement et traités pendant 4 mois de plus sous observation directe et suivis pendant 2 ans (total d'observation

28 mois). La cause de décès a été déterminée par le certificat de décès, l'autopsie et/ou l'observation clinique.
RÉSULTATS : Sur 1.075 participants, il y a eu 71 décès (6,6%), dont 15/71 (21%) infectés par le VIH et 56/1.004 (5,6%) non-infectés par le VIH ($P < 0,001$). Un décès seulement a été attribué à la TB. Une analyse de régression multiple de Cox a identifié quatre facteurs indépendants de risque pour le décès après avoir contrôlé pour l'âge : le cancer (risque relatif [RR] 5,28 ; $P < 0,0001$), le VIH (RR 3,89 ; $P < 0,0001$), la consommation quotidienne d'alcool (RR 2,94 ; $P < 0,0001$) et le fait d'être sans emploi (RR 1,99 ; $P = 0,01$). Le risque de décès augmente avec le nombre de facteurs indépendants de risque présents ($P < 0,0001$). L'étendue de la maladie et les échecs/rechutes de traitement ne sont pas associés à un accroissement du risque de décès.
CONCLUSIONS : Les décès dus à la TB sont rares. Il est nécessaire d'intervenir pour traiter les cancers, le VIH et la consommation d'alcool chez les patients tuberculeux si l'on veut réduire la mortalité dans cette population de patients.

RESUMEN

MARCO DE REFERENCIA : En América del norte, los pacientes con tuberculosis (TB) suelen presentar características que pueden aumentar la mortalidad global por TB.
OBJETIVOS : Identificar los factores de riesgo que podrían modificarse, a fin de mejorar así el desenlace clínico.
MÉTODO : Se evaluó la mortalidad en un amplio ensayo terapéutico llevado a cabo en los Estados Unidos y Canadá. Se incluyeron en el estudio personas con TB pulmonar y cultivos positivos, 2 meses después de haber comenzado el tratamiento ; recibieron 4 meses más de tratamiento directamente supervisado y se llevó a cabo un seguimiento de 2 años (tiempo total de observación 28 meses). La causa de muerte se estableció a partir del certificado de defunción, la autopsia o la observación clínica.
RESULTADOS : De los 1075 participantes, 71 (6,6%) fallecieron : 15 de 71 pacientes (21,1%) con infección por el VIH y 56 de 1004 pacientes (5,6%) sin infección VIH ($P < 0,001$). Sólo una muerte se atribuyó a la TB. Mediante el análisis Cox de variables múltiples se identificaron cuatro factores pronósticos independientes de muerte, tras un ajuste por la edad : enfermedad maligna (cociente de riesgos instantáneos [HR] 5,28 ; $P < 0,0001$), infección por el VIH (HR 3,89 ; $P < 0,0001$), consumo diario de alcohol (HR 2,94 ; $P < 0,0001$) y desempleo (HR 1,99 ; $P = 0,01$). El riesgo de muerte aumentó con el número de factores de riesgo independientes presentes ($P < 0,0001$). La extensión de la enfermedad, el fracaso del tratamiento o la recaída no se correlacionaron con un mayor riesgo de muerte.
CONCLUSIONES : La muerte por TB fue rara. Se precisan intervenciones para el tratamiento de las enfermedades malignas, el consumo de alcohol y la infección por el VIH, a fin de reducir la mortalidad en esta población de pacientes.