ELSEVIER

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

http://intl.elsevierhealth.com/journals/ijid

HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death

Nara Kingkaew [a], Burachat Sangtong [a], Waraya Amnuaiphon [a],
Jessada Jongpaibulpatana [a], Wiroj Mankatittham [b], Somsak Akksilp [c],
Chawin Sirinak [d], Sriprapa Nateniyom [e], Channawong Burapat [f],
Wanitchaya Kittikraisak [f,*], Patama Monkongdee [f], Jay K. Varma [f,g]

[a] Vachira Hospital, Phuket, Thailand
[b] Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand
[c] Office of Disease Prevention and Control 7, Ubon Ratchathani, Thailand
[d] Department of Health, Bangkok Metropolitan Administration, Bangkok, Thailand
[e] Thailand Ministry of Public Health, Nonthaburi, Thailand
[f] Thailand Ministry of Public Health—US Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand
[g] Centers for Disease Control and Prevention, Atlanta, GA, USA

Summary
Background: We conducted a prospective, multicenter observational cohort study in Thailand to characterize the epidemiology of extrapulmonary tuberculosis (TB) in HIV-infected persons and to identify risk factors for death.
Methods: From May 2005 to September 2006, we enrolled, interviewed, examined, and performed laboratory tests on HIV-infected adult TB patients and followed them from TB treatment initiation until the end of TB treatment. We conducted multivariate proportional hazards analysis to identify factors associated with death.
Results: Of the 769 patients, pulmonary TB only was diagnosed in 461 (60%), both pulmonary and extrapulmonary TB in 78 (10%), extrapulmonary TB at one site in 223 (29%), and extrapulmonary TB at more than one site in seven (1%) patients. Death during TB treatment occurred in 59 of 308 patients (19%) with any extrapulmonary involvement. In a proportional hazards model, patients with extrapulmonary TB had an increased risk of death if they had meningitis, and a CD4+ T-lymphocyte count <200 cells/μl. Patients who received co-trimoxazole, fluconazole, and antiretroviral therapy during TB treatment had a lower risk of death.

* Corresponding author. Tel.: +66 580 0669; fax: +66 591 2909.
  E-mail address: wanitchayak@th.cdc.gov (W. Kittikraisak).

Conclusions: Among HIV-infected patients with TB, extrapulmonary disease occurred in 40% of the patients, particularly in those with advanced immune suppression. Death during TB treatment was common, but the risk of death was reduced in patients who took co-trimoxazole, fluconazole, and antiretroviral therapy.
Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

Introduction

Tuberculosis (TB) is a major global public health problem, causing almost nine million illnesses and two million deaths each year.[1] In adults with normal immune systems, TB disease is usually confined to the lungs, but in persons with immune suppression, such as HIV infection, *Mycobacterium tuberculosis* (MTB) bacilli frequently disseminate beyond the lungs and cause disease in other organ systems.[2] Although most TB programs focus on the control of infectious pulmonary TB, about one in five TB cases worldwide is considered extrapulmonary, which is defined as TB disease occurring outside the lung parenchyma.[1,3] In the past 20 years, countries with HIV epidemics have seen a dramatic increase in extrapulmonary TB cases and deaths; the most common sites of disease include the lymph nodes, meninges, pericardium, peritoneal cavity, and intra-abdominal organs.[4–11] Mortality in HIV-associated extrapulmonary TB is high, ascribed to a combination of advanced HIV disease, concomitant opportunistic infections, and delayed diagnosis and treatment of TB.[12]

Thailand is one of 22 World Health Organization (WHO)-designated high burden TB countries, with an estimated annual TB incidence of 142 per 100 000 population and TB mortality rate of 19 per 100 000 population.[1] An estimated 15–20% of all TB cases occur in HIV-infected persons.[13] Of all TB cases reported nationally from 2002 to 2005, extrapulmonary disease accounted consistently for 12–13%, but high HIV prevalence provinces reported that the percentage of extrapulmonary TB cases was as high as 33%.[14,15] Although national statistics for outcome of extrapulmonary TB treatment are not routinely monitored, the mortality rate is believed to be high. We conducted a prospective, multicenter observational cohort study in Thailand to characterize the epidemiology of extrapulmonary TB in HIV-infected persons and to identify risk factors for death.

Methods

Study population and setting

From May 2005 to September 2006, we recruited patients from the national infectious diseases referral hospital (Bamrasnaradura Infectious Diseases Institute) and public TB treatment facilities in Ubon Ratchathani, Phuket, and Bangkok provinces into a prospective, observational cohort study. The study population included HIV-infected adults diagnosed with active TB disease and receiving anti-TB therapy according to the national TB program guidelines for less than four weeks before study enrollment.[16] We excluded prisoners and pregnant women. For this study, we did not perform any health-related interventions; patients received usual care for TB, HIV, and other diseases. This study was approved by the ethical review committees of the Bangkok Metropolitan Administration, the Thailand Ministry of Public Health, and the US Centers for Disease Control and Prevention.

Data collection and laboratory studies

Patients had three study visits: at the beginning of TB treatment, at the end of the intensive phase of TB treatment (usually two months into treatment), and at the end of TB treatment (usually six months after treatment initiation). At the beginning of treatment, patients were interviewed using standardized study forms that asked about demographic characteristics, past and present medical history, knowledge and attitudes related to TB and HIV, and sex and drug use history. At every study visit, patients received a physical examination and provided information about medications taken and any adverse events experienced since their previous visit. Study staff reviewed medical records for any health-related problem that occurred between study visits.

At the beginning of treatment, blood samples were tested for liver function enzymes, complete blood count, viral hepatitis serology, and CD4+ T-lymphocyte (CD4) count. Sputum and specimens from extrapulmonary sites were collected for acid-fast bacilli smear and for mycobacterial culture using solid and liquid media, identification, and drug-susceptibility testing. Not all patients with sputum smears had culture results available for analysis, because culture was not performed or the culture grew nothing, a contaminant, or non-tuberculous mycobacteria. Study nurses recorded the locations in which TB was diagnosed. We classified patients as having 'disseminated' TB if extrapulmonary TB was diagnosed in more than one extrapulmonary organ system (e.g., osteoarticular and liver) or pulmonary TB was diagnosed together with any type of extrapulmonary TB.

We assessed outcomes at the end of TB treatment according to WHO guidelines; successful TB treatment comprised both cured and completed treatment.[16] For patients recorded as defaulting during TB treatment, we reviewed the government's vital status registry to determine whether patients died within 90 days of defaulting; such patients were re-classified as deaths during TB treatment.

Statistical analysis

We calculated proportions for the description of demographic characteristics and clinical features. We examined the relationship between CD4 levels and anatomic location of TB disease. A one-way Kruskal–Wallis test was performed to determine if the CD4 level across the sites significantly differed. Using pulmonary TB as a referent group, a regression with dummy variables was then fitted on log CD4 levels to determine groups that were different from the referent

group. To determine risk factors for extrapulmonary TB, we classified patients with both pulmonary and extrapulmonary TB as having extrapulmonary TB. We then performed univariate logistic regression analyses. We tested covariates that were significant at $p \leq 0.20$ for collinearity and constructed multivariate logistic regression models of all patients and of bacteriologic-confirmed TB patients (at least one specimen collected at any time before or during treatment was positive for acid-fast bacilli and/or culture-positive for MTB). Two-way interaction terms were generated as products of covariates and also entered into models. For this analysis and all other multivariate analyses, we fitted parsimonious models by using a backward stepwise procedure and assessed model fitness using the Hosmer—Lemeshow goodness-of-fit test. We also examined factors associated with death in patients with different locations of extrapulmonary TB, using pulmonary TB patients as the referent group. For this analysis, we calculated time from TB treatment initiation to treatment completion or death, confirmed that the proportional hazards model assumption was met, and then constructed a multivariate Cox proportional hazards model. We included in the model factors that were associated with death at $p \leq 0.20$ in univariate analyses for all patients and, because of small sample size, excluded patients with less common forms of extrapulmonary TB (16 pleural, four cutaneous, three osteoarticular, and three pericardial TB patients excluded). For this analysis, we did not fit a model for bacteriologic-confirmed TB patients because the small number made our model unstable.

A two-sided p-value of ≤ 0.05 was used to indicate statistical significance. We performed all analyses using Stata software version 8.0 (StataCorp LP, College Station, TX, USA).

Results

Enrollment and characteristics of patients

Of 1096 eligible patients, we enrolled 849 (78%) and, after excluding cases whose diagnosis changed, analyzed 769 (Figure 1). The median length from TB treatment initiation to study enrollment was seven days (interquartile range (IQR) 1—8 days). Of the 769 patients, pulmonary TB only was diagnosed in 461 (60%), both pulmonary and extrapulmonary TB in 78 (10%), extrapulmonary TB at one site in 223 (29%), and extrapulmonary TB at more than one site in seven (1%) patients. Of the 223 patients with extrapulmonary TB at one site, 139 (62%) had lymphatic, 29 (13%) meningeal, 29 (13%) intra-abdominal, 16 (7%) pleural, four (2%) cutaneous, three (1%) osteoarticular, and three (1%) pericardial TB. Bacteriologic confirmation was documented in 410 (76%) patients who had at least pulmonary TB (includes those who also had extrapulmonary TB) and 121 (53%) patients with extrapulmonary TB; culture confirmation occurred in 333 (62%) and 80 (35%), respectively. Of the 413 culture-confirmed TB patients, 23 (6%) were multidrug-resistant TB, 39 (9%) were isoniazid-resistant TB, and five (1%) were rifampin-resistant TB.

Table 1 displays patient characteristics stratified by type of TB. At the end of follow-up, 493 (64%) patients were successfully treated, six (1%) failed treatment, 134 (17%) died, 61 (8%) defaulted, 70 (9%) transferred out, and five (1%) were still on treatment. Death during TB treatment occurred in 43/230 (19%) patients with exclusively extrapulmonary TB (including extrapulmonary at ≥ 1 site) and 59/308 (19%) patients with any extrapulmonary involvement. When stra-
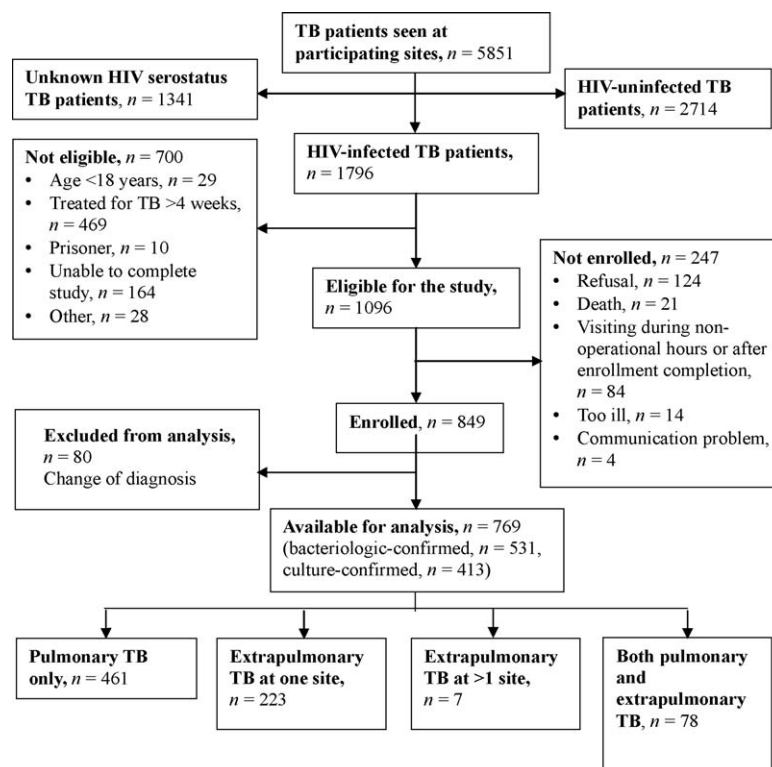

Figure 1   Enrollment of HIV-infected TB patients.

Table 1 Characteristics, clinical features at time of TB diagnosis, and treatment outcomes among HIV-infected TB patients, stratified by disease classification

	All (N = 769)	Pulmonary TB only (N = 461)	Extrapulmonary at $\geq$1 site (N = 230)	Both pulmonary and extrapulmonary TB (N = 78)
Characteristics				
Age >34 years	380 (49)	233 (50)	111 (48)	36 (46)
Male	538 (70)	347 (75)	139 (60)	52 (67)
Finished 6th grade education	300 (39)	178 (39)	95 (41)	27 (35)
CD4 <200 cells/μl[a]	608 (81)	345 (77)	192 (85)	71 (92)
Timing of HIV diagnosis in relation to TB diagnosis				
Same year	495 (64)	329 (71)	120 (52)	46 (59)
1—5 years prior	190 (25)	96 (21)	77 (33)	17 (22)
6—10 years prior	57 (7)	25 (5)	21 (9)	11 (14)
>10 years prior	15 (2)	3 (1)	8 (3)	4 (5)
Hospitalized at enrollment	205 (27)	93 (20)	81 (35)	31 (40)
Delay in HIV diagnosis[a,b]	359 (72)	235 (69)	87 (76)	37 (82)
Delay in TB diagnosis[c]	371 (48)	248 (54)	86 (37)	37 (47)
Previously had lymphoma	10 (1)	3 (1)	6 (3)	1 (1)
Registered as new case	667 (87)	387 (84)	206 (90)	74 (95)
Know anyone with TB	283 (37)	172 (37)	84 (36)	27 (35)
Medications taken during TB treatment				
2HRZE/4HR regimen	665 (86)	378 (82)	217 (94)	70 (90)
Co-trimoxazole[d]	635 (82)	369 (80)	200 (87)	66 (85)
Fluconazole[d]	434 (56)	241 (52)	148 (64)	45 (58)
Antiretroviral[d]	307 (40)	156 (34)	126 (55)	25 (32)
Physical examination				
Body mass index <18.5 kg/m^2	443 (58)	276 (60)	117 (51)	50 (64)
HBsAg reactive	70 (9)	42 (9)	21 (9)	7 (9)
Anti-HCV reactive	237 (31)	167 (36)	42 (18)	28 (36)
HBsAg and anti-HCV reactive	27 (3)	21 (4)	5 (2)	1 (1)
Albumin <2.5 g/dl	164 (21)	82 (18)	52 (23)	30 (38)
Treatment outcomes				
Cure/complete	493 (64)	301 (65)	151 (66)	41 (52)
Failure	6 (1)	5 (1)	1 (0)	0 (0)
Died	134 (17)	75 (16)	43 (19)	16 (20)
Default	61 (8)	39 (8)	14 (6)	8 (10)
Transfer out	70 (9)	37 (8)	20 (9)	13 (17)
On treatment	5 (1)	4 (1)	1 (0)	0 (0)

Results are n (%).

TB, tuberculosis; CD4, CD4+ T-lymphocyte; 2HRZE/4HR, two months of rifampin, isoniazid, pyrazinamide, and ethambutol followed by four months of rifampin and isoniazid; HBsAg, hepatitis B surface antigen; anti-HCV, hepatitis C antibodies.

[a] Those with available results only.

[b] Patients were considered to have a delay in HIV diagnosis if their CD4+ T-lymphocyte count at the time of HIV diagnosis was <200 cells/μl; standard assumptions were used to estimate CD4+ T-lymphocyte count at the time of HIV diagnosis for patients with a pre-existing HIV diagnosis, no CD4+ T-lymphocyte count recorded at the time of HIV diagnosis, and no history of ART treatment.

[c] Patients were considered to have a delay in TB diagnosis if they reported: (a) having a cough lasting greater than one month before TB diagnosis; or (b) having other symptoms that lasted longer than 14 days and self-assessed these symptoms as being severe.

[d] Those starting opportunistic infection prophylaxis and antiretroviral medicines within 30 days of TB treatment completion were classified as not receiving these medicines.

tified by anatomic site, death occurred in 75/461 (16%) pulmonary only, 20/139 (14%) lymphatic, 11/29 (38%) meningeal, 10/29 (34%) intra-abdominal, 1/16 (6%) pleural, 16/85 (19%) disseminated, 1/4 (25%) cutaneous, 0/3 (0%) osteoarticular, and 0/3 (0%) pericardial TB cases.

Anti-TB treatment and duration

The standard anti-TB regimen including two months of rifampin, isoniazid, pyrazinamide, and ethambutol followed by four months of rifampin and isoniazid was prescribed in 378/

461 (82%) patients diagnosed with pulmonary TB only, 70/78 (90%) patients with pulmonary and extrapulmonary TB, and 217/230 (94%) patients with extrapulmonary TB at ≥1 site. Directly observed therapy by healthcare workers or village health volunteers was offered to all patients; 246 (32%) opted to participate. The median duration of TB treatment among patients with pulmonary TB only was 190 (IQR 159—249) days, in patients with pulmonary and extrapulmonary TB was 204 (IQR 161—272) days, and in patients with extrapulmonary TB at ≥1 site was 192.5 (IQR 122—237) days. Most patients reported having an array of symptoms at two months into TB treatment. The most common symptom was itching rash (reported by 45% of the patients), followed by fatigue (41%) and pain in muscles or joints (35%).

Extent of immunosuppression and clinical manifestation of TB disease

Figure 2 shows the percentage of patients with extrapulmonary TB according to CD4 count. As CD4 decreased from over 400 cells/μl to 200 cells/μl, the percentage of TB patients with extrapulmonary TB increased from 19% to 35%. The percentage of extrapulmonary involvement was relatively stable when CD4 dropped below 200 cells/μl. Osteoarticular TB was the most common location of disease among patients with high levels of CD4 (Table 2). Pleural TB occurred at a significantly higher CD4 than pulmonary TB; intra-abdominal, lymphatic, and disseminated at a significantly lower CD4.

Risk factors for extrapulmonary TB

In multivariate logistic regression analysis of all patients, factors associated with extrapulmonary TB included being hospitalized at enrollment (adjusted odds ratio (AOR) 1.6, 95% confidence interval (CI) 1.1—2.3), treated for TB at the national infectious diseases institute (AOR 2.3, 95% CI 1.6—3.4), having been diagnosed with HIV 1—5 years (AOR 1.7, 95% CI 1.2—2.6) and >10 years before TB diagnosis (AOR 7.3, 95% CI 1.8—29.1), and having been previously diagnosed with lymphoma (AOR 4.5, 95% CI 1.1—18.4) (Table 3). Extrapulmonary TB was less likely to occur in patients who were male (AOR 0.7, 95% CI 0.5—1.0), had hepatitis C antibodies (AOR 0.6, 95% CI 0.4—0.9), and had a CD4 count >199 cells/μl (AOR
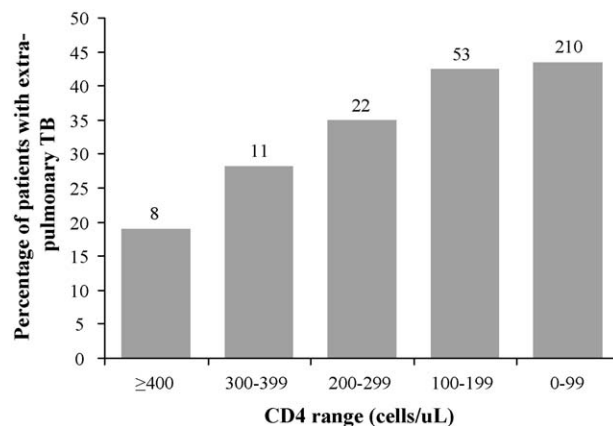

Figure 2 CD4+ T-lymphocyte count and prevalence of extrapulmonary TB among HIV-infected TB patients (number of patients is shown at the top of each bar; patients with both pulmonary and extrapulmonary TB were classified as having extrapulmonary TB).

0.6, 95% CI 0.4—1.0). In a subset of bacteriologic-confirmed patients, risk factors remaining significantly associated with extrapulmonary TB were being hospitalized at enrollment, treated for TB at the national infectious diseases institute, and having been diagnosed with HIV >10 years before TB diagnosis. Having hepatitis C antibodies remained protective for extrapulmonary TB.

Risk factors for death

In a proportional hazards model of all patients, we found a significant association between location of extrapulmonary TB and death. Meningeal TB patients died at greater rates compared to pulmonary TB patients (hazard ratio (HR) 3.5, 95% CI 1.2—9.9) (Table 4). Other factors associated with higher risk of death were having a CD4 count 0—24 cells/μl (HR 10.2, 95% CI 4.4—24.0), having a CD4 count 25—99 cells/μl (HR 4.1, 95% CI 1.7—9.6), having a CD4 count 100—199 cells/μl (HR 4.0, 95% CI 1.5—10.7), and being hospitalized at enrollment (HR 2.9, 95% CI 1.7—4.7). Co-trimoxazole (HR 0.5, 95% CI 0.3—1.0), fluconazole (HR 0.5, 95% CI

Table 2 Primary location of TB disease and CD4+ T-lymphocyte level among HIV-infected TB patients[a]

Primary location of TB disease	No. of patients	No. (%) of patients with CD4 <100 cells/μl	Median CD4 (cells/μl)	Interquartile range of CD4 (cells/μl)	p
Osteoarticular	3	1 (33)	268	4—592	0.69
Pleural	16	4 (25)	145	101—209	0.02
Meningeal	29	17 (59)	84	50—153	0.48
Cutaneous	4	2 (50)	77	22—217	0.38
Pulmonary	451	273 (60)	71	26—191	Ref.
Lymphatic	138	98 (71)	49	22—129	0.02
Pericardial	3	2 (67)	48	37—110	0.91
Disseminated[b]	84	63 (75)	42	15—101	<0.01
Intra-abdominal	28	23 (82)	37	15—65	<0.01

TB, tuberculosis; CD4, CD4+ T-lymphocyte; Ref., referent group.
[a] Only patients with available CD4+ T-lymphocyte counts.
[b] Patients diagnosed with TB in >1 extrapulmonary organ system or patients with both pulmonary and any type of extrapulmonary TB.

Table 3 Univariate and multivariate logistic regression analyses of risk factors for having extrapulmonary TB among HIV-infected TB patients

Characteristics	OR (95% CI)	AOR (95% CI)
Sex		
Male	0.5 (0.4–0.7)	0.7 (0.5–1.0)
Female	Ref.	Ref.
Treated for TB at national infectious diseases institute		
Yes	3.2 (2.3–4.4)	2.3 (1.6–3.4)
No	Ref.	Ref.
Hospitalized at enrollment		
Yes	2.3 (1.6–3.1)	1.6 (1.1–2.3)
No	Ref.	Ref.
Timing of HIV diagnosis in relation to TB		
Same year	Ref.	Ref.
1–5 years prior	1.9 (1.4–2.7)	1.7 (1.2–2.6)
6–10 years prior	2.1 (1.3–3.5)	1.5 (0.9–2.7)
>10 years prior	7.9 (2.2–28.5)	7.3 (1.8–29.1)
Previous diagnosis of lymphoma		
Yes	3.5 (0.9–13.8)	4.5 (1.1–18.4)
No	Ref.	Ref.
Hepatitis C antibodies reactive		
Yes	0.5 (0.4–0.7)	0.6 (0.4–0.9)
No	Ref.	Ref.
Registered as new case		
Yes	1.9 (1.2–3.0)	1.8 (1.0–3.0)
No	Ref.	Ref.
CD4+ T-lymphocyte count (cells/μl)		
0–24	Ref.	Ref.
25–99	0.9 (0.6–1.3)	0.9 (0.6–1.3)
100–199	0.9 (0.6–1.4)	1.0 (0.6–1.6)
>199	0.5 (0.3–0.8)	0.6 (0.4–1.0)

TB, tuberculosis; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; Ref., referent group.

Table 4 Multivariate Cox proportional hazards analysis of risk factors for death among HIV-infected extrapulmonary TB patients[a]

Factors	HR	95% CI		p
		Lower	Upper	
CD4+ T-lymphocyte count (cells/μl)				
0–24	10.2	4.4	24.0	<0.01
25–99	4.1	1.7	9.6	<0.01
100–199	4.0	1.5	10.7	<0.01
>199	Ref.			
Hospitalized at enrollment				
Yes	2.9	1.7	4.7	<0.01
No	Ref.			
Received co-trimoxazole during TB treatment[b]				
Yes	0.5	0.3	1.0	0.05
No	Ref.			
Received fluconazole during TB treatment[b]				
Yes	0.5	0.3	0.9	0.01
No	Ref.			
Received ART during TB treatment[b]				
Yes	0.2	0.1	0.3	<0.01
No	Ref.			
Platelet level at enrollment ≤150 × 10^9 cells/l				
Yes	1.0	0.5	2.0	0.91
No	Ref.			
Type of extrapulmonary TB				
Intra-abdominal	0.7	0.1	3.0	0.59
Disseminated	0.6	0.3	1.3	0.22
Meningeal	3.5	1.2	9.9	0.02
Lymphatic	0.7	0.3	1.5	0.37
Pulmonary	Ref.			

TB, tuberculosis; HR, hazard ratio; CI, confidence interval; ART, antiretroviral therapy; Ref., referent group.

[a] Patients starting opportunistic infection prophylaxis and antiretroviral medicines before TB treatment initiation were excluded.

[b] Those starting opportunistic infection prophylaxis and antiretroviral medicines within 30 days of TB treatment completion were classified as not receiving these medicines.

0.3–0.9), and antiretroviral (ART) use (HR 0.2, 95% CI 0.1–0.3) were associated with a lower risk of death. Among patients receiving ART during TB treatment, the most common regimen was a nevirapine-containing regimen, followed by an efavirenz-containing regimen.

Discussion

Among HIV-infected patients with TB, extrapulmonary disease occurred in 40% of the patients, particularly in those with advanced immune suppression. Death during TB treatment was common, but the risk of death was reduced in patients taking co-trimoxazole, fluconazole, and ART.

Consistent with previous studies, we found that advanced HIV was strongly correlated with the occurrence of extrapulmonary TB.[8] The major risk factors for extrapulmonary TB in our study were low CD4 level, first HIV diagnosis more than one year before TB diagnosis, and lymphoma, a malignancy that may be HIV-associated. Of note, the relationship between CD4 level and extrapulmonary involvement was not absolute; the median CD4 count for pleural TB patients

was significantly higher than that of pulmonary TB patients, and there was trend toward a higher CD4 count for osteoarticular and meningeal TB patients. Pleural TB is more common in HIV-uninfected persons and may be more common among HIV-infected persons with high CD4 counts, because TB pleural effusions are usually caused by delayed type hypersensitivity to mycobacterial antigens.[17] The reason for a possible association between high CD4 count and osteoarticular or meningeal TB, however, are not as clear. We also found a relationship between extrapulmonary TB and female sex, a relationship hypothesized in other studies to be due to differential exposure of women to infectious TB patients, smoking, and medical care compared with men.[4–6,18–24]

Pulmonary TB in HIV-infected patients is frequently sputum smear-negative, making diagnosis challenging and increasing the possibility that TB disease will disseminate

outside the lungs.[25] In 2006, WHO released guidelines to improve diagnosis of smear-negative TB and extrapulmonary TB in HIV-prevalent settings; simple, standardized guidelines were provided for diagnosing peripheral lymph node, pleural, pericardial, meningeal, and disseminated (miliary) TB based on clinical findings.[12] Because HIV-infected patients may have multiple concomitant infections, microbiologic confirmation of clinical diagnosis is still important, even though we found that it is not often done, as in other published reports.[26] Research is needed to develop less invasive and more sensitive tools for diagnosing extrapulmonary TB.

In our study, we evaluated a large number of factors that could increase the risk of death in patients with extrapulmonary TB, including delays in TB and HIV diagnosis, social and economic conditions, and concomitant illnesses. We found that the strongest independent determinants of survival were use of ART and opportunistic infection prophylaxis during TB treatment. In several observational studies, ART has been shown to be life-saving in HIV-associated TB.[27–30] We do not know why some patients did not receive ART, even though such care is widely available in Thailand and has been demonstrated to improve survival. Possible reasons include lack of physician knowledge about the benefits of early ART, fear of immune reconstitution inflammatory syndrome or drug toxicity, patient reluctance to take many pills, or other health system barriers. One clinical trial and several observational studies have shown a similar benefit to co-trimoxazole, and one previous observational study in Thailand has shown a benefit to fluconazole.[31–35] Our study is the only one to have evaluated these interventions prospectively in HIV-infected patients with extrapulmonary TB.[17,36] In multivariate analysis, the risk of death was not significantly greater for patients with different sites of extrapulmonary TB compared with pulmonary TB, except for meningeal TB, which had an over 3-fold increased risk of death. Meningeal TB is particularly challenging to diagnose, because cerebrospinal fluid is frequently smear- and culture-negative.[37] Regardless of HIV infection, treatment outcomes are poor, requiring adjunctive corticosteroids and early initiation and prolonged use of TB treatment.[38] At least one clinical trial is ongoing to evaluate the added benefit of early ART in patients already receiving optimum clinical care for meningeal TB.[39]

Our study is subject to several important limitations. First, and most important, many patients did not have microbiologic confirmation of TB and were diagnosed based on a constellation of clinical, laboratory, and radiographic findings. We did not apply rigorous criteria for extrapulmonary TB, because the study was aimed to describe the features of patients routinely diagnosed and treated in the public health system, where such criteria do not exist. To account for the possibility of misclassification, we restricted some analyses to only those patients with bacteriologic or culture confirmation of MTB. The consistency of our findings among those with microbiologic confirmation suggests that misdiagnosis, although a common problem, would not explain the findings of this study. Second, extrapulmonary TB refers to a heterogeneous group of pathological entities, each with unique diagnostic and treatment challenges. Our sample size was too small for us to evaluate some well-known types of extrapulmonary TB (e.g., pleural, cutaneous, pericardial) and to construct independent models for each type. Lastly, there is a discrepancy between the proportion of smear-positive and the number of positive cultures, because cultures were not performed, were contaminated, or did not grow MTB for some patients.

In conclusion, we found that extrapulmonary TB occurred predominantly in patients with advanced HIV and that appropriate HIV-related care and treatment was the single most important determinant of survival in patients with extrapulmonary TB. At a population level, improving survival will require awareness of clinicians about the diverse manifestations of extrapulmonary TB in patients with AIDS, expanded use of existing diagnostic tools, research into new diagnostic tools, and universal access to HIV care and treatment.

References

1. World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. Geneva: World Health Organization; 2007.
2. Iseman MD. Extrapulmonary tuberculosis in adults. In: Iseman MD, editor. *A clinician's guide to tuberculosis*. Philadelphia: Lippincott, Williams and Wilkins; 2000. p. 145–97.
3. World Health Organization. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. Geneva: World Health Organization; 2003.
4. Noertjojo K, Tam CM, Chan SL, Chan-Yeung MM. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. *Int J Tuberc Lung Dis* 2002;**6**:879–86.
5. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of risk factors for extrapulmonary tuberculosis. *Clin Infect Dis* 2004;**38**:199–205.
6. Musellim B, Erturan S, Sonmez Duman E, Ongen G. Comparison of extra-pulmonary and pulmonary tuberculosis cases: factors influencing the site of reactivation. *Int J Tuberc Lung Dis* 2005;**9**:1220–3.
7. Ilgazli A, Boyaci H, Basyigit I, Yildiz F. Extrapulmonary tuberculosis: clinical and epidemiologic spectrum of 636 cases. *Arch Med Res* 2004;**35**:435–41.
8. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993;**148**:1292–7.
9. Solomon SS, Kumarasamy N, Celentano DD, Yepthomi TH, Arvind VP, Solomon S. Trends in HIV-related morbidity among patients admitted to a South Indian tertiary hospital between 1997 and 2003. *AIDS Care* 2006;**18**:366–70.
10. Cailhol J, Decludt B, Che D. Sociodemographic factors that contribute to the development of extrapulmonary tuberculosis were identified. *J Clin Epidemiol* 2005;**58**:1066–71.

11. Narain JP, Lo YR. Epidemiology of HIV-TB in Asia. *Indian J Med Res* 2004;**120**:277–89.

12. World Health Organization. *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents*. Geneva: World Health Organization; 2006.

13. Nateniyom S, Jittimanee SX, Wiriyakitjar D, Jittimanee S, Kaophaithool S, Varma JK. Provider-initiated HIV testing and counseling in tuberculosis clinics in Thailand. *Int J Tuberc Lung Dis* 2008;**12**:955–61.

14. Varma JK, Wiriyakitjar D, Nateniyom S, Anuwatnonthakate A, Monkongdee P, Sumnapan S, et al. Evaluating the potential impact of the new Global Plan to Stop TB: Thailand, 2004–2005. *Bull World Health Organ* 2007;**85**:586–92.

15. World Health Organization. World Health Organization South-East Asia Regional Office. Fourth review of the National Tuberculosis Programme in Thailand, 16–25 July 2007. New Delhi: World Health Organization; 2008.

16. TB Cluster Bureau of AIDS TB and STIs. National TB program guidelines. Bangkok: Department of Diseases Control, Ministry of Public Health; 2005.

17. Kourbatova EV, Leonard Jr MK, Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. *Eur J Epidemiol* 2006;**21**:715–21.

18. Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal—a hospital-based retrospective study. *BMC Infect Dis* 2008;**8**:8.

19. Chan-Yeung M, Noertjojo K, Chan SL, Tam CM. Sex differences in tuberculosis in Hong Kong. *Int J Tuberc Lung Dis* 2002;**6**:11–8.

20. Thompson BC. The pathogenesis of tuberculosis of peripheral lymph nodes. A clinical study of 324 cases. *Tubercle* 1940;**1940**:141.

21. Lam TH, Ho SY, Hedley AJ, Mark KH, Peto R. Mortality and smoking in Hong Kong: case—control study of all adult deaths in 1998. *BMJ* 2001;**323**:1–6.

22. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. *Int J Tuberc Lung Dis* 1998;**2**:96–104.

23. Hudelson P. Gender differentials in tuberculosis: the role of socio-economic and cultural factors. *Tuber Lung Dis* 1996;**77**:391–400.

24. Martinez AN, Rhee JT, Small PM, Behr MA. Sex differences in the epidemiology of tuberculosis in San Francisco. *Int J Tuberc Lung Dis* 2000;**4**:26–31.

25. Diagnostic standards and classification of tuberculosis in adults and children. American Thoracic Society. *Am J Respir Crit Care Med* 2000;**161**:1376–95.

26. Kwara A, Roahen-Harrison S, Prystowsky E, Kissinger R, Adams R, Mathison J, et al. Manifestations and outcome of extra-pulmonary tuberculosis: impact of human immunodeficiency virus co-infection. *Int J Tuberc Lung Dis* 2005;**9**:785–93.

27. Akksilp S, Karnkwainpoing O, Wattanaamornkiat W, Viriyakitja D, Mongkongdee P, Sitti W, et al. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. *Emerg Infect Dis* 2007;**13**:1001–7.

28. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis* 2004;**190**:1670–6.

29. Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002;**16**:75–83.

30. Sanguanwongse N, Cain KP, Suriya P, Nateniyom S, Yamada N, Wattanaamornkiat W, et al. Anti-retroviral therapy for HIV-infected TB patients saves lives, but needs to be used more frequently in Thailand. *J Acquir Immune Defic Syndr* 2008;**48**:181–9.

31. Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, et al. Efficacy of trimethoprim—sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999;**353**:1469–75.

32. Trinh TT, Shah NS, Mai HA, Do TN, Duong T, Truong L, et al. HIV-associated TB in An Giang Province, Vietnam, 2001–2004: epidemiology and TB treatment outcomes. *PLoS ONE* 2007;**2**:e507.

33. Mwaungulu FB, Floyd S, Crampin AC, Kasimba S, Malema S, Kanyongoloka H, et al. Co-trimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi. *Bull World Health Organ* 2004;**82**:854–63.

34. Boeree MJ, Sauvageot D, Banda HT, Harries AD, Zijlstra EE. Efficacy and safety of two dosages of co-trimoxazole as preventive treatment for HIV-infected Malawian adults with new smear-positive tuberculosis. *Trop Med Int Health* 2005;**10**:723–33.

35. Grimwade K, Sturm AW, Nunn AJ, Mbatha D, Zungu D, Gilks CF. Effectiveness of co-trimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS* 2005;**19**:163–8.

36. Garcia de Olalla P, Martinez-Gonzalez MA, Cayla JA, Jansa JM, Iglesias B, Guerrero R, et al. Barcelona AIDS-TB Study Group. Influence of highly active anti-retroviral therapy (HAART) on the natural history of extra-pulmonary tuberculosis in HIV patients. *Int J Tuberc Lung Dis* 2002;**6**:1051–7.

37. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculosis meningitis: a 30-year review. *Clin Infect Dis* 1993;**17**:987–94.

38. Harries A, Maher D, Graham S. *TB/HIV: a clinical manual*. 2nd ed. Geneva: World Health Organization; 2004.

39. US National Institutes of Health. Clinical trials. Available at: www.clinicaltrials.gov (accessed January 2009).