

TUBERCULOSIS IN HIV/AIDS PATIENTS: A MALAYSIAN EXPERIENCE

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Abstract. This retrospective study was conducted at the National Tuberculosis Center (NTBC) where 252 HIV-positive patients coexisting with tuberculosis (TB/HIV) were examined. We found that patients with pulmonary (PTB) and extrapulmonary tuberculosis (EPT) had similar mean age. A higher sex ratio between male to female (10.7:1) was observed in patients with PTB. The other characteristics of patients with pulmonary and extrapulmonary tuberculosis were not statistically different from each other. Cough (88%) and hemoptysis were the most common presenting symptoms, significantly related to patients with PTB. Lymphadenopathy (33.5%) was the most common sign in patients with EPT. The majority of patients with pulmonary and extrapulmonary tuberculosis had CD4 cell counts of less than 200 cells/mm³ (range 0-1,179 with a median of 57 cells/mm³). Lung (89%) and miliary (55.6%) forms were the most frequent disease locations in patients with PTB and EPT, respectively. A higher percentage of patients with PTB (42%) were treated successfully with short-course (6 months) therapy, whereas in patients with EPT (43%) needed a longer period (9 months) for successful treatment. Of the patients who defaulted treatment, a higher proportion (87%) had PTB. No MDR-TB or relapse cases were found in this study.

INTRODUCTION

Over the past two decades, HIV has emerged as a global public health pandemic, to become a modern day "plague". Tuberculosis (TB) is a disease of great antiquity and remains a major challenge worldwide both in terms of disease burden and resistance to conventional antibiotic therapy (Eltringham and Drobniewski, 1998). The rising incidence of TB due to the effect of HIV in both developed and developing countries is well recognized (Narain *et al*, 1992). In Malaysia, tuberculosis is among the top 5 communicable diseases. The number of reported cases of tuberculosis and HIV coinfection have increased from 6 cases in the year 1990 to 933 cases in the year 2002 (Ministry of Health Malaysia, 2002). Infection with HIV has modified the epidemiology, pathogenesis and clinical manifestations of tuberculosis (Pulido *et al*, 1997) and

is by far the most important risk factor known for the progression of latent *M. tuberculosis* infection to active TB and for the rapid progression of new infection to TB (Johnson and Ellner, 1999). TB now is the leading opportunistic infection causing death in HIV-infected persons globally, accounting for about 44% of all AIDS-related deaths annually (Jones *et al*, 1999). We conducted this study in order to compare the characteristics of HIV-positive patients with pulmonary and extrapulmonary tuberculosis, and to describe the organ involvement, clinical diagnosis and treatment outcomes.

MATERIALS AND METHODS

Patients. A total of 252 HIV-positive patients registered for tuberculosis treatment from 1 January 2001 to 31 December 2002 at the National Tuberculosis Center (NTBC) were included in this study. This center is a tertiary level national reference center for respiratory diseases situated in Kuala Lumpur, Malaysia. Any person with a respiratory problem can attend this center without a physician referral. Majority of notified TB

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cases in Kuala Lumpur territory each year are treated. The data were retrospectively reviewed from each patient's medical record. Socio-demographic profiles, clinical presentations, investigation results, treatment, patient compliance with therapy, and outcomes of therapy response were included in a standardized data collection sheet. AIDS defining illnesses were also based on the 1993 CDC classification.

The case definitions were obtained from the World Health Organization (WHO, 2002).

A case of tuberculosis was defined as a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a clinician.

A pulmonary tuberculosis, sputum smear positive (PTB+) case was defined as two or more initial sputum smear examinations positive for Acid-Fast Bacilli (AFB) or one sputum smear examination positive for AFB plus radiological abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, or one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.

A pulmonary tuberculosis, sputum smear negative (PTB-) case was defined as a case of pulmonary tuberculosis which does not meet the above definition for smear positive TB. In keeping with good clinical and public health practices, diagnostic criteria should include: at least three sputum specimens negative for AFB, and radiographic abnormalities consistent with active pulmonary tuberculosis, and no response to a course of broad spectrum antibiotics, and decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

An extrapulmonary tuberculosis case was defined as tuberculosis of organs other than the lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, and meninges. Disease should be based on one culture positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary tuberculosis, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Categories of patients for registration

New: A patient who has never had treat-

ment for TB or has taken anti-tuberculosis drugs for less than one month.

Relapse: A patient previously treated for TB who has been declared cured or has completed treatment, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

Failure: A patient who, while on treatment, is sputum smear positive at 5 months or later during the course of treatment.

Return after default: A patient who returns for treatment with positive bacteriology, following an interruption of treatment for two or more months.

Transfer in: A patient who has been transferred from another tuberculosis register to continue treatment.

Categories of treatment outcomes

Cure: A patient who is sputum smear negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A patient who has completed treatment but who does not meet the criteria to be classified as cured or a failure.

Treatment failure: A patient who is sputum smear positive at five months or later during treatment.

Died: A patient who dies for any reason during the course of treatment.

Defaulter: A patient whose treatment was interrupted for 2 or more consecutive months.

Transfer out: A patient who has been transferred to another unit and for whom the treatment outcome is not known.

Treatment success: A patient who is cured and who has completed treatment.

Statistical analysis

The data was analyzed by using the statistical software, SPSS version 10. (SPSS Inc, Chicago, Ill, USA). The data with quantitative variables were expressed by mean (\pm SD) and range while the qualitative variables were estimated by frequency and percentage. Statistical analysis was estimated using either the chi-square test or Student's *t*-test where appropriate. Further analysis using the multiple logistic regression was employed to determine the predictors of type of

tuberculosis. A p-value of <0.05 was regarded as statistically significant.

RESULTS

Table 1 demonstrates the socio-demographic characteristics of 252 TB/HIV patients. One hundred and ninety-eight patients were diagnosed as having pulmonary tuberculosis (PTB) including only PTB or PTB with its dissemination; while the other 54 patients were diagnosed as having extrapulmonary tuberculosis (EPT). We found that patients with PTB and EPT were similar in their mean ages. A sex ratio between males and females (10.7:1) was apparently higher in patients with PTB. The other characteristics of patients with pulmonary and extrapulmonary tuberculosis showed no statistically significant differences between the two groups. A higher percentage of smoking and/or drinking alcohol, history of previous tuberculosis, and history contact with TB patients was seen in patients with PTB.

Cough (88%), loss of weight and/or appetite (82%), and fever (73%) were the most common presenting symptoms in patients with PTB. There were significant associations between cough, sputum and hemoptysis with PTB patients ($p < 0.05$). Multiple logistic regressions showed that only cough and hemoptysis were significantly associated with PTB patients. Lymphadenopathy (33.5%) was the most common sign in patients with EPT. Majority of 35 patients with pulmonary and extrapulmonary tuberculosis had CD4 cell counts of less than 200 cells/mm³ (range 0-1,179 with a median of 57 cells/mm³) at the time of diagnosis. We were unable to obtain the CD4 cell count of the other patients as they were being jointly managed with infectious Disease units located in other hospitals. Lung (89%) was the most frequent disease location in patients with PTB, whereas the miliary (55.6%) form was the most common in patients with EPT, as shown in Tables 2 and Fig 1, respectively.

Table 3 illustrates that among the 252 TB patients, the 6 month anti-tubercular therapy regimen was the most common successful regimen for both types of TB patient; but had a

Table 1
The socio-demographic characteristics of 252 TB/HIV patients attending the National Tuberculosis Center, January 2001 to December 2002.

Variables	PTB (198) n (%)	EPT (54) n (%)	p-value
Range of ages	18-68 years	23-82 years	
Mean \pm SD	37.2 \pm 7.8	38.9 \pm 9.5	0.168
Sex ratio (M:F)	10.7:1	6.7:1	
Age group (years)			0.744
\leq 24	7 (3.5)	3 (5.6)	
25-34	72 (36.4)	15 (27.8)	
35-44	83 (42)	26 (48.2)	
45-54	31 (15.7)	8 (14.8)	
\geq 55	5 (2.5)	2 (3.7)	
Sex			0.331
Male	181 (91.4)	47 (87)	
Female	17 (8.6)	7 (13)	
Race			0.114
Malay	120 (60.6)	24 (44.4)	
Chinese	38 (19.2)	18 (33.3)	
Indian	28 (14.1)	9 (16.7)	
Others ^a	12 (6.1)	3 (5.6)	
Marital status			0.904
Single	141 (71)	38 (70)	
Married	57 (29)	16 (30)	
Address			0.389
Kuala Lumpur	90 (44.5)	21 (38.9)	
Outsider	108 (54.5)	33 (61.1)	
Occupation			0.170
Laborer	35 (17.7)	4 (7.4)	
Nonlaborer	26 (13.1)	7 (13)	
Unemployed	137 (69.2)	43 (79.6)	
Risk factors of HIV transmission			0.875
Heterosexual	61 (30.8)	19 (27.8)	
Homosexual	2 (1)	-	
Intravenous drug use	145 (73.2)	39 (72.2)	
Not known	1 (0.5)	-	
Smoking			0.773
Yes	86 (43.4)	22 (40.7)	
No	112 (56.6)	32 (59.3)	
Drinking alcohol			0.399
Yes	9 (4.6)	4 (7.4)	
No	189 (95.4)	50 (92.6)	
Case category ^b			0.006
New case	173 (87.4)	54 (100)	
History of previous tuberculosis			
Relapse	11 (5.6)	-	
Return after defaulted	14 (7.1)	-	
History of contact with tuberculosis patients			0.140
Yes	20 (10)	2 (3.7)	
No	178 (90)	52 (96.3)	

^aOther: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.

^b $p < 0.05$ for differences between PTB and ETB groups by χ^2 test.

Table 2
Clinical manifestations and investigations of 252 TB/HIV patients.

Variables	PTB (198) n (%)	EPT (54) n (%)
Symptoms		
Cough ^a	175 (88.4)	30 (55.6)
Loss of appetite and/or weight	163 (82.3)	40 (74.1)
Fever	145 (73.2)	33 (61)
Sputum ^a	102 (51.5)	18 (33.3)
Dyspnea	53 (26.8)	12 (22.2)
Pain (chest, back, and abdomen)	47 (23.7)	9 (16.7)
Hemoptysis ^a	38 (19.2)	4 (7.4)
Dysphagia	2 (1)	1 (2)
Signs		
BCG vaccination status		
Yes	108 (54.5)	34 (63)
No	23 (11.5)	3 (5.5)
No information	67 (34)	17 (31.5)
Tuberculin skin test (Mantoux test)		
Positive (≥ 10 mm)	25 (12.6)	14 (26)
Negative (< 10 mm)	34 (17.2)	6 (11)
No information	139 (70.2)	34 (63)
Lymphadenopathy^a		
Cervical	29 (14.7)	17 (31.5)
Supraclavicular	2 (1)	-
Other site	-	-
Mixed (at least 2 sites)	4 (2)	1 (2)
Lesion or swelling (abscess or lump)	1 (0.5)	1 (2)
Others	4 (2)	4 (7.4)
Erythrocyte sedimentation rate (ESR)		
≥ 10 mm in the first hour	182 (92)	52 (96.3)
< 10 mm in the first hour	1 (0.5)	-
No information	15 (7.5)	2 (3.7)
X-ray findings		
Not available	-	1 (2)
Normal finding	-	12 (22.2)
Abnormalities		
Opacity (≥ 2 lobes = 116)	116 (58.6)	-
Cavity (one = 1)	1 (0.5)	-
Opacity and cavity (1 lobe involvement)	61 (30.8)	-
Pleural effusion (uni = 18; bilateral = 4)	17 (8.6)	5 (9.3)
Fibrotic changes	1 (0.5)	-
Pneumothorax	1 (0.5)	-
Spine	3 (1.5)	6 (11.1)
Miliary	-	30 (55.6)
Other results: CT scan, MRI, ultra-sound, echocardiogram, PCR and ophthalmoscopic examination	2 (1)	4 (2)
Sputum smear positive for AFB		
Positive	67 (33.8)	7 (13)
Negative	125 (63.1)	44 (81.4)
No information	6 (3.0)	3 (5.6)
Sputum culture positive for <i>M. tuberculosis</i>		
Positive	98 (49.5)	15 (27.8)
Negative	76 (38.4)	29 (53.7)
No information	24 (12.1)	9 (16.7)
Fluid analysis (smear, culture and biochemical analysis)		
Positive	-	1 (1.8)
No information	198 (100)	53 (98.2)
Tissue biopsy		
Positive lymph node	5 (2.5)	6 (11.1)
Positive pleura	-	2 (3.7)
Positive intestine	1 (0.5)	-
No information	192 (97)	46 (85.2)
CD4 cell count		
Range 0-1,179, median = 57 cell/mm ³	25 (12.6)	10 (18.5)
< 200	18 (9.1)	10 (18.5)
200-499	3 (1.5)	-
≥ 500	4 (2)	-

^ap < 0.05 for differences between PTB and ETB groups by χ^2 test.

Table 3
The anti-tuberculous therapy and outcomes of TB/HIV patients.

Duration	PTB (198) n (%)	EPT (54) n (%)	Total
At least 6 months			
Treatment success/completed			
6 months	28 (42)	8 (38)	36
9 months	25 (37)	9 (43)	34
12 months	14 (21)	4 (19)	18
Total	67 (100)	21 (100)	88
Less than 6 months			
Continuing	12 (37.5)	3 (50)	15
Transferred out	20 (72.5)	3 (50)	23
Total	32 (100)	6 (100)	38
Nonadherence			
Defaulted	79 (87)	21 (81)	100
Absconded	1 (1)	1 (4)	2
Drug allergy	11 (12)	4 (15)	15
Total	91 (100)	26 (100)	117
Death			
Tuberculosis-related	8 (100)	-	8
AIDS-related	-	1 (100)	1
Total	8 (100)	1 (100)	9

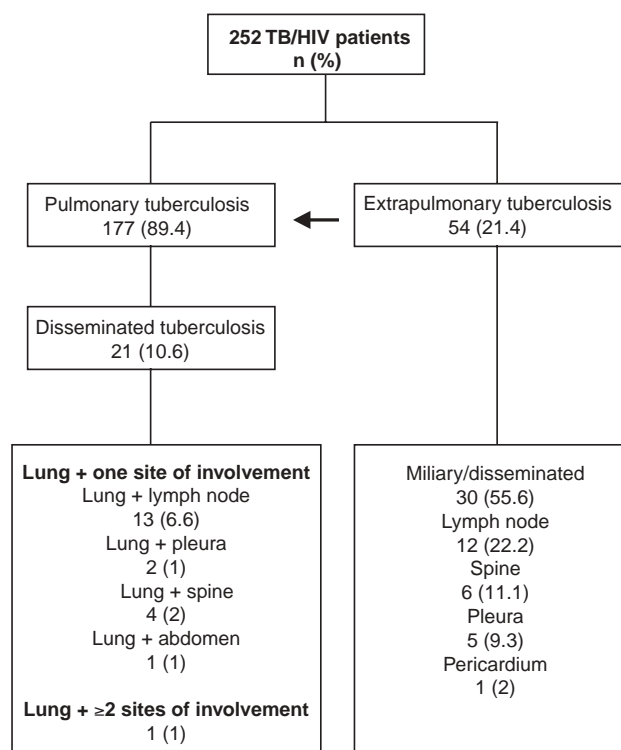


Fig 1—Disease location of 252 TB/HIV patients.

higher success rate in the PTB patients (42%). More EPT patients (43%) had treatment success with a longer duration (9 months) of therapy than the other regimens. Defaulting treatment was the most common type of nonadherence to anti-tubercular therapy in both groups of TB patients. There was no MDR-TB or relapse cases found during this study. Unfortunately, 9 patients died, of which 8 patients had only tuberculosis and 1 patient had tuberculosis with MRSA and septicemia.

DISCUSSION

Pulmonary tuberculosis was the most common disease location found among the patients in this study. This finding is in agreement with those reported in the literature (Whalen *et al*, 1997; Lado Lado *et al*, 1998; Perlman *et al*, 1999; Chakraborty and Chakraborty, 2000). However, it is contrary to some other studies (Vazquez *et al*, 1994; Sudre *et al*, 1996; Sharma *et al*, 1997; Chiu *et al*, 1999; Inverarity *et al*,

2002; Song *et al*, 2003). HIV is regarded as the most devastating infection that has caused a resurgence of tuberculosis, and continues to be a real time challenges. We suggest that self-health awareness be included in TB control programs particularly in highly prevalent areas of patients with coexisting tuberculosis and HIV infection. Cough, loss of appetite and/or weight, and fever were the main clinical presentations seen in these patients. These findings are in agreement with those reported in a previous study (Kimerling *et al*, 2002). This indicates that most cases of tuberculosis are pulmonary, therefore, physicians should aggressively pursue a diagnosis of TB in HIV infected patients presenting with respiratory symptoms in which fever and cough predominate (Pedro-Botet *et al*, 1992). We also found that more than half of these patients had post-primary TB as opacities with or without cavitation, which was the most common abnormal radiologic finding. This suggests that routine chest x-rays should be used to screen all newly diagnosed HIV-infected patients in order to obtain baseline data, and to further evaluate the risk-group of the patient. HIV-infected patients with TB and CD4 cell counts of less than 200 cells/mm³ or those receiving HARRT frequently present with post-primary patterns (Asimos and Ehrhardt, 1996; Busi Rizzi, 2003). Our data showed that only 18 patients with PTB had CD4 cell counts of <200 cells/mm³, and only 3 patients were receiving antiviral therapy. This suggests that further studies need to be done in order to evaluate these associations. We further support the prevention in TB/HIV-infected patients with isoniazid prophylaxis; which has been practically recommended in many settings.

In this study, the incidence of extrapulmonary tuberculosis was 21.4%; miliary tuberculosis was surprisingly the more common site of involvement found among these patients, followed by lymph nodes and spine. This finding is in agreement with one earlier study (Hill *et al*, 1991). Miliary tuberculosis is a life-threatening disease resulting from the hematogenous spread of *Mycobacterium tuberculosis*, and may present as an unusual cause of acute respiratory distress syndrome (Kim *et al*, 2003). Over the past two decades, the incidence of extrapulmonary

tuberculosis has not only increased at an even faster rate than of pulmonary tuberculosis, but is also considered a diagnostic criterion for acquired immunodeficiency syndrome. The incidence of severe cases, which include miliary tuberculosis, tuberculous meningitis, and other extrapulmonary tuberculosis cases is high among AIDS-related tuberculosis patients (Elder, 1992; Nagai, 2003). In the US, 36.9% of HIV-infected persons with EPT had miliary tuberculosis (Barnes *et al*, 1993). From this study, we found that in the sex distribution of extrapulmonary tuberculosis among these patients, 87% were men, intravenous drug users and of a specific racial origin. These risk factors were also noted by other investigators (Slutsker *et al*, 1993). This indicates that certain socioeconomic risk factors still play an important role in contributing to the course of disease. Extrapulmonary tuberculosis is a public health concern in Malaysia, and will become more prevalent along with the incidence of HIV-infected patients, as has been occurring over the past few years.

As for the role of immune status, 35 patients with CD4 cell counts were found in the medical record. In 25 PTB patients, 18 had CD4 cell counts of less than 200 cells/mm³, and 7 cases had either a CD4 cell count between 200-499 or \geq 500 cells/mm³. Ten patients with EPT had CD4 counts of less than 200 cells/mm³ at the time of the diagnosis. Our findings show that patients who had very low CD4 counts were more likely to develop extrapulmonary tuberculosis than those higher counts. This has also been documented in other studies (Ackah *et al*, 1995; Castilla *et al*, 1997; Lee *et al*, 2000). We conclude that the CD4 count is recommended as a prognostic marker, indicating the severity of immune deficiency, which determines the morbidity and mortality in HIV-related tuberculosis patients. In addition, a paradoxical reaction to antituberculous therapy after immunorestitution is induced by combined antiviral therapy has also been reported (Gerard, 2000).

Our results show that not even half the total number of these patients with tuberculosis completed treatment or were declared as a cure. This observation is the same as in other settings. We found that most patients with PTB were suc-

cessfully treated with 6 months short-course therapy, compared to patients with EPT who took a longer time, at least 9 months. This observation is consistent with other studies (Gerard, 2000; Wang *et al*, 2000). This is due to the fact that extrapulmonary tuberculosis can be rapidly fatal but is a treatable condition, therefore diagnostic procedures should be implemented early and empirical treatment given in suspected cases. We found that nearly half of patients with either PTB or EPT were noncompliant with therapy; a slightly higher rate was seen in patients with PTB. The factors that may contribute to nonadherence in this study were being male, having a low socioeconomic status, being single, being an injecting drug user, and having certain racial origins (data were not shown). These findings are supported by other previous investigations (Tansuphaswadikul *et al*, 1998; Wobeser *et al*, 1999; Tanguis *et al*, 2000; Santha *et al*, 2002). Nonadherence to anti-tubercular therapy has a significant impact on, and is a long-standing problem for involved medical personnel in Malaysia; a country considered to be an intermediate zone of tuberculosis burden. Nonadherence may contribute to the spread of tuberculosis and the emergence of drug resistance, and may increase the cost of treatment (Pablos-Mendez *et al*, 1997) and relapses (Brucker-Davis *et al*, 1993). The special problem of prophylaxis of persons exposed to multidrug-resistant tuberculosis is important (Sepkowitz *et al*, 1995). DOT program has been implemented for all TB patients in Malaysia. In TB/HIV-infected patients with history of nonadherence to antitubercular therapy for any cause, closer monitoring is carried out by medical personnel in this center.

Tuberculosis is very common in Malaysia. Pulmonary and extrapulmonary tuberculosis predominantly occurs in men, of certain racial origins, low socioeconomic status, and in intravenous drug users. Lung and miliary were the most common sites of involvement in pulmonary and extrapulmonary tuberculosis, respectively. Most PTB patients were treated successfully treated with 6 months short-course therapy. Nonadherence to anti-tubercular therapy was noted more frequently in patients with pulmonary tuberculosis.

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