

MYCOBACTERIUM TUBERCULOSIS INFECTION AMONG HIV/AIDS PATIENTS IN THAILAND: CLINICAL MANIFESTATIONS AND OUTCOMES

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Abstract. A one year retrospective study, was conducted at Bamrasnaradura Hospital, Nonthaburi Province, Bangkok, Thailand, of 271 subjects with both TB and HIV/AIDS. Single males (median age group 31 to 40 years) were most likely to develop co-infection. The commonest clinical manifestations on initial presentation included a low grade fever, cough, weight loss, lymphadenopathy with pancytopenia, and lung infiltrates. Multi-drug resistant TB (MDR-TB) was found in 26.6% of the subjects which was significantly associated with a past history of anti-TB treatment ($p = 0.005$; OR=2.5); it was also significantly associated with disseminated TB ($p = 0.022$; OR=1.9) and mortality ($p = 0.013$; OR=2.8). Analysis of clinical outcomes showed that 46.7% were lost to follow-up and 13.3% had died by the time of follow-up. Among those who survived, only 11.4% had been successfully treated; the rest had not improved due to relapse (2.9%), therapeutic failure (8.8%), treatment in progress (5.9%), and failure to complete treatment (10.7%).

INTRODUCTION

Asia's most dramatic AIDS pandemics have been in India and Thailand; the most common opportunistic infection among HIV/AIDS patients in Thailand is, as in other developing countries, tuberculosis (TB) (WHO, 1994; Burwen *et al*, 1995; Raviglione *et al*, 1995; Zumla *et al*, 1999). We describe the clinical manifestations and outcomes of TB among HIV/AIDS patients. This study provides basic information regarding the condition of TB-HIV/AIDS patients of the Bamrasnaradura Hospital, Thailand, and considers the state of TB-HIV/AIDS patients in general. Knowledge of the outcome of dual infection would help clinicians to implement changes that would further improve case management and the planning of prevention programs. TB among HIV/AIDS patients is unique in that while it

is contagious, it is both readily treatable with standard drugs and potentially preventable (Raviglione *et al*, 1995). The early diagnosis and prompt management of TB among HIV patients may ensure longer life and reduced morbidity.

MATERIALS AND METHODS

A retrospective study was conducted at the Bamrasnaradura Hospital, Nonthaburi Province, Bangkok, Thailand, from October 1998 to September 1999. Inclusion criteria were: male and female patients of 15 years of age or more; two positive ELISA HIV assays; TB of any body site confirmed by culture.

Initially, 550 TB-HIV/AIDS cases were included; however only 350 records were retrieved. Baseline demographic profiles, symptoms, signs, laboratory and radiologic findings were recorded. Subjects were evaluated after 12 months and were categorized by the type of TB and by clinical outcome.

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Pulmonary TB (PTB) was defined as being: sputum smear positive in at least two microscopic examinations; or sputum smear positive in one microscopic examination plus an abnormal chest X-ray consistent with TB; or sputum smear positive in one microscopic examination plus a positive culture. PTB was also defined as being sputum smear negative but with an abnormal chest X-ray consistent with TB or sputum smear negative but culture positive.

Extra-pulmonary TB was defined as TB of any organ other than the lungs *eg*, pleura, meninges, reproductive system, urinary system, abdominal system, bones, joints and skin. Disseminated TB was defined as the presence of TB in the lungs and in at least one other body site or the presence of TB in liver biopsy samples, bone marrow aspirates or blood cultures.

All data collected by questionnaires were analyzed using Epi-info (version 6) and presented as median and range for quantitative variables non-parametrically distributed. Frequency and percentage were used for qualitative variables. The chi-square test was used to determine the association between two categorical variables.

RESULTS

Of the 350 records retrieved, only 271 were included in the study. Subject age ranged from 15 to 78 years with median age group of 31 to 40 years. Subjects were mostly single (76.8%) males (86.3%) and nearly half of the subjects (41.7%) had no past history of anti-TB treatment.

Analysis of the clinical manifestations of TB-HIV/AIDS subjects showed that cough was present in 57.9%, followed by low grade fever in 55.5%; other manifestations included weight lost (40%) and lymphadenopathy (36.9%). Laboratory findings showed a decrease in all hematological parameters, with a median hemoglobin of 9.9 mg/mm³, a median platelet count of 180 x 10⁹/mm³, and a median WBC count of 4,190/mm³.

Table 1
Classification of TB found among HIV/AIDS patients.

Type	Frequency (n=271)	%
Pulmonary	96	35.4
Extra-pulmonary	52	19.2
lymph node	45	16.6
CSF	3	1.1
pleura	2	0.7
colon	1	0.4
abdominal fluid	1	0.4
Disseminated	123	45.4
blood/liver	46	17.0
miliary/disseminated	8	3.0
lung + other	69	25.4

Table 2
Drug susceptibility profile among TB-HIV/AIDS patients.

Findings	Frequency (n=271)	%
Sensitive	147	54.2
Multi-drug resistant (MDR)	72	26.6
Multiple drug resistant	17	6.3
Rifampicin	17	6.3
Isoniazid	10	3.7
Streptomycin	7	2.6
Ethambutol	1	0.4

Chest X-rays showed the presence of infiltrates in 54.2% of subjects; were normal in 19%; showed adenopathy in 12.5% and, rarely, cavitation (5.6%).

Table 1 shows the types of TB among HIV/AIDS patients: disseminated TB was the most common type, followed by PTB and extra-pulmonary TB. The commonest site for extra-pulmonary TB was the lymph nodes; in disseminated TB, the lungs plus other body site was the most common variety.

Table 2 shows the anti-TB drug susceptibilities among the subjects: 54.2% were still sensitive to first line anti-TB regimens while MDR-TB was present in 26.6%.

Table 3

Association of drug susceptibility with other variables among TB-HIV/AIDS patients (n=271).

	MDR	Non-MDR	p-value	OR
Treatment history			0.005	2.5
Positive	34	20		
Negative	64	93		
TB Type			0.022	1.9
Disseminated	41	31		
Non-disseminated	82	117		
Mortality rate			0.013	2.8
Dead	17	30		
Alive	19	78		

Table 4

Final outcome among TB-HIV/AIDS patients.

Final outcome	Frequency (n=271)	%
Lost to follow up	127	47.0
Survived	108	39.7
Successfully treated	31	11.4
Not successfully treated	77	28.3
Dead	36	13.3

Table 3 shows the association of drug susceptibilities with other variables among TB-HIV/AIDS patients. Subjects who were previously treated with anti-TB drugs were 2.5 times more likely to develop MDR-TB compared with subjects who were not previously treated with anti-TB drugs ($p = 0.005$). HIV/AIDS subjects with disseminated TB were 1.9 times more likely to develop MDR-TB compared with subjects with non-disseminated TB ($p = 0.022$). Finally, HIV/AIDS subjects with MDR-TB were 2.8 times more likely to die compared with subjects with non-MDR TB ($p = 0.013$).

Table 4 shows that nearly half of the subjects (47%) were lost to follow-up, while 13.3% had died by the time of follow-up (12 months); furthermore, among those who survived, only 11.4% were successfully treated (cured and had completed anti-TB treatment) while 28.3% had not undergone successful full

treatment because of relapse (2.9%), therapeutic failure (8.8%), failure to complete treatment (10.7%) and treatment in progress (5.9%).

DISCUSSION

TB is one of the most important AIDS associated infectious disease worldwide; TB has become one of the leading causes of death among people with AIDS (WHO, 1994; Whalen *et al*, 1995; Vallop *et al*, 1999). Although patients with HIV-associated TB mostly have typical clinical pictures, the frequency of atypical manifestations is increased in states of advanced immunosuppression, thus making the diagnosis more difficult. In the present study, more than half of the cases presented with cough and weight loss. The lower proportion of cough could be attributed to the much higher frequency of extra-pulmonary TB and disseminated forms of TB featured in this study.

Most of the subjects showed low grade fever (between 37.5°C and 38.5°C) followed by high grade fever (39°C and over). The presence of fever among these patients could be explained by TNF- α , a cytokine produced during the immune response to TB-HIV infection (Alpert *et al*, 1997; Garait *et al*, 1998; Paton *et al*, 1999). Previous studies also reported the presence of fever on initial presentation (Maung, 1994; Poprawski, 1998; Min Min Soe, 1999). Lymphadenopathy was also a common

finding: its frequent occurrence is noted by many researchers and is probably due to the pathological process of clearance of infected macrophages (Shafer and Edlin, 1996).

Hematological abnormalities such as anemia, thrombocytopenia and leukopenia were present in more than 50% of subjects, findings that were similar to those of previous studies (Tansuphaswadikul *et al*, 1992; Reurn, 1996) and might signify bone marrow involvement, especially in disseminated forms of infection (Horne, 1996).

Radiological findings showed infiltrates to be the most common abnormality; cavitation was uncommon. These results were consistent with those of other studies in developed and developing countries (Pitchenick and Rubunson, 1984; Raviglione *et al*, 1992; Shafer and Edlin, 1996; Alpert *et al*, 1997; Poprawski, 1998; Min Min Soe, 1999), signifying the advanced immunosuppression associated with a poor granulomatous response. Normal chest X-rays could be explained by extra-pulmonary forms of TB and disseminated forms of TB in the blood and the liver. Similar clinical findings showed that there was no common distinctive radiographic finding that could help to identify TB among HIV/AIDS subjects; cavitation, while specific, was rarely seen (Selwyn *et al*, 1998).

In keeping with previous studies, evidence of disseminated TB existed in nearly half of the subjects (Garrait *et al*, 1997; Alpert *et al*, 1997). A possible explanation is that extensive CD4 T-cell depletion in HIV infection results in impaired immunity against TB, leading to the development and dissemination of active TB.

Extra-pulmonary TB was found in previous studies in Thailand (Hsieh *et al*, 1997; Alpert *et al*, 1997; Poprawski, 1998; Min Min Soe, 1999). This may be caused by the easier spread of the bacilli when the body's defences are unable to mount an efficient challenge.

Pulmonary TB among HIV/AIDS patients has been reported as having variable prevalence and its frequency depends upon study

location: western countries tend to see this form of TB more often (70% to 90% of cases). In the present study, pulmonary TB was found in 35.4% of cases. Previous studies in Thailand seem to indicate that fewer than half of all cases are purely pulmonary (Poprawski, 1998; Min Min Soe, 1999). This difference may be attributed to many factors including the fact that western patients are less likely to be significantly immunocompromised and more likely to have access to antiretroviral - in these circumstances, a more typical picture of TB can be expected (Shafer *et al*, 1996).

The rising trend of drug-resistant TB has been correlated with an increase in the incidence of HIV infection (Fischl *et al*, 1992; Small *et al*, 1991; O'Brien, 1994). In the present study, nearly half of the subjects (45.8%) were resistant to one or more drugs - an alarming result. A similar study showed that the proportion of isolates that were resistant to first line anti-microbial agents equaled or exceeded 50% (Frieden *et al*, 1996). The present study showed that MDR-TB occurred in 26.6% of subjects and was high compared with the 17.7% of cases of MDR-TB found in the same institute two years earlier (Min Min Soe, 1999). Possible reasons for the dramatic increase in MDR-TB among these subjects included interruptions in treatment due to intercurrent infections, adverse drug reactions and non-compliance. The premature cessation of treatment also led to the development of more resistant strains. More than half of the cases had disseminated TB, signifying advanced immunosuppression caused possibly by delayed treatment. Recent studies have shown that nosocomial transmission and delays in the isolation of hospitalized HIV-infected patients with TB contribute significantly to outbreaks of MDR-TB (Frieden *et al*, 1996). Thus, the causes of MDR-TB emergence are multi-factorial and are more closely related to human behavior than to the natural evolution of the tubercle bacillus (Riley *et al*, 1989; O'Brien, 1994).

As in a previous study (Min Min Soe, 1999), patients who had an history of anti-TB treatment were 2.5 times more likely to

develop MDR-TB compared with patients who had no history of treatment ($p = 0.005$). Patients with disseminated TB were 1.9 times more likely to have MDR-TB compared with patients without disseminated TB ($p = 0.022$). Finally, mortality was 2.8 times higher among MDR-TB patients compared with non-MDR-TB patients ($p = 0.013$).

Nearly half of the subjects (47%) were lost to follow-up while 13.3% had died by follow-up at 12 months. Among those who survived, only 11.4% were successfully treated (patients who were both cured and had completed an anti-TB regimen), a very low success rate compared with those cited in studies done overseas (Pablos-Mendez *et al*, 1997). Local studies however seem to support the present study (Punnotok *et al*, 1997; Poprawski, 1998; Min Min Soe, 1999). In the present study, 28.3% of subjects were not successfully treated due to relapse (2.9%), therapeutic failure (8.8%), failure to complete treatment (10.7%) and treatment in progress (5.9%).

Finally, many cases did not improve for a variety of reasons: first, most of the subjects had disseminated TB on presentation (45.4%); second, there was a poor response to treatment due to drug resistance in 45.8% of the subjects; third, more than half of the subjects had an incomplete course of treatment; fourth, those who survived for longer could have acquired concomitant opportunistic infections such as MAC, PCP and CMV; lastly, since the criteria for enrolment were based on positive culture, it could have been that some cases of TB and early stages of HIV were undetected, introducing a selection bias towards cases of advanced immunosuppression.

Conclusion

The commonest clinical manifestations of TB among HIV/AIDS patients were cough, weight loss, low grade fever, lymphadenopathy and chest X-ray that showed infiltrates; these findings are also frequent manifestations of several other opportunistic infections. Disseminated TB occurred in nearly half of the subjects, followed in prevalence by pulmonary

and extra-pulmonary TB. Drug resistance to anti-TB regimens was quite marked, particularly MDR-TB (26.7%), and this was associated with a past history of anti-TB treatment ($p = 0.005$), disseminated TB ($p = 0.022$) and mortality ($p = 0.013$). A very small proportion of patients had been successfully treated. It is therefore recommended that clinicians treating TB among HIV/AIDS patients consider the factors that increase the risk of a poor clinical response, *eg* lack of adherence to TB treatment, delayed conversion of *Mycobacterium tuberculosis* sputum cultures from positive to negative, and delayed clinical response, when deciding the total duration of TB treatment. It is also suggested that other members of a patient's family should be encouraged to accompany the patient to consultations to facilitate a more holistic approach to care. Finally, the use of direct observed therapy (DOT), the 'gold standard' strategy in sites of high prevalence of drug resistant TB, should be applied to HIV/AIDS patients.

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