MORTALITY AMONG HIV/AIDS PATIENTS COINFECTED WITH MYCOBACTERIUM TUBERCULOSIS IN SOUTHERN THAILAND

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Abstract. The purpose of this study was to investigate the mortality rate among HIV/AIDS patients coinfected with Mycobacterium tuberculosis in southern Thailand. A prospective, hospital-based cohort study was conducted among 52,459 HIV/AIDS patients registered at hospitals in 14 provinces of southern Thailand between January 1990 and April 2010. Twenty-seven point nine percent of the subjects were coinfected with Mycobacterium tuberculosis. Coinfection with Mycobacterium tuberculosis was not significantly associated with an increased mortality among subjects (HR 1.01; 95%CI 0.96-1.05). Subjects with pulmonary tuberculosis infection were 19% more likely to have a longer life (HR 0.81, 95%CI 0.73-0.91) and subjects with extrapulmonary tuberculosis were 31% more likely to have a longer life (HR 0.69; 95%CI 0.57-0.83). Early treatment of tuberculosis in HIV/AIDS patients can decrease mortality rates in southern Thailand.

Keywords: HIV, AIDS, tuberculosis, mortality, Thailand

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a serious public health problem and AIDS is a leading cause of death worldwide (Coovaida and Hadingham, 2005). There has been an increase in the number of HIV infections worldwide (Coovaida and Hadingham, 2005; WHO, 2011f). The epidemic is more prevalent in Eastern Europe, Central Asia and Southern Africa (Au-Yeung *et al*, 2011). Africa has the highest death rate of any region worldwide (Au-Yeung *et al*, 2011). In 2009, approximately 60 million individuals were infected with the HIV virus worldwide, 30 million had died from AIDS, 33.3 million were living with HIV and 2.6 million were newly infected (WHO, 2011c).

Having AIDS is a risk factor for developing other opportunistic infections (OIs) (Ylitalo *et al*, 2006). Mycobacterium tuberculosis infection is the most common cause of morbidity and mortality among HIV-infected individuals (Corbett *et al*, 2003). Globally, the prevalence and incidence of tuberculosis infection is decreasing (Corbett *et al*, 2003). The absolute incident rate of tuberculosis infections declined by 1.3% between 2002 and 2006

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(Corbett *et al*, 2003). It is unlikely the target of 50% reduction in tuberculosis infection set by world health organization for 2015 (WHO, 2011a) will be reached.

In 2010, there were 8.8 million (8.5-9.2 million) new and relapsed tuberculosis cases and 1.4 million (1.2-1.5 million) people who died from tuberculosis worldwide; while 0.35 million (0.32-0.39 million) individuals were living with HIV (Harries and Dye, 2006; WHO, 2011b,c). In Southeast Asia, 50% of HIV-infected patients die during tuberculosis treatment (Verma *et al*, 2009). There are approximately 727,000 deaths worldwide from tuberculosis yearly; 47 per 100,000 population (Corbett *et al*, 2003). Four countries (Cambodia, China, the Philippines and Vietnam) accounted for 93% of the total HIV-tuberculosis coinfected patients in the Asia Pacific region in 2000 (Corbett *et al*, 2003). Every year an estimated 300,000 individuals die from tuberculosis worldwide (van Maaren, 2010). In Thailand, between 1990 and 2009, the incidence of tuberculosis remained stable at 137 (95%CI 111-165) per 100,000 population. The prevalence of tuberculosis declined from 209 to 189 per 100,000 population during the same period in Thailand (WHO, 2011d). Sixty-one percent (50-78%) of people with advanced HIV infection receive an antiretroviral drug (WHO, 2011d) in Thailand.

The impact of tuberculosis infection on mortality among AIDS patients varies. Several studies have shown a lower mortality rate among AIDS patients with tuberculosis infection (Kittiyaporn *et al*, 1996; Nunn *et al*, 2008; Kingkaew *et al*, 2009; Schmaltz *et al*, 2009; Abdool Karim *et al*, 2010; Chaimay *et al*, 2011b). While some studies have shown a higher risk of death among HIV/AIDS patients with tuberculosis (Lopez-Gatell *et al*, 2008; Ige and Akindele, 2011). Some studies have a smaller sample size so the results can not be generalized to other groups (Chaimay *et al*, 2011b). However, the effect of routine treatment HIV/AIDS patients with Mycobacterium tuberculosis is rarely presented. In the present study, a large sample size of HIV/AIDS patients from southern Thailand was studied. The purpose of this study was to investigate the mortality rate among HIV/AIDS patients coinfected with Mycobacterium tuberculosis in southern Thailand.

METERIALS AND METHODS

This prospective cohort study used data from the HIV/AIDS database system of the Center for Diseases Prevention and Control, located in Nakhon Si Thammarat and Songkhla Provinces, Thailand. These two HIV/AIDS databases were merged for this study. The HIV/AIDS subjects were routinely followed for their treatment. The study covered 14 provinces in southern Thailand. A total 52,428 patients were included in the study.

The first variable determined was the time from HIV/AIDS diagnosis to death. This was presented as a continuous outcome. The second variable was the cause of death in those who died, including Mycobacterium tuberculosis coinfection. Mycobacterium tuberculosis was classified into pulmonary and extrapulmonary tuberculosis. The primary outcome of tuberculosis was recorded by health personnel responsible for epidemiological surveillance and disease prevention and control; and the procedure and instrument used for data collection is described elsewhere (Chaimay *et al*, 2011a,b).

Baseline characteristic data were presented using descriptive statistics. The Kaplan-Meier method was used to estimate the probability of survival among subjects

experiencing Mycobacterium tuberculosis infection, including pulmonary and extrapulmonary tuberculosis. To quantify the magnitude of the effect of Mycobacterium tuberculosis infection on mortality among subjects, the Cox's Proportional Hazard model was used for bivariate and multivariate analysis. The censored data was defined as incomplete observations that might not have been observed during the study period. The model was constructed by counting from the time of HIV/AIDS diagnosis to death and used backward elimination. Each independent variable was separately analyzed in the multivariate model, accounting for confounding factors shown elsewhere (Chaimay *et al*, 2011a). The results of this study are presented as hazard ratios (HR), which are comparable to relative risk (RR) with 95 percent confident intervals (95% CI). The result was interpreted as having no association if the HR was 1, as a risk association if the HR was >1, and as a protective effect if the HR was <1.

Ethical approval to use the HIV/AIDS database was obtained from the 11th and 12th regional office of the Center for Diseases Control and Prevention, Nakhon Si Thammarat and Songkhla Provinces, Thailand. This study was also approved by the Ethics Committee on Human Rights Related to Human Experimentation, Thaksin University, Thailand.

RESULTS

More than two-thirds of subjects (69.1%) were male. The average age was 32 years (SD = 9.80); the minimum age was 8 months and the maximum age was 72 years. More than half the subjects (53.6%) were married and more than one-third (37.7%) were single. Most subjects (95.9%) were Thai nationals. Half the subjects (45.4%) were employees and 17.8% were farmers. Thirty-seven point four percent, 33.8% and 28.8% of subjects were from the west coast provinces (Andaman Sea), east coast provinces (Thai Bay Sea) and southern border provinces, respectively. Nearly two-thirds of subjects (60.4%) resided in rural areas. Fourteen point one percent received treatment from other services during their HIV/AIDS illness. After beginning HIV/AIDS treatment, 65.5% had to be admitted to the hospital. Fifty-eight point five percent of subjects were heterosexual. Sixty-eight point three percent of subjects contracted HIV infection through sexual intercourse, 11.77% contacted it through intravenous drug use and 16.5% had an unknown risk factor for contracting HIV infection.

During the study period, 11,767 subjects died (22.4%, 95%CI 22.07-22.79). One third of subjects were infected by Mycobacterium tuberculosis (n = 14,658, 28.0%). Of the total number of patients, 4.18% (n = 2,193) had pulmonary tuberculosis and 1.47% (n = 770) had extrapulmonary tuberculosis.

Bivariate analysis (Table 1) using the Cox's Proportional Hazard model showed HIV subjects coinfected with Mycobacterium tuberculosis were 1.25 times more likely to die (HR 1.25; 95%CI 1.21-1.30). However, among HIV subjects coinfected with pulmonary tuberculosis, 20% more likely to have a longer life (HR 0.80; 95%CI 0.72-0.88) and among HIV subjects coinfected with extrapulmonary tuberculosis, 30% more likely to have a longer life (HR 0.70; 95%CI 0.58-0.83).

Multivariate analysis using the Cox's Proportional Hazard model (Table 1) reveal Mycobacterium tuberculosis were not significantly associated with mortality among subjects (HR 1.01; 95%CI

Table 1
Multivariate analysis of tuberculosis and mortality among HIV/AIDS patients in southern Thailand.

Factors	Crude HR (95%CI)	Adjusted HR[a] (95%CI)	*p*-value
Mycobacterium tuberculosis			0.707
No	1	1	
Yes	1.25 (1.21-1.30)	1.01 (0.96-1.05)	
Pulmonary tuberculosis			<0.001
No	1	1	
Yes	0.80 (0.72-0.88)	0.81 (0.73-0.91)	
Extrapulmonary tuberculosis			<0.001
No	1	1	
Yes	0.70 (0.58-0.83)	0.69 (0.57-0.83)	

[a]Adjusted for confounding factors: sex, race, marital status, occupation, residence area, receiving treatment from other services, type of patients, sexuality and risk for infection.

0.96-1.05), compared to those without Mycobacterium tuberculosis. On the contrary, there was significant reduction in mortality among subjects coinfected with pulmonary tuberculosis. Subjects coinfected with pulmonary tuberculosis were 19% more likely to have a longer life (HR 0.81; 95%CI 0.73-0.91) and subjects with extrapulmonary tuberculosis were 31% more likely to have a longer life (HR 0.69; 95%CI 0.57-0.83) after accounting for confounding factors, including sex, race, marital status, occupation, residential area, history of having received treatment from other services, type of patient, sexuality and risk of HIV infection. The Kaplan-Meier showed the probability of survival among subjects with and without Mycobacterium tuberculosis (Fig 1), including; pulmonary (Fig 2) and extrapulmonary tuberculosis (Fig 3).

DISCUSSION

In our study we found HIV subjects coinfected with pulmonary and extrapulmonary tuberculosis were both more likely to have a lower mortality rate.

The strength of this study was the large sample size. This is the first study to investigating the effect of routine treatment on subjects. Our findings had a narrow 95% confidence interval.

This study had several limitations. Many patients were lost to follow-up; therefore, information bias may have occurred. We may have underestimated the risk of death. However, the numbers were unlikely to be large enough to affect the results. This study was based on HIV/AIDS database information. The results are likely to be only generalizable to populations similar to this. The HIV/AIDS data used in this present study were gathered prior to the present analysis. The impact of mortality on potential factors was unaccounted for by factors such as hemoglobin level, CD4, T-lymphocyte count, weight loss and opportunistic infections (Rajagopalan *et al*, 2009).

In this study Mycobacterium tuberculosis was not associated with mortality among subjects and when classified into

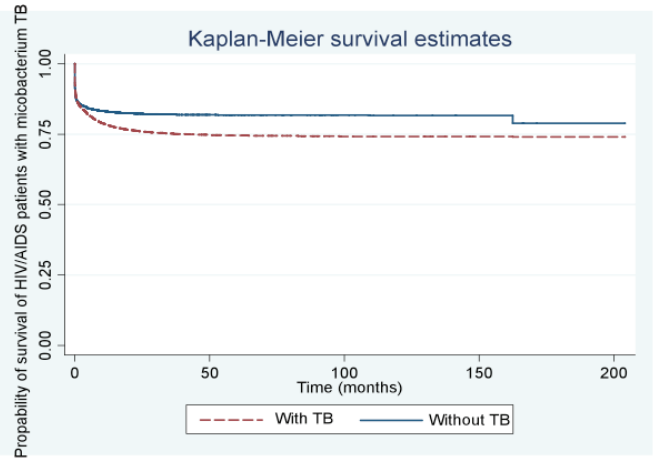

Fig 1–Kaplan-Meier survival time estimate for HIV/AIDS patients with Mycobacterium tuberculosis coinfection.

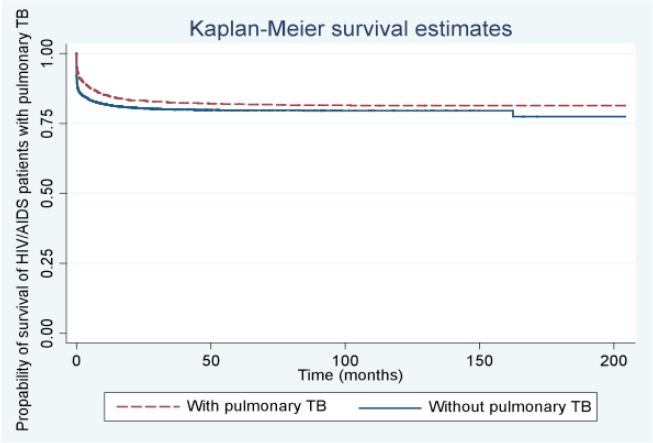

Fig 2–Kaplan-Meier survival time estimate for HIV/AIDS patients with pulmonary tuberculosis coinfection.

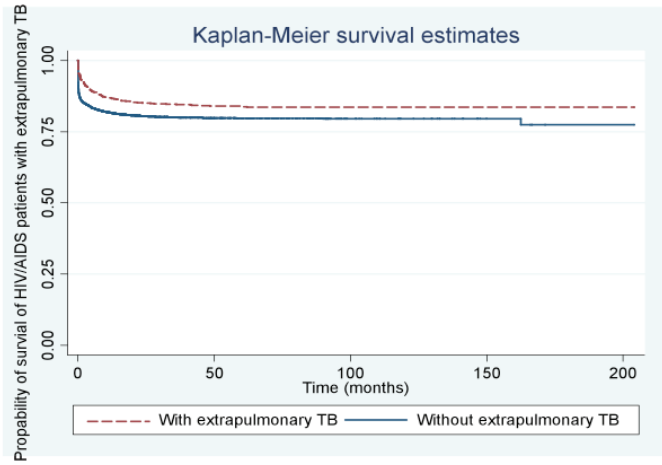

Fig 3–Kaplan-Meier survival time estimate for HIV/AIDS patients with extrapulmonary tuberculosis coinfection.

pulmonary and extrapulmonary tuberculosis, patients with these types of tuberculosis were less likely to die. One-third of subjects had Mycobacterium tuberculosis (14,658; 27.9%). Of these, only one in five were classified into a specific type of tuberculosis (2,970; 20.3%), either pulmonary or extrapulmonary tuberculosis (15.0 and 5.3%). However, in this study most subjects (79.7%) were not classified into the specific type of tuberculosis. It is possible subjects coinfected with Mycobacterium tuberculosis might be lost to follow-up of tuberculosis or were not classified as having a specific type of tuberculosis. Subjects classified into the specific type of tuberculosis were more likely to have specific treatment and follow-up, resulting in a longer life.

This study demonstrated subjects were more likely to have a lower mortality if classified as being coinfected with pulmonary or extrapulmonary tuberculosis. This implies these subjects coinfected with tuberculosis were initially treated appropriately. There was a benefit of treating subjects coinfected with tuberculosis who received parallel antiretroviral treatment (ART). The HIV/AIDS and tuberculosis treatments appeared to have been early enough to reduce HIV-associated mortality that occurs due to tuberculosis infection (Chaimay *et al*, 2011b).

More than half of subjects (61%) were treated with antiretroviral drugs (WHO, 2011d). Eighty-six percent of tuberculosis cases are successfully treated in Thailand (WHO, 2011e).

Our findings are similar to those by Nunn *et al* (2008) who found HIV-infected patients newly diagnosed with tuberculosis had a lower mortality rate than those who received tuberculosis treatment for a relapse. However, our findings are not consistent with some previous studies, where death rates were higher among patients with HIV/tuberculosis co-infection (Lopez-Gatell *et al*, 2008; Nunn *et al*, 2008; Kingkaew *et al*, 2009; Rajagopalan *et al*, 2009; Rajasekaran *et al*, 2009; Abdool Karim *et al*, 2010; Ige and Akindele, 2011; Chaimay *et al*, 2011a; WHO, 2011e). In Spain, there are frequent fatalities among individuals who are co-infected (OR 9.93; 95%CI 1.48-11.77) (Cayla *et al*, 2009).

About 5-10% of HIV-infected individuals are likely to develop symptomatic tuberculosis during their illness (Harries and Dye, 2006). The risk of developing clinical manifestations of an opportunistic infection is greatly increased by HIV-coinfection (Harries and Dye, 2006); however, the previous study showed a reduced mortality in patients. HIV/AIDS patients with tuberculosis were 29% more likely to live longer (HR 0.71; 95%CI 0.55-0.93), compared to those patients without tuberculosis after accounting for demographic factors (Chaimay *et al*, 2011b).

In one epidemiological study (Kingkaew *et al*, 2009) conducted in Thailand among HIV-infected patients with tuberculosis, extrapulmonary tuberculosis was associated with advanced immune suppression. Kingkaew *et al* (2009) found a reduction in the risk of death among HIV-infected patients with tuberculosis who took Co-trimoxazole, fluconazole and antiretroviral therapy. Kitayaporn *et al* (1996) studing AIDS patients with extrapulmonary tuberculosis at a public tertiary care hospital in Bangkok, Thailand found these patients had a longer survival rate (HR 0.55; 95%CI 0.35-0.86). More than half of patients on HIV-tuberculosis combined therapy had a reduction in the death rate (HR 0.44, 95%CI 0.25-0.79) (Abdool Karim *et al*, 2010). Among HIV-infected patients, tuberculosis-related mortality tended to be lower in patients treated with HAART (HR: 0.58) (Schmaltz *et al*, 2009).

Tuberculosis treatment is a key factor in tuberculosis control (Cayla *et al*, 2009). Evidence regarding the effect of tuberculosis on HIV progression remains a problem. HIV-tuberculosis coinfected patients are twice as likely to die than HIV patients without tuberculosis (HR 2.4, 95%CI 1.2-4.7) (Lopez-Gatell *et al*, 2008). A study from Nigeria (Ige and Akindele, 2011) revealed one-third (33.1%) of tuberculosis patients were HIV positive and the mortality rate was higher among those who were HIV positive than those who were HIV negative ($p<0.001$). A study from Kenya found HIV positive patients had a statistically significant poorer tubercolosis treatment success rate (85%), compared to HIV negative patients (94%) ($p = 0.004$) (Chakaya *et al*, 2002).

Subjects coinfected with pulmonary and extrapulmonary tuberculosis were more likely to have a longer life, compared to HIV/AIDS patients without pulmonary or extrapulmonary tuberculosis coinfection. These findings accounted for confounding factors. These results show the benefits of routine treatment programs for HIV/AIDS and tuberculosis in southern Thailand. However, HIV/AIDS and tuberculosis still pose significant challenges.

Future research is needed to explore the use of antiretroviral drugs and its effect on opportunistic infections to determine whether they are associated with mortality among subjects.

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