Research Journal of Medical Sciences 6 (4): 214-221, 2012
ISSN: 1815-9346

The Associated Factors with Unsuccessful Tuberculosis Treatment Outcomes among TB/HIV Co-Infected Patients in Surin Province, Thailand

[1]N. Pimchan, [2]P. Suggaravetsiri, [4]N. Tesana and [3]S. Chaiklieng
[1]Graduate School, [2]Department of Epidemiology, [3]Department of Environmental Sciences,
Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand
[4]The Office of Disease Prevention and Control 6th, Khon Kaen Province, Khon Kaen, Thailand

Abstract: This study aimed to identify the factors associated with unsuccessful TB treatment outcomes among TB/HIV co-infected patients. A retrospective cohort study was conducted among 466 TB/HIV patients who were registered during September 2006 to August 2011. Risk factors were conducted by multiple logistic regression and was reported as Relative Risk (RR) with 95% confident interval.

Key words: Tuberculosis, HIV/AIDS, co-infection, unsuccessful treatment outcome

INTRODUCTION

The advent of the worldwide epidemic of the Human Immunodeficiency Virus (HIV) in the late decades of the last century has fuelled the resurgence of Tuberculosis (TB) in some regions of the world, notably Africa and South-East Asia (Chasombat *et al*., 2009). Thailand has experienced a severe TB/HIV syndemic, i.e., two diseases act synergistically to cause excess morbidity and mortality. Regarding the recent statistics, an increase in TB/HIV co-infected patients had been documented most clearly in the most rural Northern provinces, the region of the country with the highest HIV prevalence rates (Punnotok *et al*., 2000). Thailand ranks 18th in the list of 22 high TB burden countries. The prevalence of TB was estimated at 192.0 per 100,000 population for all forms in 2007 with an incidence rate of 62 new smear-positive cases per 100,000 population (WHO, 2009). Almost 600,000 persons are currently HIV infected and >90,000 TB cases are estimated to occur annually (Akksilp *et al*., 2007; WHO, 2007). The interface between TB and HIV is increased where both TB and HIV infection are maximally prevalent in people of 15-49 years. Tuberculosis is the most common opportunistic infection and cause of death in HIV infected persons in Thailand. One-fourth of persons first diagnosed with AIDS have TB and an estimated 10.0-15.0% of TB cases in Thailand are HIV-associated although, the proportion is as high as 40.0% in some HIV high-endemic provinces (Akksilp *et al*., 2007). In general, TB treatment is the same for HIV-infected as for HIV-negative TB patients (WHO, 2004). The preferred regimen for the treatment of drug-susceptible TB in HIV-uninfected individuals is a 6 months, rifampicin based regimen that includes pyrazinamide during the initial 2 months phase. There continues to be controversy about the optimal duration of treatment for TB in HIV-infected patients (Nahid *et al*., 2007).

Anti-Retroviral Therapy (ART) improves survival in patients with advanced HIV infection but the magnitude of benefit in HIV infected patients receiving TB treatment remains uncertain and population-based data from developing countries are limited (Manosuthi *et al*., 2006). Now a days, the ART programme in Thailand has been expanded to every provincial and district hospitals. As a result, HIV infected persons in Thailand now can get easy access to ART. However, most of the previous studies have reported in HIV treatment outcomes in TB/HIV co-infected that were done in special hospitals such as Bamrasnaradura Institute and tertiary hospital in Bangkok (Cain *et al*., 2009; Kingkaew *et al*., 2009; Kittikraisak *et al*., 2009; Manosuthi *et al*., 2006; Sanguanwongse *et al*., 2008; Tansuphasawadikul *et al*., 2007; Varma *et al*., 2009). Few studies were carried out in Northeastern region, Thailand, only one study has performed in Ubonratchathani province also reported in TB treatment outcomes in TB/HIV co-infected and found that ART is associated with a substantial reduction in deaths during TB treatment for HIV infected TB patients (Akksilp *et al*., 2007). Therefore, very few studies determine risk factors of TB treatment outcomes in TB/HIV co-infected in rural area.

Surin province is one of the high-burden for TB notification rate and has an emerging AIDS epidemic in Thailand more than two hundred TB/HIV co-infected in Surin province were registered and cured in TB clinic or

Corresponding Author: N. Pimchan, Graduate School, Faculty of Public Health, Graduate School, Khon Kaen University, Khon Kaen, Thailand

ART clinic in Surin provincial hospital, district hospitals and private hospitals in each year but limited information is known about risk factors of TB treatment outcomes in TB/HIV co-infected patients (Surin Provincial Public Health Office, 2008). Therefore, this study aims to assess TB treatment outcomes, the relationship between the risk factors in TB/HIV co-infected patients and TB treatment outcomes during the 1st 6 months of initiating anti-TB regiments. The knowledge from this study would helpfully adjust the programme to achieve more satisfactory and possible results.

MATERIALS AND METHODS

An observational, retrospective cohort study was conducted among TB/HIV co-infected patients who were diagnosed pulmonary and all forms extrapulmonary TB. All of them had registered at TB clinic or ART clinic in 13 district hospitals and provincial hospital at Surin province since, September 2006 to August 2011. The sample size was calculated to detect the factors associated with unsuccessful TB treatment outcome using the approach of a simple method of sample size calculation for linear and multiple logistic regression (Hosmer and Lemeshow, 2000; Hsiehl *et al*., 1998).

The interested covariate is related to the binary response variable (unsuccessful TB treatment outcome) is Co-Trimoxazole (CTX) using. The event rate of the response at CTX used is 27% ($P_0 = 0.27$), anticipated OR = 2.0 and the event rate of the response at did not use CTX approximate is 42% ($P_2 = 0.42$) (Akksilp *et al*., 2007). Calculate base on balance design (B = 0.50), at significant level of 95% ($\alpha = 0.05$) and power of 80% ($\beta = 0.20$). A minimum requirement sample size in simple logistic regression is 233 TB/HIV infected patients. The required sample size for the multivariable logistic regression can also be approximated from the univariate case by inflating it with the same factor $1/(1 - \rho^2_{1,2,3...,p})$. Following the relationship of the variances thus $n_p = n_1/(1 - \rho^2_{1,2,3...,p})$ where n_p is the sample sizes required for a logistic regression model with p covariates and $\rho^2_{1,2,3...,p}$ is the squared multiple correlation coefficient $\rho^2_{1,2,3...,p}$ also, known as R^2 is equal to the proportion of the variance of X_1 explained by the regression relationship with X_2,..., Xp and this study set $R^2 = 0.50$. Finally, the required minimum number of TB/HIV co-infected patients was 466 patients recruited in this study. The TB/HIV co-infected patients enrolled into the study were met inclusion criteria as follows:

- Older than 15 years old
- Diagnosed pulmonary TB or extra pulmonary TB by physicians
- Receiving antituberculosis therapy

Isoniazid, rifampicin, Pyrazinamide and Ethambutol were initiated for the 1st 2 months and followed by isoniazid and rifampicin for the subsequent 4 months. If there is evidence of slow response, prolongation of the continuation phase to 7-9 months was administered. A standardize Case Report Form (CRF) was developed by researchers and checked for completeness and correctness by three of TB/HIV experts. Data was extracted from a clinical record form and relevant reports in TB and ARV-clinics. Final TB treatment outcome were divided into two categories which were successful and unsuccessful. A successful treatment outcome was TB/HIV co-infected patients who were cured or completed treatment. An unsuccessful includes failure, death or default.

Initially, the baseline characteristics were presented as descriptive analysis. In univariate analysis, risk factors for an unsuccessful outcome were identified from analysis of all of explanatory variables. This part of analysis, the results were presented as crude Relative Risk (RR) with 95% confidence intervals and p-value of Wald test. In multivariable logistic regression analysis, the selected variables for inclusion base were on plausibility, a priori evidence, completeness of data or a p-value from Wald test ≤0.25 in univariate analysis. Variables were also, checked for linear relationship, co-linearity and interactions term. The final model was assessed with the Likelihood-Ratio test (G^2). The results were presented as adjusted Relative Risk (RR_{adj}) and 95% confidence intervals. The protocol for this project was approved by the ethical review committees of Faculty of Medicine, Khon Kaen University and Ethics Committees of Medical Organization Surin Provincial Hospital, Ministry of Public Health, Thailand.

RESULTS AND DISCUSSION

A total of 466 TB/HIV co-infected patients were enrolled in the study. Most of the participants (63.9%) were male and 46.4% were married. The mean age was 37.5 years (SD = 8.3). A half of them had age ranging from 33-42 years old and nearly a half of them had weight at started TB treatment between 43-54 kg with mean 48.1 kg (SD = 9.1). Nearly 70.0% of participants graduated in primary school while 2.3% completed bachelor degree. About history of smoking and alcohol drinking, currently smoke and drink were 11.4 and 11.8%, respectively. At the final of TB treatment, 138 patients (29.6%) were unsuccessful outcome (95% CI: 25.5-33.9) and a successful rate on TB treatment outcome was 70.4% (95%

CI: 66.0-74.5). In univariate analysis, three TB-related factors consisted of previous TB treatment, category of TB registry and patients who were poor adherence to anti-tuberculosis were significantly associated with unsuccessful treatment outcome. In part of HIV/AIDS-related factors, eight factors were significantly associated with unsuccessful treatment outcome included registry at clinic, CD4 count, plasma viral load, receiving ART, type of ART regimen, receiving Opportunistic Infection (OI) prophylaxis during TB treatment, stage of HIV/AIDS and adherence to ARV (p-value <0.05) (Table 1).

Multivariable logistic regression analysis, the final model was constructed by using Backward Elimination Method and accounted for setting to control for the design effect. There was no interaction effect entered into the model. The factors associated with unsuccessful TB treatment outcome in a final 6 months TB treatment among HIV-TB co-infected patients were consisted of CAT2 regimen, CAT4 regimen or other compared with CAT1 regimen, CD4 count <25 cell μL^{-1}, unknown CD4 count, AIDS stage, currently smoke and poor adherence to Anti-TB (ATB). Patient's poor adherence to ART is considerably high risk of unsuccessful TB treatment outcome. In contrast, patients who were former smoker, received fluconazole, received ART before TB treatment or received ART during TB treatment were precisely protective factors (Table 2).

Table 1: Crude effect of each factor on unsuccessful TB treatment outcome among TB/HIV co-infected patients

Factors	n	Unsuccessful (%)	RR	95% CI of RR	p-value
Age groups (years)					
15-32	127	21.3	1.00	-	0.002*
33-42	231	37.2	2.19	1.32-3.62	
43-70	108	23.2	1.11	0.60-2.06	
Body weight groups (kg)					
25-42	128	33.6	1.00	-	0.150
43-54	228	25.4	0.67	0.42-1.08	
>54	110	33.6	1.00	0.58-1.71	
Monthly income (baht)					
<1,000	76	46.1	1.00	-	0.003*
1,000-3,000	315	26.9	0.43	0.26-0.72	
>3,000	75	24.0	0.37	0.18-0.74	
Network support group					
No	357	34.2	1.0	-	<0.001*
Yes	109	14.7	0.43	0.27-0.69	
Co-morbidities disease					
No	445	29.2	1.00	-	0.380
yes	21	38.1	1.30	0.74-2.29	
History of smoke					
Never smoke	360	30.0	1.00	-	0.210
Former smoker	53	20.7	0.61	0.30-1.23	
Currently smoker	53	35.8	1.30	0.71-2.38	
History of alcohol drinking					
Not drink	340	29.7	1.0	-	0.160
Former drinker	71	22.5	0.7	0.4-1.3	
Currently drinker	55	38.2	1.5	0.8-2.6	
Previous TB treatment					
No	421	28.0	1.00	-	0.026
Yes	45	44.4	2.05	1.09-3.84	
Category of TB registry					
New case	407	28.0	1.00	-	<0.001*
Relapse	17	11.7	0.34	0.07-1.52	
Treatment after failure	10	60.0	3.85	1.06-13.91	
Treatment after default	11	81.8	11.56	2.46-54.34	
Transfer in	21	33.3	1.28	0.50-3.26	
TB regimen					
CAT 1	406	27.8	1.00	-	0.100
CAT 2	23	43.5	1.99	0.85-4.68	
CAT 4 or Others	37	40.5	1.77	0.88-3.53	
Drug resistance					
Not MDR-TB	458	29.3	1.00	-	0.200
MDR-TB	8	50.0	1.71	0.84-3.47	
Adherence of ATB					
Good (>95%)	148	12.8	1.00	-	<0.001*
Poor (≤95%)	318	37.4	2.91	1.87-4.54	
Registry clinic					
TB-clinic	160	36.9	1.00	-	0.013
HIV-clinic	306	25.8	0.59	0.39-0.70	
CD4+T-lymphocyte count (cell μL^{-1})					
>200	87	13.8	1.00	0.85- 4.49	<0.001*
100-199	67	23.9	1.96	0.86-3.75	
25-99	134	22.4	1.80	1.45-6.71	
0-24	81	33.3	3.12	3.63-15.60	
Unknown	97	54.6	7.53		
Plasma viral load (copies $cell^{-1}$)					
<50	138	7.9	1.00	-	<0.001*
≥50	18	27.8	4.44	1.33-14.76	
Unknown	310	39.4	7.49	3.88-14.45	
ARV received					
No	145	58.6	1.00	-	<0.001*
Before TB treatment	129	15.5	0.13	0.07-0.23	
During TB treatment	192	17.2	0.15	0.08-0.24	
ARV regimens					
D4T+3TC+NPV	125	25.6	1.0	-	0.005*
D4T+3TC+EFV	164	12.8	0.43	0.23-0.78	
AZT+3TC+NVP	5	0	-	-	
AZT+3TC+EFV	20	0	-	-	
Others	7	0	-	-	
Received OI prophylaxis during TB treatment					
No	122	45.9	1.00	-	<0.001*
CTX only	71	22.5	0.34	0.18-0.66	
Fluconazole only	25	16.0	0.22	0.07-0.69	
Both CTX and fluconazole	248	25.0	0.39	0.25-0.62	
Stage of HIV/AIDS					
Asymptomatic stage	95	26.3	1.00	-	0.018*
AIDS related complex	269	26.4	1.01	0.59-1.71	
AIDS	102	41.2	1.96	1.07-3.58	
Adherence of ARV					
Good (>95%)	261	6.5	-	-	<0.001*
Poor (≤95%)	60	60.0	9.21	5.56-15.24	

*Significant at α<0.05 and all of p-values were reported from likelihood ratio test analysis; PTB: Pulmonary Tuberculosis, EPTB :Extra Pulmonary Tuberculosis, MDR-TB: Multi-Drug Resistance Tuberculosis, ATB: Anti-Tuberculosis, ARV: Antiretroviral, CD4: T-lymphocytes carrying CD4 antigen, D4T: Stavudine, 3TC: Lamivudine, NPV: Nevirapine, EFV: Efavirenz, AZT: Zidovudine, OI: Opportunistic Infection, CTX: Cotrimoxazol, AIDS: Acquired Immune Deficiency Syndrome, HIV: Human Immunodeficiency Virus, DOTs: Directly Observed Treatment strategy, DOTS : Directly Observed Treatment Short-course, CAT1: 2 (3) HRZE (S)/4 HR, CAT2: 2 HRZES/1(2) HRZE/5 HRE, CAT4: Reserved drugs, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin

Table 2: Multivariate logistic regression analysis of risk factors for unsuccessful TB treatment outcome among TB/HIV co-infected patients

Factors	n	Unsuccessful (%)	RR	RR_{adj}	95%CI of RR_{adj}	p-value
History of smoke						
Never smoke	360	30.0	1.00	1.00	-	-
Former smoker	53	20.8	0.61	0.29	0.11-0.800	0.016
Currently smoker	53	35.9	1.30	4.14	1.47-11.59	0.007
TB regimen						
CAT 1	406	27.8	1.00	1.00	-	-
CAT 2	23	43.5	1.99	3.72	1.05-13.17	0.042
CAT 4 or other	37	40.5	1.77	3.05	1.07-8.640	0.036
CD4+T-lymphocyte count (cell μL^{-1})						
>200	87	13.8	1.00	1.00	-	-
100-199	67	23.9	1.96	2.34	0.78-7.010	0.127
25-99	134	22.4	1.80	2.28	0.85-6.060	0.098
0-24	81	33.3	3.12	2.81	1.01-7.850	0.048
Unknown	97	54.6	7.53	3.14	1.16-8.480	0.023
Received OI prophylaxis						
No	122	45.9	1.00	1.00	-	-
CTX only	71	22.5	0.34	1.00	0.35-2.830	0.993
Fluconazole only	25	16.0	0.22	0.18	0.04-0.830	0.028
CTX and Fluconazole	248	25.0	0.39	0.76	0.33-1.770	0.534
Stages of HIV/AIDS						
Asymptomatic	95	26.4	1.00	1.00	-	-
AIDS related complex	269	41.2	1.01	1.51	0.67-3.380	0.311
AIDS	102	1.00	1.96	6.48	2.36-17.78	<0.001
ARV received						
No	145	58.6	1.00	1.00	-	-
Before TB treatment	129	15.5	0.13	0.04	0.01-0.120	<0.001
During TB treatment	192	17.2	0.15	0.03	0.01-0.090	<0.001
Adherence of ATB						
Good (>95%)	148	12.8	1.00	1.00	-	-
Poor (≤95%)	318	37.4	2.91	4.68	2.37-9.230	<0.001
Adherence of ARV						
Good (>95%)	261	6.5	1.00	1.00	-	-
Poor (≤ 95%)	60	60.0	9.21	30.77	11.95-79.240	<0.001

ATB: Anti-Tuberculosis, ARV: Antiretroviral, CD4: T-lymphocytes carrying CD4 antigen, OI: Opportunistic Infection, CTX: Co-Trimoxazol, AIDS: Acquired Immune Deficiency Syndrome, HIV: Human Immunodeficiency Virus, CAT1: 2 (3) HRZE (S)/4 HR, CAT2: 2 HRZES/1(2) HRZE/5 HRE, CAT4: Reserved drugs, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin

In this study, the results from multivariable analysis shown that the factors strongly associated with unsuccessful TB treatment outcome were type of TB regimens, CD4 count, stage of HIV/AIDS, poor adherence to ATB and poor adherence to ARV. However, the unsuccessful TB treatment outcome was less likely to occur in TB/HIV co-infected patients who were received fluconazole and receiving ART. This study found that patients who had CD4 count <25 cell μL^{-1} and unknown were 2.81 and 3.14 times as likely to have unsuccessful TB treatment outcomes (95% CI: 1.01-7.85 and 1.16-8.46, respectively) as compared with CD4 count >200 cell μL^{-1}. Clearly, advance HIV-infected patients with low CD4 counts are at increased risk of HIV progression and mortality. HIV infection increases the risk of progressing from TB infection to TB disease. Furthermore, TB may act as co-factor in the progression of HIV infection by increasing the HIV viral load though inducing a fast HIV replication and contributing to a reduction in the CD4 cell count (Straetemans *et al*., 2010). Particularly in TB/HIV co-infected patients with low CD4 counts are strongly associated with unsuccessful TB treatment outcomes. This corresponds to the previous reports in Thailand (Akksilp *et al*., 2007; Kingkaew *et al*., 2009; Mankatittham *et al*., 2009; Manosuthi *et al*., 2007; Nateniyom *et al*., 2008; Sungkanuparph *et al*., 2006) and also, consistent with the studies in Vietnam (Quy *et al*., 2006). Therefore, CD4 counts are correlated factors to identify stages of HIV infection. Most TB/HIV co-infected patients were registered as a new case (87.3%) and had initially treated with CAT1 TB regimen (87.1%) for the intensive phase of standard short-course chemotherapy which has been described as the most important part of TB treatment. Remainders were registered as relapse, treatment after failure, treatment after default and transfer in who further received CAT2, CAT3 or CAT4 TB regimen and affect to be a risk factor of unsuccessful TB treatment outcomes in 1st 6 months of TB treatment. TB/HIV co-infected patients who were registered as CAT2 and CAT4 regimen or other were risk factors of unsuccessful TB treatment outcome compared with CAT1 regimen (RR_{adj} = 3.72, 95% CI: 1.05-13.17 and RR_{adj} = 3.05, 95% CI: 1.07-8.64, respectively). This corresponds to the previous reports in Vietnam (Quy *et al*., 2006). This study found that TB/HIV co-infected patients who were AIDS stage were 6.48 times more likely to have unsuccessful TB

treatment outcomes compared with asymptomatic stage (RR_{adj} = 6.48, 95% CI: 2.36-17.78). A large proportion of the patients presented very late for treatment with very poor baseline parameters such as CD4 cell count and stage of HIV/AIDS for example, nearly 80.0% presented for treatment with stage of HIV/AIDS of either AIDS related complex stage or AIDS. The predominance of low CD4 counts and late stage of AIDS in TB/HIV co-infected patients suggests that TB is a late presentation of HIV disease. This finding supports the need for a rapid scale-up of counseling and testing for early detection of asymptomatic TB/HIV co-infected cases in rural area in Thailand. In addition, TB/HIV co-infected patients who poor adhered to ATB were over 4.0 times more likely to have unsuccessful TB treatment outcome (RR_{adj} = 4.68, 95% CI: 2.37-9.23). Similarly, a studies in Spain and South Africa they also, documented that low adherence of patients to the TB treatment regimen is predictor of unsuccessful TB treatment outcome (Cayla *et al*., 2009; Cramm *et al*., 2010) and also consistent with the study in Canada (Orr, 2011) that documented poor adherence to therapy for TB disease is the most common cause of initial treatment failure and of disease relapse worldwide.

According adherence ARV, TB/HIV co-infected patients who received ARV but poor adhered to ARV (<95%) were over 30.0 times more likely to have unsuccessful TB treatment outcome (RR_{adj} = 30.77, 95% CI: 11.95-79.24). Similarly, a study in China by Fong *et al*. (2003) documented that non-adherence can lead to treatment failure, a rise in plasma viral load and the development of drug-resistant HIV strains (Fong *et al*., 2003). However, many barriers are factor related to adherence included fear of stigmatization (They afraid of people will talk bad about them when they go to the clinic), lack of money for food and transport, the belief that HIV is incurable, competition between Western and traditional medicine and a reluctance to take medication in the absence of symptoms. Disclosure of HIV status, social and family support and a supportive clinic environment positively influenced adherence (Rowe *et al*., 2005). Further research is needed to evaluate whether educating the community about the confidentiality, availability and success of curing TB at government health facilities can promote prompt utilization of public TB treatment services by HIV-infected patients in Thailand. In addition, the last factor which associated with unsuccessful TB treatment outcome is smoking. TB/HIV co-infected patients who currently smoker were over 4 times likely to have unsuccessful TB treatment outcome (RR_{adj} = 4.14, 95% CI: 1.47-11.59). This study finding is also, consistent with few previous systematic reviews and meta-analysis (Bates *et al*., 2007; Lin *et al*., 2007) and consistent with several previous studies (Kingkaew *et al*., 2009; Musellim *et al*., 2005). On the contrary, patients who were former smoker, the corresponding adjusted relative risk were 0.29 (95% CI: 0.11-0.80) suggesting a protective effect of unsuccessful TB treatment outcome. Possible reasons include awareness about harm of smoking, counsel by public health personnel or changing in health behaviors. However, a few factors were protective and reduce unsuccessful TB treatment outcome. Patient received ART before TB treatment less likely to have unsuccessful TB treatment outcome compared with patient who not received ART (RR_{adj} = 0.04, 95% CI: 0.01-0.12) and patient received ART during TB treatment (RR_{adj} = 0.03, 95% CI: 0.01-0.09) were similar protective factors. These results were similar to the previous studies had been done in referral hospitals Thailand and found a large reduction in the odds of unsuccessful TB treatment outcome for patients receiving ART before or during TB treatment (Akksilp *et al*., 2007; Kittikraisak *et al*., 2009; Varma *et al*., 2009).

In addition, this study found that patients received ART either before TB treatment or during TB treatment are protective factor of unsuccessful TB treatment outcome. Similar to the studies are ongoing in Asia and Sub-Saharan Africa (Abdool Karim *et al*., 2010; Blanc *et al*., 2010). Consideration should be given to revision of ART eligibility guideline in country where treatment is restricted to TB/HIV co-infected patients who have WHO stage 4 disease or blood CD4 cell counts of <200 cells μL^{-1} because many randomized clinical trials provide strong evidence for treating patients with CD4 counts <200 cells μL^{-1} and the optimal time to initiate antiretroviral drugs among asymptomatic patients whose CD4 cell counts are >200 cells μL^{-1} is still unknown (Kiertiburanakul and Vibhagool, 2003). The strength of recommendation and physician decision to initiate therapy must be balance in many aspects such as the readiness of the patients, prognosis of diseases as determined by CD4 and viral load level, risk of toxicity and drug interaction.

Therefore, an optimal time to start antiretroviral therapy in HIV/TB co-infected patients should be initiated much earlier in the course of disease than is currently being done. For received OI prophylaxis, this study found 344 patients (73.8%) received an OI prophylaxis during TB treatment. Three categories of OI prophylaxis regimens were demonstrated. Of these, 71 patients (20.6%) received only CTX, 25 patients (7.3%) received only fluconazole

and 248 remainders (72.1%) prescribed both CTX and fluconazole. In univariable analysis the result shown that TB/HIV co-infected patients received both CTX and fluconazole were less likely to have unsuccessful TB treatment outcome. In fact, co-trimoxazole which is known to save lives during TB treatment and the result from this study is consisted of the study in an Giang, a province in Southern Vietnam (Thuy *et al*., 2007) and two studies in Thailand (Kingkaew *et al*., 2009; Varma *et al*., 2009). However, in multivariable analysis, received both CTX and fluconazole and received CTX only were not significantly associated with unsuccessful TB treatment outcome that similar to a study by Akksilp *et al*. (2007). Notably, received fluconazole only was significantly associated with unsuccessful TB treatment outcome (RR_{adj} = 0.18, 95% CI: 0.04-0.83) that consistent with a study by Kingkaew *et al*. (2009) and Varma *et al*. (2009).

Fluconazole in one of OI prophylaxis regimens may also be used for primary prophylaxis and for long term suppressive or chronic maintenance therapy to prevent recurrence or relapse of serious fungal infections in patients considered at high risk for developing such infections such as those with HIV/AIDS patients. However, OI prophylaxis regimens prescribed for TB/HIV co-infection patients should be based on individual clinical features and physicians' decision.

CONCLUSION

The results showed that 138 (29.61%) were unsuccessful TB outcome. The factors associated with unsuccessful outcome consisted of CAT 2 regimen (RR_{adj} = 3.72, 95% CI: 1.05-13.17), CD4 count <25 cell μL^{-1} (RR_{adj} = 2.81, 95% CI: 1.01-7.85), unknown CD4 count (RR_{adj} = 3.14, 95% CI : 1.16-8.48), AIDS stage (RR_{adj} = 6.48, 95% CI: 2.36-17.78), currently smoking (RR_{adj} = 4.14, 95% CI: 1.47-11.59) and poor adherence of anti-TB (RR_{adj} = 4.68, 95% CI: 2.37-9.23). Poor adherence to ART is a great deal high risk (RR_{adj} = 30.77, 95% CI: 11.95-79.24). Patients who were former smoker (RR_{adj} = 0.29, 95% CI: 0.11-0.80), received fluconazole (RR_{adj} = 0.18, 95% CI: 0.04-0.83), received ART before and during treatment were precisely protective factors (RR_{adj} = 0.04, 95% CI: 0.01-0.12 and RR_{adj} = 0.03, 95% CI: 0.01-0.09). Therefore, counseling and increasing knowledge for stop smoking and modifying the health system for increasing an OI prophylaxis also, adherence to both ART and ATB were strongly protective against unsuccessful TB treatment outcome.

ACKNOWLEDGEMENTS

The researchers thank the Graduate School, Khon Kaen University that support the scholarship for this study and would like to thank all of the TB/HIV patients and staffs at all of TB and HIV clinic in Surin Province. Sincere thanks and appreciation are also due to Assistant Professor Dr. Jiraporn Kiewyoo and Dr. Teerawat Valaisathien for their helpful suggestion.

REFERENCES

Abdool Karim, S.S., K. Naidoo, A. Grobler, N. Padayatchi and C. Baxter *et al*., 2010. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N. Engl. J. Med., 362: 697-706.

Akksilp, S., O. Karnkawinpong, W. Wattanaamornkiat, D. Viriyakitja and P. Monkongdee, *et al*., 2007. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. Emerging Infection Dis., 13: 1001-1007.

Bates, M.N., A. Khalakdina, M. Pai, L. Chang, F. Lessa and K.R. Smith, 2007. Risk of tuberculosis from exposure to tobacco smoke: A systematic review and meta-analysis. Arch. Intern. Med., 167: 335-342.

Blanc, F.X., D. Laureillard, L. Borand, C. Rekacewicz and E. Nerrienet *et al*., 2010. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroivral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. http://pag.aids2010.org/Abstracts.aspx?SID=644&AID=17091.

Cain, K.P., T. Anekthananon, C. Burapat, S. Akksilp and W. Mankhatitham *et al*., 2009. Causes of death in HIV-infected persons who have tuberculosis, Thailand. Emerging Infection Dis., 15: 258-264.

Cayla, J.A., T. Rodrigo, J. Ruiz-Manzano, J.A. Caminero and R. Vidal *et al*., 2009. Tuberculosis treatment adherence and fatality in Spain. Respir. Res., 10: 121-121.

Chasombat, S., M.S. McConnell, U. Siangphoe, P. Yuktanont and T. Jirawattanapisal *et al*., 2009. National expansion of antiretroviral treatment in Thailand, 2000-2007: Program scale-up and patient outcomes. J. Acquir. Immune. Defic. Syndr., 50: 506-512.

Cramm, J.M., H.J.M. Finkenflugel, V. Moller and A.P. Nieboer, 2010. TB treatment initiation and adherence in a South African community influenced more by perceptions than by knowledge of tuberculosis. BMC Public Health, Vol. 10. 10.1186/1471-2458-10-72.

Fong, O.W., C.F. Ho, L.Y. Fung, F.K. Lee and W.H. Tse *et al*., 2003. Determinants of adherence to highly active antiretroviral therapy (HAART) in Chinese HIV/AIDS patients. HIV Med., 4: 133-138.

Hosmer, D.W. and S. Lemeshow, 2000. Applied logistic Regression. Wiley, New York.

Hsiehl, F.Y., D.A. Bloch and M.D. Larsen, 1998. A simple method of sample size calculation for linear and logistic regression. Stat. Med., 17: 1623-1634.

Kiertiburanakul, S. and A. Vibhagool, 2003. HIV/AIDS in Thailand: An update. Department of Medicine, Faculty of Medicine Ramathibodi Hospital. Mahidol University, Bangkok, Thailand, Bangkok.

Kingkaew, N., B. Sangtong, W. Amnuaiphon, J. Jongpaibulpatana and W. Mankatittham *et al*., 2009. HIV-associated extrapulmonary tuberculosis in Thailand: Epidemiology and risk factors for death. Int. J. Infect. Dis., 13: 722-729.

Kittikraisak, W., C. Burapat, S. Kaewsa-Ard, W. Watthanaamornkiet and C. Sirinak *et al*., 2009. Factors associated with tuberculosis treatment default among HIV-infected tuberculosis patients in Thailand. Trans. R. Soc. Trop. Med. Hyg., 103: 59-66.

Lin, H.H., M. Ezzati and M. Murray, 2007. Tobacco smoke, indoor air pollution and tuberculosis: A systematic review and meta-analysis. PLoS Med.

Mankatittham, W., S. Likanonsakul, U. Thawornwan, P. Kongsanan and W. Kittikraisak *et al*., 2009. Characteristics of HIV-infected tuberculosis patients in Thailand. Southeast Asian J. Trop. Med. Public Health, 40: 93-103.

Manosuthi, W., A. Chaovavanich, S. Tansuphaswadikul, W. Prasithsirikul and Y. Inthong *et al*., 2007. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. J. Infect., 55: 464-469.

Manosuthi, W., S. Chottanapand, S. Thongyen, A. Chaovavanich and S. Sungkanuparph, 2006. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. J. Acquir. Immune. Defic. Syndr., 43: 42-46.

Musellim, B., S. Erturan, E.S. Duman and G. Ongen, 2005. Comparison of extra-pulmonary and pulmonary tuberculosis cases: Factors influencing the site of reactivation. Int. J. Tuberc. Lung. Dis., 9: 1220-1223.

Nahid, P., L.C. Gonzalez, I. Rudoy, B.C. de Jong and A. Unger *et al*., 2007. Treatment outcomes of patients with HIV and tuberculosis. Am. J. Respir. Crit. Care Med., 175: 1199-1206.

Nateniyom, S., S.X. Jittimanee, D. Viriyakitjar, S. Jittimanee, S. Keophaithool and J.K. Varma, 2008. Provider-initiated diagnostic HIV counselling and testing in tuberculosis clinics in Thailand. Int. J. Tuberc. Lung. Dis., 12: 955-961.

Orr, P., 2011. Adherence to tuberculosis care in Canadian Aboriginal populations, Part 1: Definition, measurement, responsibility, barriers. Int. J. Circumpolar Health, 70: 113-127.

Punnotok, J., N. Shaffer, T. Naiwatanakul, U. Pumprueg and P. Subhannachart *et al*., 2000. Human immunodeficiency virus-related tuberculosis and primary drug resistance in Bangkok, Thailand. Int. J. Tuberc. Lung. Dis., 4: 537-543.

Quy, H.T., F.G. Cobelens, N.T. Lan, T.N. Buu, C.S. Lambregts and M.W. Borgdorff, 2006. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. Int. J. Tuberc. Lung. Dis., 10: 45-51.

Rowe, K.A., B. Makhubele, J.R. Hargreaves, J.D. Porter, H.P. Hausler and P.M. Pronyk, 2005. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: Implications for antiretroviral delivery in resource-poor settings?. Int. J. Tuberc. Lung. Dis., 9: 263-269.

Sanguanwongse, N., K.P. Cain, P. Suriya, S. Nateniyom and N. Yamada *et al*., 2008. Antiretroviral therapy for HIV-infected tuberculosis patients saves lives but needs to be used more frequently in Thailand. J. Acquir. Immun. Defic Syndr., 48: 181-189.

Straetemans, M., A.L. Bierrenbach, N. Nagelkerke, P. Glaziou and M.J. van der Werf, 2010. The effect of tuberculosis on mortality in HIV positive people: A meta-analysis. PLoS One, 5: e15241-e15241.

Sungkanuparph, S., W. Manosuthi, S. Kiertiburanakul and A. Vibhagool, 2006. Initiation of antiretroviral therapy in advanced AIDS with active tuberculosis: Clinical experiences from Thailand. J. Infect., 52: 188-194.

Surin Provincial Public Health Office, 2008. Situation of AIDS and TB in Surin province during 2005-2008. http://www.spho.moph.go.th/ailment/aid/index.jsp.

Tansuphasawadikul, S., W. Saito, J. Kim, B. Phonrat and J. Dhitavat *et al*., 2007. Outcomes in HIV-infected patients on antiretroviral therapy with tuberculosis. Southeast Asian. J. Trop. Med. Public Health, 38: 1053-1060.

Thuy, T.T., N.S. Shah, M.H. Anh, T. Nghia and D. Thom *et al*., 2007. HIV-associated TB in an giang province, vietnam, 2001-2004: Epidemiology and TB treatment outcomes. PLoS One, 2: e507-e507.

Varma, J.K., S. Nateniyom, S. Akksilp, W. Mankatittham and C. Sirinak *et al*., 2009. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: An observational study. BMC Infect Dis., 9: 42-42.

WHO, 2004. Toman's Tuberculosis Case Detection, Treatment and Monitoring Questions and Answer. 2nd Edn., World Health Organization, Geneva, Switzerland.

WHO, 2007. Global tuberculosis control surveillance, Planning, Financing. WHO Report 2007. World Health Organization, Geneva, Switzerland.

WHO, 2009. Tuberculosis control in South East Asia region WHO annual report 2009. World Health Organization. Geneva, Switzerland.