Original Article

Factors Associated with Treatment Success in HIV-infected Patients Receiving Standard Antituberculosis Regimens in Thailand: A Retrospective Cohort Study

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Objective: To identify the associated factors of tuberculosis (TB) treatment success in HIV/TB co-infected patients receiving standard antituberculosis regimens.

Materials and Methods: A retrospective cohort study was conducted at Vajira hospital, Navamindradhiraj University, Thailand between 1 January 2008 and 31 December 2015.

Results: Of the 323 enrolled patients, 250 (77.4%) had treatment success. Independent factors associated with treatment success were CD4 cell counts above 200 cells/mm^3 (odds ratio [OR] 2.90, 95% confidence interval [CI] 1.39 - 6.04; $p = 0.005$) and starting antiretroviral drugs while on a TB treatment course (OR 6.32, 95% CI 3.02 13.22, $p<0.001$). On the contrary, hepatitis B virus co-infection (OR 0.37, 95% CI 0.15 - 0.91, $p = 0.031$) and a positive history of previous opportunistic infection (OR 0.41, 95% CI 0.18 - 0.92, $p = 0.03$) were associated with a lower chance of TB treatment success.

Conclusion: Early initiation of antiretroviral drugs within the TB treatment course increases the chance of treatment success in HIV/TB co-infected patients.

Keywords: Antiretroviral therapy, HIV, Risk factors, Treatment success outcome, Tuberculosis

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Globally, it is estimated that over 36.7 million people were living with human immunodeficiency virus (HIV) infection in 2016. The incidence of new HIV cases is more than 1.8 million people annually[1]. Sub-Saharan Africa is the most affected region, followed by Asia-Pacific[2]. Tuberculosis (TB) is a major opportunistic infection and is a leading cause of morbidity and mortality in HIV/AIDS-infected patients nowadays[2]. HIV-infected individuals with latent TB are approximately 20 to 30 times more likely to develop TB compared to those who are HIV uninfected, at a rate of 8 to 10% per year[3]. Therefore, systematic screening for HIV infection among TB-infected individual is recommended. Overall, treatment outcomes remain disappointment for HIV-infected compared to HIV uninfected TB patients (success rate is 75% and 83%, respectively). Furthermore, mortality in HIV/TB co-infected patients is nearly 4 times greater than in TB patients without HIV[3].

In Thailand, it is estimated that there were 440,000 (400,000 to 490,000) adult people living with HIV in 2015[4]. The WHO classified Thailand as one of the 22 countries in the world with the highest TB burden, with more than 93,000 new cases each year. Estimated incidence of TB in Thailand is 117,000 people annually (172 per 100,000 people). Sixteen percent of TB-infected patient in Thailand also have HIV co-infection[5,6].

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Recently, Thailand TB profile from WHO was reported that in people newly diagnosed with TB without HIV infection, the overall treatment success rate of TB is nearly 80%, compared to HIV/TB co-infected patients whose success rate is only 67%[6]. The lower success rate of TB treatment in HIV/TB co-infected patients results mainly from a higher rate of multiple organ involvement, drug interactions between anti-TB with antiretroviral therapy [ART] or opportunistic infection medications, a higher rate of hepatitis or rash which may lead to regimen modification[7-10].

Identifying the factors associated with TB treatment success in HIV-infected patients is important because co-infection with HIV significantly complicates both the management and outcome of TB disease[11]. Previous studies show that male sex[12], elderly[12-14], the presence of comorbid diseases[14-16], low CD4 cell count[16-19] and positive AFB from sputum smear[20-22] are associated with lower success rates of TB treatment. The majority of these studies have been conducted in Africa. Compared with Asia, differences in HIV seroprevalence, rates of primary HIV drug resistance, and the incidence of drug resistant-TB may have led to the difference in factors associated with TB treatment success. Identifying these factors in Asia would help us to provide better medical care to our patients and improve the rate of TB treatment success. The objective of this study was to identify the associated factors of TB treatment success in HIV/TB co-infected patients. This will allow healthcare personnel to properly stratify patient's risk for closer surveillance and management.

Materials and Methods

Study population

We performed a retrospective study of adults (age ≥18 years) with an HIV-1/TB co-infection receiving standard anti-TB regimens seen at the TB clinic of Vajira Hospital, Navamindradhiraj University between 1 January 2008 to 31 December 2015. These were identified using electronic and paper-based medical records and the TB registry. Vajira Hospital is a 900-bed university hospital in Bangkok, Thailand. This hospital has more than 700,000 out-patient visits and around 30,000 in-patients admitted annually. TB was diagnosed according to WHO treatment of TB: Guidelines 4th edition[23]. Concisely, a case of TB is defined as both definite and clinical diagnosis of TB. Diagnosis of HIV is made by the presence of HIV antibody in serum using ELISA confirmatory assays. Patients who had a duration of anti-TB regimens less than two months were excluded from the study. Patients were identified and enrolled consecutively. Total follow-up time was calculated from the date of initiation of anti-TB drugs to the date discharged from the TB clinic with the result of TB treatment outcome. Approval was provided by the Vajira Institutional Review Board (COA13/2560).

Treatment protocol and measurements

Routinely, patients with a diagnosis of TB will be offered screening for HIV infection at the initial TB clinic attendance; if they test positive for HIV, they will be counseled and referred to the HIV clinic for further treatment. ART medications will be initiated by infectious disease physicians at HIV clinic. The first follow-up visit is set at two weeks after the initiation of anti-TB drugs, then visits are monthly to evaluate the clinical improvement, patient's adherence to treatment, and side effects of anti-TB drugs such as rash, hepatitis, etc. Sputum acid-fast bacilli will be tested at the second and fifth month to evaluate whether the patient had treatment failure or not. Chest x-ray will be performed and evaluated for radiological improvement before the end of treatment or earlier if it is required by the physician. Results of physical examination, microbiological and radiological evaluation will be recorded in the patient's medical chart and electronic database. Standard medications for TB treatment and recommend dosage consisted of two months of isoniazid (4 to 8 mg/kg/d, maximum 300 mg/d), rifampicin (8 to 12 mg/kg/d, maximum 600 mg/d), pyrazinamide (20 to 30 mg/kg/d) and ethambutol (15 to 20 mg/kg/d), followed by four months of isoniazid and rifampicin. Pyridoxine (50 mg/day) was prescribed throughout the course of TB treatment. Regimens can be adjusted by the physicians based on side effects, sputum culture for mycobacterium final results.

Treatment outcome was defined as the results of TB treatment according to definitions and reporting framework for TB 2013 revision, updated in December 2014[24]. Outcomes were categorized as: cured: a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture-negative in the last month of treatment and on at least one previous occasion; treatment completed: a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable; lost to follow-up: a TB patient who did

not start treatment or whose treatment was interrupted for two consecutive months or more; treatment failed: a TB patient whose sputum smear or culture is positive at the fifth month or later during treatment or patients found to harbor a multidrug-resistant strain at any point of time during the treatment, whether they are smear negative or positive; not evaluated: a TB patient for whom no treatment outcome is assigned, this includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit; died: a patient who dies for any reason during the course of treatment. Treatment success was the sum of cured and treatment completed. Treatment failure was the sum of treatment failed, lost to follow-up and died. Cutaneous adverse drug reactions [CADRs] were diagnosed according to the Common Terminology Criteria for Adverse Events grading criteria[25]. Hepatitis was defined by Case definition and phenotype standardization in drug-induced liver injury [DILI][26]. GFR was calculated by the MDRD equation and classification of renal impairment, using the KDOQI Clinical Practice Guidelines[27]. Time to ART initiation was defined as the time from the date of first initiation of anti-TB treatment to the time of first initiation of ART.

Data were collected by the authors using case record forms and included: clinical characteristics and baseline laboratory test, details of HIV/TB diagnosis, dose of anti-TB drugs, details of the regimens adjustment, and treatment outcome evaluated by the physician.

Statistical analysis

Categorical variables were presented as number (n) and percentage (%). Numerical variables were presented as mean and standard deviations, or medians with inter-quartile range, depending on the normality of the variable. Pearson's Chi-square test was used to assess differences in proportions between groups. To determine factors associated with cured/complete TB treatment outcome, Binary logistic regression was applied. Candidate risk factors whose *p*-value less than 0.1 in the univariate analysis were subsequently included into the multivariable model. Time to death and time to death/failure/default TB treatment outcome was analyzed using Kaplan-Meier curve and Cox's regression analysis. Data analysis was performed using the Statistical Package for Social Sciences software, version 22.0 (SPSS Inc., Chicago, IL, USA). A *p*-value less than 0.05 was considered to be statistically significant in all analysis.

Results

Between 1 January 2008 and 31 December 2015, 449 HIV/TB co-infected individuals were included in the study. A total of 126 patients were excluded from the analysis: 69 individuals who did not receive standard anti-TB regimens, 25 cases because follow-up time was less than two months, and 32 cases because there was insufficient patient information for further analysis. Overall, 323 HIV/TB co-infected individuals were analyzed for the present study with a total follow-up time of 191.9 person-years (mean follow-up time of 216.8 days/person). The study flow is provided in Figure 1.

The characteristics of the 323 study participants are provided in Table 1. The mean age was 38.1 years and 67.2% were males. The median CD4 cell count and percentage at the time TB was diagnosed was 89 (IQR, 35 to 230) cells/mm^3 and 8% (IQR, 4 to 16%), respectively. Most patients (175 patients, 54.2%) had CD4 cell counts $\leq$100 cells/mm^3 before TB treatment. Pulmonary TB was the most common organ involvement among the study patients (214/323, 66.3% patients). Prior history of TB was reported in 24 (7.4%) cases. Isolated pulmonary involvement was diagnosed in 172/323, 53.3% patients. Extrapulmonary TB was diagnosed in 151 (46.7%) patients. Of 323 patients, 296 (92%) has serologic test for viral hepatitis. Twenty-five (8.4%) patients were reactive for HBsAg, 48 (16.2%) patients were reactive for Anti-HCV, and seven (2.4%) patients were reactive for both HBsAg and Anti-HCV. There were 77 (23.8%) patients for which ART treatment was initiated before TB was diagnosed. The remaining of the 246 patients were ART naive, of which 136 (55.3%)

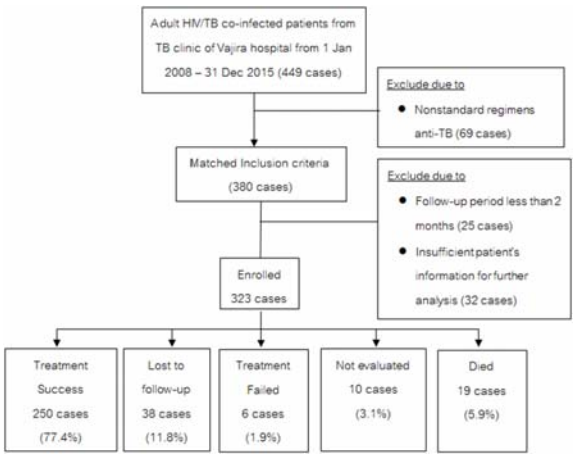

Figure 1. Study flow.

Table 1. Characteristics of 323 individuals (250 with treatment success, 73 without treatment success; 6 treatment failed, 19 died, 38 lost to follow-up and 10 not evaluated)

Variables	Total 323 patients (%)
Age (years), mean (SD)	38.1 (9.9)
18-29	68 (21.1)
30-39	124 (38.4)
40-49	89 (27.6)
≥50	42 (13)
Sex, male	217 (67.2)
BMI (kg/m^2), mean (SD)	19.6 (3.7)
Low BMI (<18.5 kg/m^2)	119 (41.3)
GFR[1)], mean (SD)	92.2 (26.6)
Normal GFR (≥90)	151 (47.9)
Mild decrease GFR (60-89)	140 (44.4)
Moderate decrease GFR (30-59)	24 (7.6)
History of previous TB treatment	24 (7.4)
Concomitant medication (at initiation of anti-TB drugs)	155 (48)
Co-trimoxazole	113 (35)
Fluconazole	79 (24.5)
Antiretroviral drugs	77 (23.8)
Viral hepatitis profiles	
Reactive for HBsAg	25 (8.4)
Reactive for Anti-HCV	48 (16.2)
Reactive for both HBsAg and Anti-HCV	7 (2.4)
Total T lymphocyte count-median (IQR)	853 (523 to 1,369.5)
CD4 cell count/percent-median (IQR)	89/8 (35 to 230)/(4 to 16)
CD4 cell count	
0-100 cells/mm^3	175 (54.2)
101-200 cells/mm^3	55 (17)
201-300 cells/mm^3	43 (13.3)
301-400 cells/mm^3	13 (4)
More than 400 cells/mm^3	37 (11.5)
Site of TB involvement	
Isolated pulmonary involvement	172 (53.3)
Extrapulmonary involvement (with/without pulmonary involvement)	151 (46.7)
Multiple sites involvements	48 (14.9)
Start ART within the TB treatment course	136 (55.3)
History of previous opportunistic infection(s)	41 (12.7)
Hepatitis within the TB treatment course	29 (9)
CADRs	48 (14.9)
Follow-up times (days), median (IQR)	186 (175 to 243)

GFR[1)] was calculated by MDRD (Modification of Diet in Renal Disease) equation (ml/min/1.73 m^2), Classification of renal impairment using KDOQI Clinical Practice Guidelines for Chronic Kidney Disease classification[27)]
ART = antiretroviral therapy; BMI = body mass index; CADRs; cutaneous adverse drug reactions; GFR = glomerular filtration rate; IQR = inter-quartile range; SD = standard deviation; TB = tuberculosis

patients started ART treatment within the TB treatment course (initiated within two months after TB treatment in 65 cases and after two months in 71 cases). The median time from TB treatment to ART initiation was 62.5 (IQR 30 to 97.5) days. In the remaining 110 cases ART was not initiated during the course of TB treatment. After anti-TB drugs were initiated, drug-induced hepatitis occurred in 29 (9%) patients and CADRs occurred in 48 (14.9%) patients.

Regarding treatment outcome, treatment was successful in 250 patients (77.4%). Among the remaining 73 patients, 38 (11.8%) were lost to follow-

Table 2. Univariate and multivariate analysis of factors associated with TB treatment success in 323 HIV/TB co-infected patients

Characteristics	Outcomes (%)		OR (Crude)	OR (Adjusted)	OR Adjusted 95% CI
	With Treatment success (250 cases)	Without Treatment success (73 cases)			
Age (years), mean (SD)	38.0 (9.9)	38.6 (10.1)	-	-	-
18-29(ref)	54 (21.6)	14 (19.2)	-	-	-
30-39	100 (40)	24 (32.9)	1.03	-	-
40-49	62 (24.8)	27 (37)	0.60	-	-
≥50	34 (13.6)	8 (11)	1.10	-	-
Gender, male	164 (65.6)	53 (72.6)	1.39	-	-
Low BMI (<18.5 kg/m^2)	96 (41)	23 (42.6)	0.94	-	-
GFR[1)], mean (SD)	91.1 (25.2)	96.1 (30.9)	-	-	-
Normal GFR (≥90) (ref)	112 (45.3)	39 (57.4)	-	-	-
Mild decrease GFR (60 - 89)	117 (47.4)	23 (33.8)	1.77$^+$	1.68	0.89 to 3.17
Moderate decrease GFR (30 - 59)	18 (7.3)	6 (8.8)	1.05	-	-
Concomitant medications					
Antiretroviral drugs	58 (23.2)	17 (23.3)	1.00	-	-
Co-trimoxazole	90 (36)	23 (31.5)	1.22	-	-
Viral hepatitis profiles					
Reactive for HBsAg	20 (8.5)	12 (19.7)	0.38*	0.38*	0.15 to 0.93
Reactive for Anti-HCV	38 (16.4)	17 (27.9)	0.51*	0.54	0.26 to 1.13
CD 4 >200 cells/mm^3	80 (32)	13 (17.8)	2.17*	2.85**	1.37 to 5.95
Extrapulmonary involvement (with or without pulmonary involvement)	123 (49.2)	28 (38.4)	1.56	-	-
Multiple sites involvements	38 (15.2)	10 (13.7)	1.13	-	-
Start ART within the TB treatment course	121 (64.0)	15 (26.3)	4.98***	6.05***	2.89 to 12.69
History of previous opportunistic infection(s)	25 (10)	16 (21.9)	0.40**	0.41*	0.18 to 0.93
History of previous TB treatment	19 (7.6)	5 (6.8)	1.12	-	-
Hepatitis within the TB treatment course	19 (7.6)	10 (13.7)	0.52	-	-
CADRs	39 (15.6)	9 (12.3)	1.31	-	-
Dose anti-TB regimens					
INH >4 mg/kg	240 (96)	69 (94.5)	1.39	-	-
RFP >8 mg/kg	232 (92.8)	66 (90.4)	1.37	-	-
PZA >20 mg/kg	227 (90.8)	68 (93.2)	0.73	-	-
ETB >12 mg/kg	238 (95.2)	71(97.3)	0.56	-	-

$^+$ p<0.1; * p<0.05; ** p<0.01; *** p<0.001

GFR[1)] was calculated by MDRD (Modification of Diet in Renal Disease) equation (ml/min/1.73 m^2)

ART = antiretroviral therapy; BMI = body mass index; CADRs = cutaneous adverse drug reactions; ETB = Ethambutol; GFR = glomerular filtration rate; INH = Isoniazid; IQR = inter-quartile range; OR = odds ratio; PZA = Pyrazinamide; RFP = Rifampicin; SD = standard deviation; TB = tuberculosis

up, 6 (1.9%) failed treatment, 10 (3.1%) not evaluated, and 19 (5.9%) cases died.

Univariate and multivariate analysis to estimated odds ratio [OR] and their 95% confidence interval (CI) is shown in Table 2. Univariate analysis revealed that HBV co-infection (OR 0.38, 95% CI 0.17 - 0.83, p = 0.012), HCV co-infection (OR 0.51, 95% CI 0.26 - 0.98, p = 0.041), and a positive history of previous opportunistic infection (OR 0.40, 95% CI 0.20 - 0.79, p = 0.007) were associated with lower chance of patients to have treatment success. While patients with CD4 cell counts more than 200 cells/mm^3 (OR 2.17, 95% CI 1.13-

4.19, p = 0.018) and patients who started ART within the TB treatment course (OR 4.98, 95% CI 2.58-9.64, p<0.001) were associated with higher chance of treatment success. Multivariate analysis revealed independent associated factors of treatment success were patients which CD4 cell counts more than 200 cells/mm^3 (OR 2.90, 95% CI 1.39-6.04, p = 0.005) and patients who started ART while TB treatment course (OR 6.32, 95% CI 3.02 to 13.22, p<0.001). On the contrary, HBV co-infection (OR 0.37, 95% CI 0.15 to 0.91, p = 0.031) and the positive history of previous opportunistic infection (OR 0.41, 95% CI 0.18 to 0.92, p = 0.03) were associated with lower chance of patients to have treatment success.

Kaplan-Meier curves of time to TB treatment unsuccess are provided in Figure 2. Kaplan-Meier curves of time to death + failure and death + failure + loss to follow-up after TB treatment stratified by ART treatment status are provided in Figure 2A and 2B. The Log rank tests show there was difference in the distribution of time to death + failure and death + failure + loss to follow-up between patients with previous ART treatment, no ART treatment, and start ART within the TB treatment course at p = 0.026 and p<0.001, respectively.

Discussion

Treatment of TB in HIV infected patients has major challenges regarding the drug interactions, overlapping toxic effects, and the occurrence of immune reconstitutional inflammatory syndrome [IRIS]. These factors could lead to unfavorable treatment outcomes. The probability of failure or death during TB treatment is significantly higher among HIV co-infected TB than HIV-negative TB patients[28,29].

In present study, 250 out of 323 patients (77.4%) had treatment success. This is higher than the 2015 WHO TB data profile reported rate for Thailand for HIV/TB co-infected patients, which was 67%[6]. This could be explained by the low prevalence rate of patients with recurrent TB in our cohort, the availability of anti-TB drugs free of charge, and full DOTS implementation in our service. This success rate was consistent with previous epidemiological studies in other parts of the world which ranged from 57% to 88%[14,18,30,31].

In our cohort, the most common site of extrapulmonary involvement was lymph node. These findings were consistent with previous studies[32,33]. The multivariate logistic regression analysis revealed HIV/TB co-infected patients with a history high baseline CD4 cell counts (≥200 cells/mm^3) and patients who start ART within the TB treatment course were associated with higher chance of TB treatment success. On the other side, patients with reactive for HBsAg and patients with a history of previous opportunistic infection (s) were associated with lower chance of TB treatment success.

Initiation of ART while TB treatment course is an independent factor associated with TB treatment success. This finding is consistent with previous studies of HIV/TB co-infected patients from Ethiopia[18] and India[34]. One study from South Africa demonstrated that initiation of ART during TB treatment

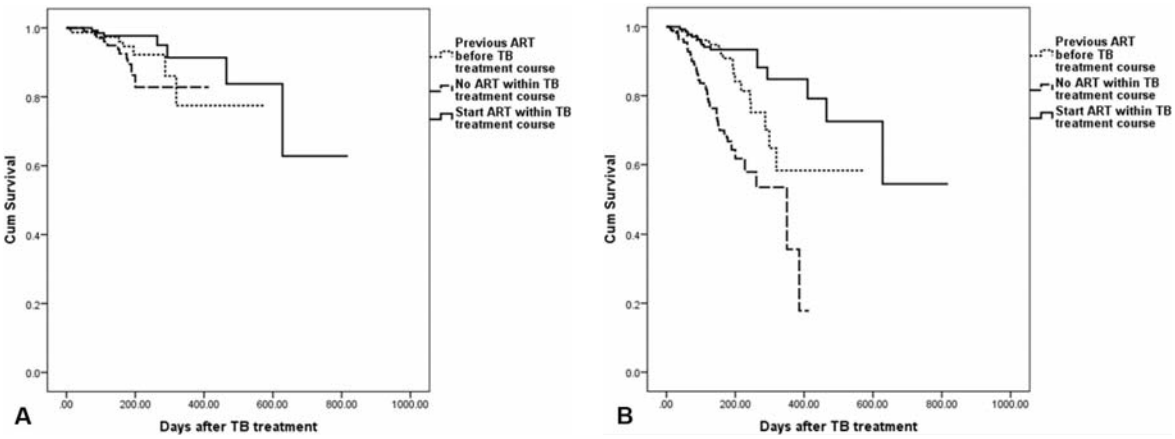

Figure 2. Kaplan-Meier curves of time to TB treatment unsuccess stratified by ART treatment status. A) Time to death and treatment failure. B) Time to death, treatment failure and lost to follow-up.

reduced mortality by more than 50%[35]. This supports the WHO guideline recommendation for early initiation of ART after anti-TB treatment despite higher risk of IRIS. Despite the apparent benefit of ART, only 136 (55.3%) patients in our study received ART while receiving anti-TB treatment. As in many developing countries, some HIV/TB co-infected patients still cannot access ART primarily due to limited ART coverage. Another interesting points is that our median time from TB treatment to ART initiation was actually delayed by more than 2 months. This is probably due to economic factors, additionally, the concern that the patients might develop IRIS during the intensive phase of TB treatment could be another explanation for this.

Interestingly, the higher CD4 cell count (≥200 cells/mm^3) was considered as an important predictor of successful TB treatment outcome. A study from Ethiopia showed that CD4 cell count was an independent factor associated with mortality in men, especially with levels <100 cells/mm^3[19]. The majority of TB/HIV co-infected patients in our cohort presented with a low baseline CD4 cell counts, which is comparable to previous studies[32,36,37]. Low CD4 cell counts indicate advanced HIV disease. Along with severely immunosuppressed state, higher risk of opportunistic infections and death are expected. This could be the explanation of lower TB treatment success in patients with a positive history of previous opportunistic infection in our cohort. Similar findings were also reported in one study from Cameroon indicating the presence of another opportunistic disease was associated with death in TB/HIV co-infected patients[16].

In our cohort, serologic evidence of HBsAg and Anti-HCV in HIV infected patients was found in 8.4 and 16.2%, respectively, which is comparable to epidemiological data from Thailand[38,39]. Reactive for HBsAg was associated with lower chance of treatment success. This finding is comparable with a study from Thailand which reported the odds of death or loss to follow-up was 2.7 (95% CI, 1.1 to 6.4) among patients with reactive for HBsAg compared to nonreactive for HBsAg[39]. The explanation of this finding could be from the higher incidence of DILI associated with anti-TB drugs in patients with HIV/HBV co-infection. A study from Brazil reported the higher incidence of TB-associated DILI in the presence of hepatitis B infection compared to patients without hepatitis B infection[40].

The present study had some limitations. First, this study was conducted in a single hospital with similarity in ethnicity, and whether Thai HIV/TB co-infected patients are representative of the Asian or, indeed, any other geographic area, is unknown. Second, incomplete data collection may occur as a nature of the retrospective study. However, in most cases, the missing data were not among the main variables of interest. To minimize this effect, we used multiple data sources (electronic, paper-based medical records, and the TB registry book). The prospective data collection could give more accurate data. The present study also had a number of strengths. First, our sample size was large and represented a wide range of disease severity. Second, the inclusion criteria, outcome definitions for TB were comparable with other studies and strictly adhered to the international guidelines of TB diagnosis and outcome definitions[23,24].

Conclusion

Based on our findings, the present study could help the physicians to develop strategies and interventions for HIV/TB co-infected patients in order to further improve the quality of TB treatment and control. Low CD4 cell counts (<200 cells/mm^3), a positive history of previous opportunistic infection (s), and HBV co-infection were associated with unfavorable treatment outcomes. Early initiation of ART within the TB treatment course increases TB treatment success and improves the quality of patients care.

What is already known on this topic?

Thailand was classified as one of the highest TB burden country. Sixteen percent of TB-infected patients in Thailand also had HIV co-infection. TB Treatment success was lower in HIV/TB co-infected patients compared to TB patients without HIV infection. Previous data show that many factors are associated with failure of TB treatment outcome in HIV co-infected patients, i.e., male sex, elderly, positive comorbid disease (s), low CD4 cell count and positive AFB from sputum smear. All patients with both HIV and TB who are not on ART should be started on ART within 2 to 8 weeks based on the CD4 cell counts.

What this study adds?

The present study revealed that in patients with HIV infection, higher CD4 cell count and ART initiation within TB treatment course were associated with higher rates of TB treatment success. In advanced stage HIV/TB co-infected patients, one important modifiable factor to improve the TB treatment success rate is the initiation of ART as soon as patients can tolerate the side effects of anti-TB drugs. Furthermore,

HBV co-infection and positive history of opportunistic infection are the factors associated with lower rate of TB treatment success. Awareness of these conditions by the physicians is important and could improve the quality of TB care in Thailand.

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Potential conflicts of interest

The authors declare no conflict of interest.

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