DOES HIV COINFECTION AFFECT THE OUTCOME OF ANTITUBERCULOSIS TREATMENT?

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Abstract **Background**: Tuberculosis (TB) is a major problem in developing countries, including Indonesia. One of the most important risk factors for developing active TB is HIV coinfection. Thus, HIV increases global burden of TB and TB is one of the leading causes of death among people with HIV. HIV patients have up to 20 times higher risk of developing active TB compared to those without HIV infection. Treatment and management of tuberculosis in HIV patients are challenging, mostly due to inadequate diagnostics and treatment.
Method: The study was conducted in 2014 using a retrospective case-control method (unsuccess TB treatment patients as case group; successful TB as control group) with purposive sampling technique. Demographic data, TB treatment, and outcome therapy were documented and analyzed to determine factors affecting successful TB treatment in HIV/TB coinfection patients. Statistical analysis was performed using univariate and multivariate logistic regression model.
Objectives: This study was aimed to analyze the outcomes of the TB treatment in HIV/TB coinfection in Bandung and the affecting factors.
Result: 531 patients (85 cases; 446 controls) were involved in this study. Demographic data showed that 7,7% of patients were HIV/TB coinfection patients and most patients (78,05%) received category 1 of antituberculosis drugs. HIV coinfection independently affected the success of TB treatment. The successful rate of TB treatment in Bandung was 83,9%. TB patients with HIV positive tended to be 2,740 times less likely to succeed in TB treatment compared to TB patients with HIV negative [OR=2,740; 95% CI (1.051-7.140), p=0.039*]. Factors affecting the successful outcome of TB treatment is gender (woman>man, p<0,05), location/access to medication (p<0,05), and the AFB-negative conversion during intensive phase of treatment (p<0,01).
Conclusion: HIV coinfection lower the successful rate of TB treatment with odds ratio 2,740. Factors affecting the successful rate of TB treatment are gender, access to medication, and AFB conversion during intensive phase of treatment.
Keywords: HIV/TB coinfection; treatment outcomes, factors.

Background

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and of the leading causes death worldwide from single infectious agent (ranking above HIV/AIDS). Etiology of Tuberculosis is Mycobacterium tuberculosis, which can be transmitted through expelled bacteria from respiratory organs. It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). Management of tuberculosis is challenging, mostly due to its high incidence, low rate of successful treatment, HIV/TB coinfection, medication adherence, and drug resistance. In 2021, the Incidence of TB was increased from 2020 to 2021, it was estimated that 10.6 million

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people suffered from TB. Interestingly, the number people with undiagnosed and untreated TB infection were also growing, resulting in an increase number of mortality, community transmission, and an increase of TB incidence. Mortality rate among TB patients was increased from 2019 and 2021. In 2021, an estimated 1.4 million deaths occurred in HIV-negative TB patients and 187,000 deaths in HIV-positive people (WHO, 2022). Globally, the success rate of TB treatment was around 80,1% in drug-sensitive adult and 84,8% ini children with HIV/TB coinfection (Torres, et al., 2019). In Indonesia, based on data provided by Ministry of Health, the success rate of TB treatment in 2013 was lower than global number (74%), meanwhile in West Java, the number was quite similar with global rates (81%). In resistant-TB infection, the number of successful rates of TB treatment was much lower (MDR TB 58,4%; XDR TB 27,1%), meanwhile the incidence rate was growing rapidly. In 2021, it was estimated around 450.000 incidence of Rifampicin-resistant TB infection (WHO, 2022; Torres, et al., 2019).

The global population is today seriously at risk of co-infection with TB and HIV. HIV and TB control programs are still facing a challenge, and it would be considerably harder and more complex for both preventative efforts if the two illnesses are linked. HIV and TB both are a heavy burden and require early treatment. HIV/TB coinfection individuals who receive adequate TB therapy can lower their high morbidity and mortality, avoid treatment failure, and increase their success rate of treatment. Both TB and HIV have a strong synergistic effect in worsening patients' conditions. HIV virus could deplete of CD4 numbers (lymphocytes, macrophages and monocytes) and alter its function in maintaining immune system. Immune system played a critical role against pathogenic microorganism infection, including Mycobacterium tuberculosis. This condition could substantially increase the risk of active tuberculosis (TB) in HIV patient. HIV infection will lead to increase proliferation of TB bacteria and activate latent TB. Meanwhile, the presence of TB will increase HIV replication, accelerate the progression of the disease thus aggravate the condition of patients. Ultimately this will increase the risk of transmission and spread of the disease, affecting the clinical manifestations of TB in people living with HIV (PLWH) and the treatment outcome (Yusria, et al., 2017; Bell, et al., 2018). Another problem faced by HIV/TB coinfection patients was the complexity of medication regiment, drug therapy problem, and the possible outcomes of TB treatment (Resende, et al., 2022). Thus, this study was aimed to determine the outcomes of the TB treatment in HIV/TB coinfection patients and its affecting factors. We hoped this study would serve as references in setting the policy to reduce the burden of TB and lower morbidity, mortality, and TB treatment failure in Indonesia, particularly in West Java.

METHODS

Study setting and design

The study was conducted using a case-control retrospective study design. The study population was registered TB patient at public healthcare facilities (9 Public Health Center and 1 Public Hospital) in Bandung in 2013 who had completed TB treatment.

Study population and sampling procedure

A total 513 subjects were enrolled in this study. The inclusion criteria were: TB patients aged over 15 years; TB patients with HIV positive or negative status (coinfection); pulmonary TB (PTB) or extrapulmonary TB patients (EPTB); AFB positive or negative smear; new or established TB patients; with or without ARV consumptions; TB patients receiving antiretroviral category 1 and 2, or second line therapy. The exclusion criteria were: TB patients with incomplete data; and TB patients who transferred during the treatment period.

The necessary sample size (n) was computed by single population proportion formula ($[n = [(1+1/c)pq(Z1-\alpha/2+Z1-\beta)]2 /[(p1-p0)]2$) assuming 95% confidence level of $Z\ a/2 = 1.96$, 5% margin of error, and proportion (p) of 60% according to the previous similar study, OR from previous study = 3,14. The calculated sample was 80 subjects for case group and 240 subjects for control group.

Data collection and variable measurement

Data collected from medical record provided by healthcare facilities. Data collection related to demographic characteristic includes gender, age, and location of patients. Clinical characteristic includes TB classification based on infected organs and based on laboratory findings, type of patients, sputum smear, HIV coinfection, AFB conversion, and antituberculosis regimen. Clinical case and treatment outcome definitions were used according to the standard definitions of WHO Guideline. Treatment outcomes were divided into (cured, completed treatment, defaulted/interrupted, failed, and died). Successful outcome was considered for TB patients who were cured and/or completed. Unsuccessful outcome was considered for TB patients resulted in treatment failure, default or death.

Data analysis

A total of 531 TB patients (with or without HIV coinfection) were enrolled in the study. Descriptive statistics (mean (SD), proportion) was aimed to summarize patients' demographic and clinical characteristic. Findings were described using words and tables. The outcome was

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categorized as successful (cure + treatment completed) and unsuccessful (default, failure, death) therapeutic outcomes.

Correlation between successful TB treatment outcomes and each independent variable (factor) was analyzed using univariate and multivariate logistic regression model. Correlation between outcome and its factors was calculated using adjusted odds ratio at p-value<0.05 and 95% confidence interval.

Ethical consideration

Ethical approval was obtained from the Ethical Clearance Committee of the Faculty of Medicine, Universitas Pajajaran (No. 368/UN6.C2.1.2/KEPK/PN/2014) prior to the study.

RESULT AND DISCUSSION

Table 1 shows the demographic and clinical data of 531 TB patients from 9 Public Health Center and a public hospital in Bandung. The average age of the patients was 35.9 years (17 – 87). Majority of TB patients live in Bandung (97.0%) and 3.0% live outside Bandung and seek treatment in Bandung. TB patients in Bandung are dominated by men. Men are more likely to be diagnosed with TB than women, with a male-to-female ratio of 1.6:1, globally. Different factors have been proposed to explain this gender gap including biological differences in disease and disease presentation and different access to health care specifically in developing countries. Additionally, men are more likely to report risk factors associated with TB exposure. Smoking is the most important risk factor for COPD and lung cancer and is also associated with pulmonary TB. Generally, men smoke more than women. Consequently, smoking is a larger contributor to the TB disease burden for men (Marçôa, et al., 2018; Smith, et al., 2015). Based on age, TB cases in HIV positive patients tend to be 6.67 times higher in the 17-45 years age group compared to those over 45 years old. This result is in line with the national report on HIV/AIDS from Directorate General of Disease Control and Environmental Health, Indonesian Ministry of Health in 2013. This tendency may be attributed by the proportion of HIV risk factors (injection drug users, heterosexuals, MSM, etc) are higher in this age group. HIV/TB coinfection patients also had a 5.55 times higher tendency to develop extrapulmonary TB (EPTB) compared with HIV negative TB [OR=5.550 (2.602-11.839), p=0.000**]. HIV/AIDS is a known risk factor for the development of extrapulmonary tuberculosis (EPTB). The most common EPTB reported sites were lymph node, pleura and urogenital tuberculosis. EPTB site has been associated with the immune status of TB patients (Shivakoti, et al., 2017; Ayed, et al., 2018).

Table 1. Demographic and Clinical Characteristic of TB Patients

Characteristic	Frequency (n)	Percentage (%)	Characteristic	Frequency (n)	Percentage (%)
Gender			**Type of Patient**		
Woman	221	(41.6)	New	451	(84.9)
Man	310	(58.4)	Transfer	17	(3.2)
Age (years)			Relaps	42	(7.9)
17 – 25	142	(26.7)	Default	13	(2.5)
26 – 35	157	(29.6)	Failure	5	(0.9)
36 – 45	106	(19.9)	Others	3	(0.6)
46 – 55	70	(13.2)			
56 – 65	37	(7.0)	**Sputum Smear**		
> 65	19	(3.6)	Negative	193	(36.4)
Location			Positive	338	(63.7)
Bandung	515	(97)	BTA +	38	(7.2)
Outside Bandung	16	(3)	1+	122	(23.0)
TB Classification based on Infected Organs			2+	65	(12.2)
Pulmonar	479	(90.2)	3+	113	(21.3)
Extrapulmonar	46	(8.7)	**HIV Coinfection**		
Pulmonar + Extrapulmonar	6	(1.1)	Negative	490	(92.3)
TB Classification based on Laboratory Findings			Positive	41	(7.7)
Pulmonar (BTA +)	338	(63.6)	**Antituberculosis Regimen**		
Pulmonar (Rontgen +)	147	(27.7)	Category 1	469	(88.3)
Extrapulmonar[c]	46	(8.7)	Category 2	62	(11.7)
n	531	(100,0)	n	531	(100,0)

Among 531 patients, 469 patients received category 1 antituberculosis regimen. This regimen includes isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S) (WHO, 2007). The optimal timing to commence ART in HIV-infected patients

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with TB is relatively complex. It must balance the risk of morbidity and mortality in very advanced HIV disease with the potential occurrence of additive toxicities, drug–drug interactions, and TB-associated immune reconstitution inflammatory syndrome (IRIS) (Manosuthi et al., 2016). The World Health Organization guidelines recommend that ARV should be started as soon as possible within the first 8 weeks of starting antituberculosis treatment and within the first 2 weeks for patients who have CD4 cell counts less than 50 cells/mm^3. In many resource-limited settings where HIV and TB are epidemic, NNRTI-based ARV remains a first-line regimen (WHO, 2018).

TB treatment in HIV patients is often challenging. Several studies showed the high number of drug related problems in HIV/TB medication and the most prevalent was adverse event of medication. Study showed that majority (70.4%) of the adverse events were detected during the first week of therapy, 92% of these events were mild moderate, and 25.5% had serious adverse events (Michael, et al., 2016; Marks, et al., 2009). Another study showed that single-HIV infected had better clinical indicators compared to HIV/TB coinfected patients (higher CD4 cell counts, better physical improvement, and low prevalence of adverse drug events) (Kadima, et al., 2014).

TB treatment in HIV-infected patients is a priority and should be started as soon as active TB has been diagnosed. Treating TB promptly will reduce TB-related mortality and the risk of transmission. ARV treatment has to be adjusted to decrease the risk of drug interaction while maintaining viral suppression activity of ARV (Manosuthi, et al., 2016). Study showed that HIV/TB coinfection patient receiving ARV are having a more successful outcome compared to untreated HIV (Zachariah, et al., 2007; van de Water, et al., 2022). ART reduces the risk of TB by 67% (95% CI 61–73), halves TB recurrence rates, reduces mortality risk by 64–95% in cohorts and prolongs survival in patients with HIV-associated drug-resistant TB (Lawn, et al., 2011)

The outcomes of TB treatment can be measured during two phases of TB treatments, which are after intensive phase of treatment (first 2 months of therapy), and at the end of treatment (6 months). AFB conversion after intensive phase of treatment is a major predictor of good therapeutic treatment. Several studies showed that patient with AFB-positive smear in intensive phase had a tendency to have an unsuccess therapeutic outcome at the end of 6-months treatment with (Babalık, et al., 2012; Andriyanto, et al., 2022; Fibriana, et al., 2020). In this study, among 338 pulmonary TB patients with AFB-positive smear, 78.4% of patients encounter a positive smear conversion. Meanwhile in HIV/TB coinfection, patients with AFB conversion during intensive phase were lower (60.0%).

Table 2. Univariate Analysis of Factors Affecting the Successful Therapeutic Outcome in TB Patients

Factors	TB Therapeutic Outcome				Total (n=531)		OR 95% CI (low-up)[a]	p-value
	Control (n = 446) Success		Case (n = 85) Unsuccess					
	n	(%)	n	(%)	n	(%)		
Gender								
Woman	197	(44.00)	24	(28.00)	221	(41.62)	2.011	0,007 **
Man	249	(56.00)	61	(72.00)	310	(58.38)	(1,210 - 3,342)	
Age (years)								
17-45	340	(76.00)	64	(75.00)	404	(76.08)	1.052	0.852
>45	106	(24.00)	21	(25.00)	127	(23.92)	(0,614 - 1,804)	
Location								
Bandung	439	(98.00)	76	(89.00)	515	(96.99)	7.427	0,000**
Outside Bandung	7	(2.00)	9	(11.00)	16	(3.01)	(2,685 - 20,540)	
TB Classification								
Pulmonary	408	(91.00)	73	(91.00)	481	(90.58)	1.116	0.789
Extrapulmonary	38	(9.00)	12	(9.00)	50	(9.42)	(0,501 - 2,484)	
Type of Patient								
New	381	(85.00)	71	(84.00)	452	(85.12)	1.156	0.653
Established	65	(15.00)	14	(16.00)	79	(14.88)	(0,615 - 2,171)	
Sputum Smear								
Negative	160	(36.00)	33	(39.00)	193	(36.35)	0.882	0.605
Positive	286	(64.00)	52	(61.00)	338	(63.65)	(0,547 - 1,421)	
HIV Coinfection								
Negative	422	(95.00)	68	(80.00)	490	(92.28)	4.396	0,000**
Positive	24	(5.00)	17	(20.00)	41	(7.72)	(2,245 - 8,608)	
Antituberculosis Regimen								
Category 1	396	(89.00)	73	(86.00)	469	(88.32)	1.302	0.445

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Category 2	50	(11.00)	12	(14.00)	62	(11.68)	(0,661 - 2,564)	
AFB-negative conversion								
Yes	405	(91.00)	53	(62.00)	458	(86.25)	5.964	0,000 **
No	41	(9.00)	32	(38.00)	73	(13.75)	(3,462 - 10,273)	

Table 2 showed univariate analysis to determine factors affecting the successful therapeutic outcome in TB patients. Results showed that the overall successful rate of TB treatment in Bandung was 83,9%. In case group (unsuccessful TB therapeutic outcome), there were 20% of HIV/TB coinfection patient, meanwhile in control group (successful TB therapeutic outcome), the number of HIV/TB coinfection patient were much lower (5%) [OR = 4,396; 95% CI (2,245-8,608); p<0,01]. It can be concluded that HIV/TB coinfection patient had a 4,396 times risk for having unsuccessful therapeutic outcomes.

Based on univariate analysis, several factors also contributed in therapeutic outcome of TB treatment, such as gender, location/access to medical treatment, and AFB conversion during intensive phase. Woman significantly had 2,011 times for having a successful therapeutic outcome compared to man [OR = 2,011; 95% CI (1,210 - 3,342); p<0,01], TB patients living in Bandung tended to be 7.47 times more likely to succeed in TB treatment compared to TB patients living outside Bandung and seeking treatment in Bandung [OR = 7.427; 95% CI (2,685–20,540); p<0.01].

In control group, there were 90,8% of patient undergo AFB conversion during intensive phase of treatment, meanwhile in case group, there were only 62,4% of patient undergo AFB conversion. TB patients with AFB conversion in the intensive phase tend to be 5,964 times more likely to succeed in TB treatment than those who are not converted [OR = 5,964; 95% CI (3.462-10.273), p=0.000**].

Based on the univariate analysis in Table 2, it can be concluded that the success of TB treatment is not attributed by : age group (17-45 y.o, >45 y.o) [OR=1.052 ; 95% CI (0.614–1.804); p=0.852]; the classification of TB (pulmonary, extrapulmonary) [OR=1,668; 95% CI (0.836-3.332); p=0.147]; Sputum smear (positive, negative) [OR = 0.882; 95% CI (0.547-1.421); p=0.605]; type of patients (new, established) [OR=1,156 ; 95% CI (0.615-2.171); p=0.653] and the type of antituberculosis category used (category 1, category 2) [OR = 1,302 ; 95% CI (0.661-2.564); p=0.445].

Table 3. Multivariate analysis of Factors Affecting the Successful Therapeutic Outcome in TB Patients

Factors	OR[a]	95% CI[b] (lower - upper)	p - value
Gender	1,960	(1,136 - 3,381)	0,016 *
Location	4,358	(1,095 - 17,336)	0,037*
HIV/TB coinfection	2,740	(1,051 - 7,140)	0,039*
AFB-negative conversion	6,591	(3,735 - 11,627)	0,000**

[a] Odds Ratio
[b] OR interval (minimun-maximum) in 95% confidence interval
* significant at 95% confidence interval
** significant at 99% confidence interval

Multivariate analysis (Table 3) showed that HIV coinfection independently affected the success of TB treatment. TB patients with HIV positive tended to be 2,740 times less likely to succeed in TB treatment compared to TB patients with HIV negative [OR=2,740; 95% CI (1.051-7.140), p=0.039*]. The findings of this study are consistent with previous research showing a 3,09-times increased risk of failure therapeutic outcomes (Sanchez., et al, 2012), 1,56-times of risk of default outcome (Muture B. N., et al., 2011), and in 3-times less likely to reach an AFB conversion in HIV/TB coinfection patients compared to regular TB patients (Kayigamba F.R., 2013).

Gender independently affects the success of TB treatment, women tend to be 1.96 times more successful in TB treatment compared to men [OR=1.960; 95% CI (1.136-3.381), p=0.016*]. This result is consistent with several studies that have been conducted where men tend to fail (default in treatment) 1.43 - 4.73 times compared to women. (Babalık, A., et al., 2013; Muture, B. N., et al., 2011; Boateng, S.A., et al., 2010; Gebre, M. K., 2009).

The location of TB patients affects the success of TB treatment. Patients who live in Bandung tend to be 4,348 times more likely to succeed in TB treatment compared to TB patients who live outside Bandung and seek treatment in Bandung [OR=4,358; 95% CI (1.095-17.336), p<0.05*]. Care seekers' characteristics were prominent barriers due to the poor accessibility to the health center (long distance, poor roads and trail conditions, lack of availability of public transport), economical constraints (direct and indirect costs associated with the travel). These barriers were further augmented by poor awareness regarding the TB, delayed treatment seeking, alternative visits for treatment seeking (for example traditional healers and on the counter medication), regimen complexity

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and stigma associated with the TB (Marahatta, et al., 2020)

Another factor affecting the successful therapeutic outcome is AFB-negative conversion during intensive therapy phase. TB patients who failed to reach AFB-negative conversion during intensive therapy phase were 6.591 less likely to be successful at the end of TB treatment (6 months) compared to TB patients who had AFB-negative conversion [OR=6.591; 95% CI (3,735 - 11,627), p=0,000**]. Conversion of AFB status in the intensive phase is a variable that contributes to the success of TB treatment (Andriyanto, et al., 2022; Fibriana, et al., 2020).

Pharmacists play vital roles in optimizing HIV/TB treatment outcomes in multiple ways and in all medical settings, such as ensuring patients are taking a complete and appropriate regimen, recommending alternative therapy, dose or formulation adjustments, preventing and managing drug-drug interactions, and modifying drug schedules to optimize the outcome therapy and reducing medication errors and adverse drug reaction.

CONCLUSION

HIV coinfection does affect the outcome of tuberculosis treatment. Tuberculosis patient with HIV coinfection had a 2.740 times risk for having unsuccessful therapeutic outcomes compared to those without HIV coinfection. Therapeutic outcomes of tuberculosis treatment are affected by HIV/TB coinfection, AFB conversion during intensive phase of treatment, access of medicine (location), and gender.

COMPETING INTERESTS

All authors had none to declare

AUTHOR'S CONTRIBUTION

MH. Roseno conceived of the presented idea, data collection and analysis, and drafting manuscript; Maria Immaculata Iwo and Ridad Agoes helped supervise the findings of the project and provided critical feedback; and Widyastiwi writing the manuscript with input from all authors. All authors contributed to the final manuscript.

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