ORIGINAL ARTICLE

Tuberculosis Infection and Incidence of Loss to Follow Up among HIV Patients at Saiful Anwar General Hospital, Indonesia: A Retrospective Study

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ABSTRACT

Introduction: Tuberculosis (TB) is the most common opportunistic infection experienced by HIV patients that can affect the success of antiretroviral (ARV) therapy. This study aimed to determine the association between tuberculosis infection and loss to follow-up (LTFU) among HIV patients after ARV therapy initiation. **Methods:** This retrospective cohort study was conducted by observing HIV patients in Saiful Anwar General Hospital, Indonesia who were diagnosed in 2015 for 39 months based on medical records data. The number of samples that met the inclusion and exclusion criteria was 170 patients. Kaplan Meier and Cox Regression were the statistical tests used to analyze data in this study. **Results:** The probability of HIV patients to retain in ARV therapy for 39 months was 90% among HIV co-infected TB patients and 84% among HIV without TB co-infection. However, no significant difference was found (p-value = 0.41). Most of the incidence of LTFU in both groups occurred in the first year after ARV initiation. Cox Regression analysis showed that TB infection did not have a significant relationship with the incidence of LTFU ARV therapy (HR 0.62; 95% CI 0.18 – 2.08; p-value = 0.44). **Conclusion:** This study found that TB infection did not have a significant association with LTFU after ARV initiation. However, most of LTFU in both groups (the co-infection group and without TB co-infection) occurred in the first year of ARV therapy. Providing intensive counseling in the initial phase could increase the commitment of HIV patients for staying in ARV therapy.

Keywords: HIV, Loss to follow up, Antiretroviral therapy, Tuberculosis

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INTRODUCTION

Globally, People Living with Human Immunodeficiency Virus (PLHIV) has reached 38 million at the end of 2019 and 1.7 million of them are newly infected (1). Even though the trend of new HIV cases shows a gradual decline, HIV remains a major public health problem (1). The presence of various opportunistic infections that threaten PLHIV further increases the burden of HIV. The decreased immune function puts PLHIV at those risky conditions. Tuberculosis (TB) is the most common opportunistic infection experienced by HIV patients (2). The risk of developing TB active among PLHIV is approximately 20 times higher (3,4). Tuberculosis is also reported as the leading killers among PLHIV (1). One of three PLHIV death is due to TB infection (1). In 2018, 9% of 10 million TB patients were living with HIV, 44% of them were not aware of their condition (1). In Indonesia, it is estimated that around 78,000 PLHIV also suffer from TB (5).

Currently, HIV prevention and treatment programs are getting better and accessible, as well as its service quality (6). However, only 67% of all PLHIV or 81% of PLHIV who knew their infection status accessed the ARV treatment in 2019 (1). Long-term treatment that requires high adherence has a higher risk of ending up in worse outcomes, such as loss to follow-up (LTFU). Globally, the average incidence of LTFU in HIV patients in the first 12 months of ARV therapy initiation was 20% (7). The incidence of LTFU reported by health facilities has increased significantly in the last 12 years. It doubled from 11.9% in 2004 to 24.5% in 2012 (7). Studies in sub-Saharan countries found that the incidence of LTFU after ARV initiation ranges from 9% to 56% (8–10), while in Asia countries, the cumulative LTFU incidence ranges from 4.3% to 48% (11,12). This situation needs to be a concern, considering that HIV patients have to take ARV medication for their lifetime. LTFU is reported to have poor outcomes and can lead to drug resistance (3). Previous studies showed that 21% to 34.2% of LTFU patients who were successfully traced had died (13,14).

The dual burdens of HIV and TB can be a barrier to end the HIV epidemic as well as the TB epidemic. TB infection is associated with an increased risk of LTFU

and mortality in PLHIV (15–18). The risk of LTFU among PLHIV with TB infection is approximately two times higher than those without TB infection (15,16). However, some studies showed inconsistent results. Other studies found that there was no difference in the incidence of LTFU in those groups (19–23). Early identification of TB infection in HIV patients can make ARV therapy more effective, considering the potential drug interactions between TB and ARV treatment (24).

Indonesia has implemented a TB-HIV collaboration program to reduce the burden of HIV and TB disease since 2009 (25). As one of 30 TB/HIV high burden countries, Indonesia is very concerned to reduce the morbidity and mortality of those cases (26). East Java is the province with the second-highest estimated cumulative number of HIV cases in Indonesia and the highest new HIV cases in 2019 (27). Saiful Anwar General Hospital is an HIV and TB referral center hospital in East Java province that has also carried out collaborative TB-HIV activities. The relationship of TB infection with LTFU incidence has not been identified in HIV patients at Saiful Anwar General Hospital. Therefore, this study was conducted to determine the relationship of TB infection in HIV patients with the occurrence of LTFU in ARV therapy. Identifying the association of TB infection with LTFU after initiating ART is essential to determine the appropriate action for ensuring all HIV patients retain in the treatment.

MATERIALS AND METHODS

A retrospective cohort study was conducted in the division of tropical diseases and infections, Saiful Anwar General Hospital in January 2020. All HIV patients who were registered in2015 were the population in this study (288 patients). Inclusion criteria that were used in the selection of samples, in both the exposed and unexposed groups, were HIV patients who were eligible for receiving ARV treatment and received TB screening at the initial stage. HIV patients who had TB infection were defined as the exposed group. HIV patients without TB infection were classified as the unexposed group. Patients who had received ARV treatment before, included those that had ever received post-exposure prophylaxis (PEP) or for prevention of mother-to-child transmission, were excluded. Patients who had incomplete data on the variables studied (no date of ART initiation, no date of the last visit, unknown WHO clinical staging, no documented the functional status) were also excluded from this study. A total of 170 HIV patients who met the criteria were included as sample study. Data were collected from medical records.

The time of LTFU was the dependent variable in this study. The occurrence of LTFU was calculated based on the difference between the date of the last visit and the start of ARV therapy. Patients were observed for 39 months to find out their LTFU status. Patients were categorized as having LTFU if they did not visit for three consecutive months (21,22). The independent variable in this study was the TB infection status. This variable was measured based on the results of TB screening conducted before starting ARV therapy. Patients who had pulmonary TB or/and extra-pulmonary TB were categorized as having TB infection. Other variables were also collected, such as age that was calculated by subtracting the date of ARV started from the patient's date of birth (0-14, 15-24, 25-34, 35-44, and > 45 years old) (27), sex (male and female), and WHO clinical stage at ARV therapy initiation (I, II, III, and IV) (28). The clinical staging of HIV was determined based on clinical manifestations. It was classified based on the revised WHO clinical staging (29). This classification was adjusted according to the criteria in each patient's age group (children or adolescent and adult) (29). Functional status at enrollment was classified into three categories, namely working, ambulatory, and bedridden (22,30). Patients who were able to do their daily activities normally, either work inside or outside the home, were categorized as working (31). Ambulatory meant the patient was unable to work normally and spent <50% of the time lying down(31). Patients who were unable to perform any activities or continuously lying on the bed were classified as bedridden (31). The number of other opportunistic infections was calculated based on the type of opportunistic infection suffered by the patient. The opportunistic infections included candidiasis, diarrhea, cryptococcal meningitis, pneumocystis pneumonia, cytomegalovirus, herpes zoster, herpes simplex, toxoplasmosis, and hepatitis (30). The statistical tests used in this study were Kaplan Meier and Cox Regression by using SPSS 22.

This study was approved by the Saiful Anwar General Hospital health research ethics commission with No: 400/271 / K.3 / 302/2019.

RESULTS

From 170 data of HIV patients, it was known that most of them aged 25-34 years old (35%) and male (67%). Based on clinical conditions, as many as 20% of HIV patients had TB infection and 27% had one or more opportunistic infections. At the beginning of the observation, the proportion of HIV patients who were at WHO clinical stage-III was 35%, while 29% were at the WHO clinical stage-IV. The majority of HIV patients (70%) had functional working status. The distribution of characteristics of HIV patients in Saiful Anwar General Hospital at the beginning of the observation (baseline) was shown in Table I.

Kaplan-Meier graph showed that the cumulative probability of TB-HIV co-infected patients that remained in ARV therapy for 39 months was 90%, while in HIV patients without TB infection, the probability was 84%. In other words, the incidence of LTFU in TB-HIV co-infected patients was 10% and 16% in HIV

Table I: Respondent characteristics at baseline

Variable	Frequency	Percent
	n	%
Age		
0-14 years old	12	7
15-24 years old	25	15
25-34 years old	60	35
35-44 years old	46	27
> 45 years old	27	16
Sex		
Male	114	67
Female	56	33
TB infection		
Yes	34	20
No	136	80
Number of other opportunistic infections		
0	124	73
≥ 1	46	27
WHO clinical stage		
I	39	23
II	22	13
III	59	35
IV	50	29
Functional status		
Working	119	70
Ambulatory	27	16
Bedridden	24	14

patients without TB infection. However, no statistically significant differences were found (p-value = 0.41). The highest incidence of LTFU occurred in the first year starting antiretroviral therapy, in both the TB co-infected and without TB co-infection group (Figure 1). The Cox Regression analysis confirmed that the TB infection status at the initiation of ARV therapy had no relationship with LTFU (HR 0.62; 95% CI 0.18 – 2.08; p-value = 0.44) (Table II).

In the age group < 25 years old, HIV patients with TB co-infection (67%) had a lower cumulative probability of retaining in ARV treatment than HIV patients without TB infection (93%). The opposite finding was found in

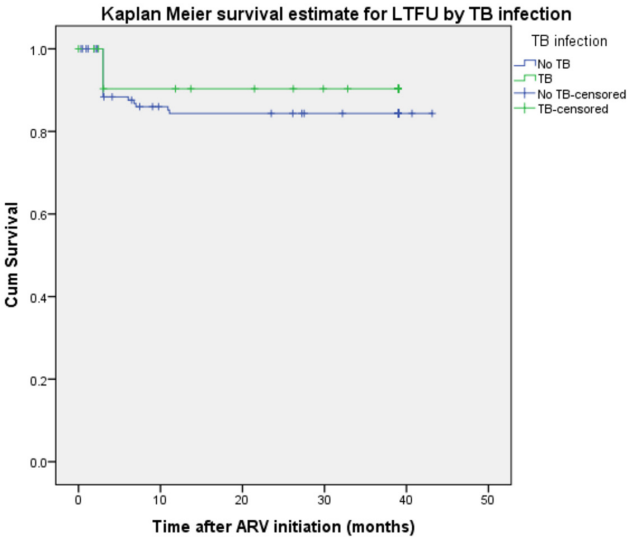

Figure 1: Kaplan-Meier survival curves to compare LTFU between HIV-TB co-infected patients and without TB co-infection at Saiful Anwar General Hospital, Indonesia

Table II: Association between TB infection and incidence of LTFU among HIV patients

Variable	B	SE	Wald	Sig.	HR	95% HR
TB infection	-0.48	0.62	0.60	0.44	0.62	0.18 – 2.08
Yes						
No						

HR = hazard ratio

the age group ≥ 25 years old. HIV patients with TB co-infection (93%) had a higher cumulative probability of persisting in ARV treatment than HIV patients without TB infection (82%). However, this difference was not statistically significant (p-value > 0.05). The cumulative probability of HIV patients with TB co-infection that stay in ARV therapy for 39 months has a lower value than in HIV patients without TB co-infection in the sex strata, in both the female and male groups. The opposite was found in WHO clinical strata, functional status, and the number of other opportunistic infections. In these strata, HIV patients without TB co-infection had a lower probability of complying with ARV therapy than patients with TB co-infection. Nevertheless, the results of this stratification analysis were not statistically significant (Table III).

DISCUSSION

This study found that one of twelve TB-HIV co-infected patients wereLTFU after 39 months of ARV therapy initiation. This finding was almost the same as the results of studies in South Africa and Zambia (32,33). Compared to studies in Ethiopia, Vietnam, and Myanmar, the incidence of LTFU in TB-HIV co-infected patients in this study was lower (3,16,34). TB-HIV co-infected patients faced a double burden of diseases (35).

Table III: Association between TB infection and incidence of LTFU among HIV patients by strata

Strata	TB infection	*Survival rate* from LTFU (%)	Log-rank	Sig.
Age				
< 25 years old	Yes	67	2.33	0.13
	No	93		
≥ 25 years old	Yes	93	1.87	0.17
	No	82		
Sex				
Male	Yes	82	1.84	0.175
	No	93		
Female	Yes	80	0.51	0.48
	No	90		
Number of other opportunistic				
0	Yes	88	0.04	0.85
	No	86		
≥ 1	Yes	100	1.66	0.20
	No	81		
WHO clinical stage				
Non-AIDS (I-III stages)	Yes	89	0.07	0.80
	No	86		
AIDS (IV stage)	Yes	94	1.11	0.29
	No	82		
Functional status				
Working	Yes	94	0.62	0.43
	No	88		
Ambulatory	Yes	89	0.44	0.51
	No	77		
Bedridden	Yes	86	0.25	0.62
	No	77		

LTFU = loss to follow up

Besides taking ARV therapy, they must also adhere to anti-tuberculosis therapy. HIV and TB treatment requires a high commitment because non-compliance can affect treatment outcomes (17). Although the burden faced by these patients was high, the TB-HIV integration program might have a contribution to this lower LTFU rate. Collaborative and integrated activities make monitoring more optimal (35).

Most of LTFU in both groups (the TB co-infection and without TB co-infection) occurred in the first year of ARV therapy. This finding was consistent with studies conducted in Zambia (33). The incidence of LTFU in Ethiopia also increased within 12 months after ARV therapy was initiated (36). Studies conducted in South Africa found a similar finding (15). The incidence of LTFU occurred within the first year. The first six months were the most vulnerable period for LTFU (15). It was confirmed by studies conducted in Vietnam and Central Kenya (16,37). Multicenter studies that were conducted in the six Asian regions also found that one-third of LTFU occurred in the first six months after ART initiation (12). The occurrence of LTFU in the initial period of therapy might be related to the patient's adaptation process. It was closely related to the side effects of the drugs consumed (38). The most common side effects experienced during the initial therapy, such as gastrointestinal disorders, can persist throughout treatment (38). Side effects that arise are known to be related to patient adherence in carrying out antiretroviral therapy (39,40). However, the side effects that occurred from antiretroviral drugs were not examined in this study. The current strategy "test and treat" which screened the population at risk and treat individuals diagnosed with HIV immediately regardless of CD4 cell count might also explain this finding. Such patients were not feeling sick at treatment initiation. They thought that their conditions were fine and did not have serious problems (8,23). Therefore, there was a possibility that they did not fully understand the consequences of treatment that must be followed (8,23). The lack of information about the importance of treatment adherence might relate to this case (23). When patients had been diagnosed with HIV or TB-HIV co-infected, health education and intensive counseling are needed to ensure their understanding, readiness, and commitment to undergo the treatment completely (41).

This study found that TB infection did not have a significant association with LTFU. This result was consistent with studies conducted in Hanoi, Ethiopia, and Uganda (19–23). This finding might be related to the implementation of the TB-HIV collaboration program. This program had been implemented in Indonesia since 2009 (25). This program aims to reduce the burden of TB in HIV patients and reduce the burden of HIV in TB patients. The implementation of the HIV and TB program has been carried out in an integrated way so patients can get comprehensive services. HIV testing and counseling services are not only done voluntarily by patients (Voluntary Counseling and Test) but also carried out at the initiation of health workers or called the Provider Initiative Counseling and Test (PICT) (25). Thus, the status of TB infection in HIV patients and HIV status in TB patients can be known as early as possible. Early identification of TB infection status in HIV patients can help determine the appropriate treatment. This collaborative and integrative program also makes monitoring of HIV treatment better. The improved quality of life of HIV patients causes them to stay longer or more compliant in undergoing treatment (20,22).

Based on stratification analysis, this study found that in younger aged (< 25 years old), the retention of HIV treatment was lower in TB-HIV co-infected than in HIV patients without TB infection although this was not statistically significant. TB-HIV co-infection put the younger age group at risk for ending up at LTFU (42). Two treatments that required high adherence put them in a chaotic situation (42). Very young children usually required a specific combination of drugs to reduce the variety of side effects that will arise (42). The existence of stigma, psychological pressure, the lack of social support were the barriers for younger aged to retain in long-term treatment (42,43).

The main limitation of this study is related to the availability of data. The data that were available in the medical record did not record other potential factors that might affect the occurrence of LTFU. Not all patients had TB screening results before initiating antiretroviral therapy so they had to be excluded from this study. It might affect external validity. Bias could occur due to differences in characteristics between patients who were involved in the study and those who were excluded. Nevertheless, this retrospective cohort study could explain the causal relationship between TB infection and the incidence of LTFU in ARV therapy.

The findings of this study indicate that strengthening disease management needs to be done optimally, in both HIV and TB-HIV co-infected cases, so the LTFU rate decreases. Monitoring adherence to ARV treatment needs to be tightened, especially in the early stages of treatment. The conditions of HIV patients shall be followed up regularly to detect the possibility of LTFU. Contact tracing and intensifying counseling sessions some actions that can be done to prevent LTFU. The integration of TB-HIV disease management can also be strengthened by the presence of community-based support. Community-based support can help patients to have a strong commitment to their treatment. Further research is needed to explore the predictors of LTFU, such as the impact of community-based support and TB-HIV integration program.

CONCLUSION

This study found that TB infection did not have a

significant association with LTFU after ARV initiation. However, most of LTFU in both groups occurred in the first year of ARV therapy. The initial period of ARV therapy is a crucial time that can determine continuity and treatment outcomes. Therefore, intensive counseling during the initial therapy period shall be conducted to increase the commitment of HIV patients so that LTFU can be prevented. Regular monitoring of ARV therapy needs to be optimized to determine the condition of HIV patients.

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