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EPIDEMIOLOGICAL ASPECTS OF HIV-TB CO-INFECTION IN PEOPLE WITH HIV/AIDS (PLWHA): A HOSPITAL-BASED STUDY

Rico Januar Sitorus[1*], Jaka Murinata[2], Nyoman Yudi Antara[3], Reymart V. Sangalang[4], Merry Natalia Panjaitan[5]

[1]Department of Epidemiology Public Health Faculty Sriwijaya University, Palembang, Indonesia
[2] Department of Epidemiology Public Health Faculty Sriwijaya University, Palembang, Indonesia
[3]Biotechnology Program, Faculty of Mathematics and Natural Sciences, Universitas Halu Oleo
[4] De La Salle University, Manila, Philippines
[5]Port Health Office, Palembang, Indonesia
Correspondence Address: Rico Januar Sitorus
Email:rico_januar@fkm.unsri.ac.id

ABSTRACT

Introduction : Tuberculosis (TB) is one of the co-infections with high morbidity and mortality in patients with HIV/AIDS (PLWHA). The prevalence of Tuberculosis in HIV patients in Indonesia ranges from 19.7% to 61.5%. **Aims:** This study aimed to identify predictors of incident HIV-TB co-infection in PLWHA. **Methods**: This observational study used a case-control design. Cases were defined as patients with HIV/AIDS co-infected with TB, while controls were those with HIV/AIDS without TB co-infection. The study population included 180 PLWHA, comprising 60 cases and 120 controls. Exclusion criteria for the case group were patients who had not completed their medical records and those who were previously infected with TB before HIV infection. **Results**: Bivariate analysis showed that variables significantly related to TB-HIV were clinical stage, CD4 levels, anemia status, and opportunistic infections. Multivariate logistic regression analysis showed that CD4 levels were the dominant predictor, with an adjusted odds ratio (AOR) of 5.71, 95% confidence interval (CI) 2.84-11.84, p = 0.0001. Meanwhile, clinical stage, anemia status, and opportunistic infections were confounding variables. **Conclusion:** CD4 levels were found to be a dominant predictor of increased TB-HIV risk. Further efforts should be made to encourage home assistant care initiation and improve medication compliance based on these results.

Keywords: Co-infection, HIV-TB, AIDS, CD4 levels

INTRODUCTION

The Human Immunodeficiency Virus (HIV) continues to be a major worldwide health issue due to its weakening effects on the immune system. It is estimated that about 37.7 million individuals are currently affected by HIV, with approximately 680,000 deaths caused by HIV-related illnesses and 1.5 million new cases reported (Stover *et al.*, 2021). Around 4-5 million people worldwide are believed to have HIV with co-infection. Experiencing multiple infections, including tuberculosis, malaria, or herpes simplex virus, alongside HIV can lead to a rise in the amount of HIV in the body. This can disrupt the equilibrium between the replication of the HIV virus and its management by the host's immune system. People who have HIV co-infection are more likely suffering from complications during clinical care and have a greater chance of morbidity and mortality in comparison with those with mono-infection. Therefore, healthcare providers should optimize treatment strategies for people with HIV co-infection.(Petersdorf *et al.*, 2016; Platt *et al.*, 2016; Mattingly, Pandit and Onukwugha, 2019)

Tuberculosis (TB) is prevalent among individuals who are living with Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) (PWLHA). Considered to be one of the most widespread opportunistic infections, it has high rates of morbidity and mortality worldwide. Global data show that TB afflicts around 10 million individuals and is responsible for

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causing the death of 1.6 million individuals, of which 26% are caused by HIV and TB coinfection (WHO, 2019). Individuals with TB-HIV co-infection typically experience more severe immunosuppression with a Cluster of Differentiation-4 (CD4) count of less than 200 cell/mm3, necessitating regular treatment (Sitorus *et al.*, 2021).

Currently, it is estimated that ten million new TB cases are identified in HIV-positive individuals. In 2019, globally, approximately 208,000 people living with HIV/AIDS (PWLHA) died from TB, a disease that may have been exacerbated by COVID-19. In Indonesia, an estimated 3% of TB patients are co-infected with HIV, and 49% of AIDS patients experience opportunistic infections (Ministry of Health, 2015; wWHO, 2020). Individuals with co-infection of HIV and TB are more vulnerable to developing psychological and social problems, a lower quality of life, and poorer physical health compared to those who only have HIV. Tuberculosis significantly contributes to HIV-related mortality, thus early treatment initiation is necessary to reduce the risk (Teklu *et al.*, 2017; Alene *et al.*, 2018). TB elimination is one of the Sustainable Development Goals (SDGs) and the World Health Organization (WHO)'s program. The goal is to reduce TB mortality by 95% and TB incidence by 90% by 2035 (Castro and Colvin, 2018) .

The prevalence of HIV-positive tuberculosis patients in South Africa is 58%, which means there are approximately 7.7 million patients with HIV (WHO, 2020). The elevated rates of illness and death among individuals with HIV and tuberculosis co-infection are influenced by various risky behaviors, such as the use of injection drugs and engaging in unsafe sex GBD 2019 Tuberculosis Collaborators. 2021). Additionally, HIV is associated with increased resistance due to pharmacokinetic effects, such as the malabsorption of tuberculosis drugs like Rifampin (Rockwood *et al.*, 2015).

Clinical risk factors, such as delays in starting antiretroviral therapy (ART) or receiving a TB diagnosis and treatment, as well as multidrug-resistant TB, can exacerbate patients' conditions. Individuals living with HIV are particularly vulnerable to contracting TB disease, as the risk of developing TB is 16-27 times higher compared to those without HIV (WHO, 2020). To address this challenge, the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) launched the "90-90-90" program. This initiative aims to identify 90% of all HIV-infected individuals in the community and provide ART to 90% of the identified ones. It also aims to achieve viral suppression among 90% of treated individuals' communities (United Nations, 2014). In countries like Indonesia, in which economic resources are constrained, the co-occurrence of TB and HIV infections can deter the achievement of the sustainable development goals. Several patient-related factors are attributed to the high incidence of TB-HIV co-infection and exhibit specific characteristics for individuals affected by TB and HIV co-infection. Therefore, understanding the predictors of TB-HIV incidence in HIV patients is necessary, particularly in Indonesia, to tackle the double epidemic threat posed by TB-HIV.

METHODS

The purpose of this case-control observational study was to examine the relationship between independent factors and HIV co-infection among patients at RSUD Raden Mattaher Jambi from 2016 to 2020. The study utilized a retrospective design since the researchers traced back the exposure related to HIV co-infection. The cases were patients diagnosed and registered at RSUD Raden Mattaher Jambi from 2016 to 2020 with HIV/AIDS co-

infected by TB. The controls were patients with HIV/AIDS without TB co-infection who were also diagnosed and registered at RSUD Raden Mattaher Jambi from 2016 to 2020.

The inclusion criteria for both case and control samples were patients aged above 20 years old, while the exclusion criteria included patients with incomplete medical records and patients who had been diagnosed with TB before HIV. The population for this study consisted of all PLWHA patients who sought treatment at RSUD Raden Mattaher Jambi between 2016 and 2020. The minimum sample calculation formula for the odds ratio test, as described by Lemeshow and Lwanga (1991) was applied. The results indicated a minimum sample size of 180 was obtained, with a total of 60 cases and 120 controls (Lemeshow and Lwanga, 1991).

The dependent variable for this study is HIV co-infection in patients at RSUD Raden Mattaher Jambi between 2016 and 2020. The study used microscopic and radiological test results from medical records to determine whether PLWHA patients were also diagnosed with TB. The independent variables included anemia status, CD4 levels, clinical stage, education level, employment status, gender, marital status, and opportunistic infections. Three-stage statistical data analysis was applied on the data. The first stage involved completing the data through editing, coding, and entering. Univariate, bivariate, and multivariate analysis methods were then carried out on the refined data.

Each variable's characteristics and distribution, encompassing duration of HIV (in years), clinical stages, anemia status, opportunistic infections, level of education, marital status, occupation, and sex, were described through univariate analysis. The relationship between HIV co-infection and independent variables was explored using a bivariate statistical analysis through a Chi-square test. A multiple logistic regression test was conducted to determine dominant factors at a significance level of alpha 5%. Independent variables were declared significant predictors of HIV-coinfection when the p-value < 0.05.

Confounding potential was calculated based on the change in odds ratio of more than 10% in the multivariate analysis using the Enter method. Ethical approval was obtained for the study. This research has passed ethical standards from the Faculty of Public Health Universitas Sriwijaya under a reference number of 119/UN9.FKM/TU.KKE/2021.

RESULT

The results of this study showed that the number of respondents was 180 people consisting of 60 cases and 120 controls. Demographic respondent characteristics, shown by analysis, suggested a higher number of male relative to female patients in both the case and control groups. Table 1 reveals that, within the case group, 58.8% had a Senior High School degree, and 50% had a job as an entrepreneur. Most of the participants in this study had been suffering from the illness for over five years (56.6%), were in clinical stage 3 (55%), did not suffer from anemia (57.77%), and did not suffer from opportunistic infections (71.11%).

In this study, bivariate analysis was done to identify the association of the independent variables with TB-HIV. Variables significantly associated with TB HIV were clinical stages OR 13.95% CI 4.86-34.76, p = 0.0001), CD4 levels (COR 11.48%, 95% CI 5.41-24.38, p = 0.0001), anemia status (OR 6.68%, 95% CI 3.34-13.29, p = 0.0001), and opportunistic infection (OR 5.71%, 95% CI 2.84-11.48, p = 0.0001) (Table 2). Predictors of TB-HIV were examined using multivariate logistic regression. CD4 levels, according to the results, were dominant predictors with an AOR of 5.71, 95% CI 2.84-11.48, p = 0.0001. CD4 levels < 200 cell/mm^3 were 5.71 times more at risk to suffer HIV

coinfection than CD4 levels ≥ 200 cell/mm^3 as shown in Table 2.

However, the other variables, such as clinical stages (AOR of 0.130, 95% CI 0.74–9.88, p = 0.301), opportunistic infection (AOR of 1.62, 95% CI 0.702–3.75, p = 0.257), and anemia status (AOR of 1.76, 95% CI 0.73–4.28, p = 0.206), were proven as confounding factors (Table 3).

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Table 1. Predictors of HIV Co Infection

Variables	HIV Coinfection				P value	OR	95 % CI
	HIV-TB (Cases)		HIV (Control)				
	n	%	n	%			
Gender							
Male	32	53.3	71	59.2	0.558	0.789	0.422-1.473
Female	28	46.7	49	40.8			
Occupation							
Unemployed	16	26.7	39	32.5	0.529	0.755	0.380-1.503
Employed	44	73.3	81	67.5			
Level of Education							
Low	14	23.3	31	25.8	0.855	0.874	0.423-1.803
High	46	76.7	89	74.2			
Marital Status							
Not Married	16	26.7	34	28.3	0.953	0.920	0.458-1.846
Married	44	73.3	86	71.7			
Clinical Stages							
III and IV	55	91.7	55	45.8	<0.001*	13.00	4.862-34.756
I and II	5	8.3	65	54.2			
CD4 levels (cell/mm^3)							
< 200	48	80	31	25.8	<0.001*	11.484	5.408-24.388
≥200	12	20	89	74.2			
Anemia Status							
Yes	43	71.7	33	27.5	<0.001*	6.668	3.345-13.293
No	17	28.3	87	72.5			
Opportunistic Infection							
Yes	32	53.3	20	16.7	<0.001*	5.714	2.842-11.488
No	28	46.7	100	83.3			

Reference categories: Female, Employed, High Education, Married, I and II Clinical Stages, ≥200 CD4 levels (cell/mm^3), No Anemia Status, and No Opportunistic Infection.

Table 2. Multivariable logistic regression modeling to assess the risk of HIV CO-Infection

Variables	p-value	Adjusted OR	95% CI
CD4 Levels	0.007	3.928	1.463-10.547
Clinical Stages	0.130	2.728	0.745-9.987

Variables	p-value	Adjusted OR	95% CI
Anemia Status	0.206	1.769	0.730-4.286
Opportunistic Infection	0.257	1.623	0.702-3.750

Logistic regression; significant at $p < 0.05$

DISCUSSION

CD4 levels (OR 3.928 (1.463-10.547)) were the most influential and predictive factor for TB-HIV incidence in patients with HIV. Individuals whose CD4 count was less than 200 cells/mm3) had nearly 3.928-times greater chance of developing HIV TB compared to those whose CD4 count exceeded 200 cells/mm3.

Other factors such as clinical stage, anemia status, and opportunistic infections also affected the incidence of TB-HIV as confounding variables. The study shows that 80% of TB PLWHA had CD4 count below 200 cells/mm3. The average CD4 cell count in cases was 128.3 cells/mm3, with a median of 9.1 cells/mm3, which was lower than the average CD4 count in the controls (360.12 cells/mm3), whose median was 309.5 cells/mm3.

The CD4 cell count was regularly used as an indicator of HIV disease progression to monitor infection (Maartens, Celum and Lewin, 2014) This finding is consistent with a previous study, which reported that 75% of TB-HIV patients had CD4 levels lower than 350 cells/mm3. Poor CD4 cell count in people living with HIV/AIDS (PLWHA) was affected by delays in accessing ART therapy and adhering to medication. Access to health facilities, low socioeconomic factors, and spatial conditions also influenced CD4 cell count in PLWHA (Maore *et al.*, 2017; Sifuna *et al.*, 2019).

Currently, early initiation of ART (Antiretroviral Therapy) is still considered the gold standard for co-infection controlling in individuals having HIV/AIDS (PLHWA). The ART treatment program could elevate CD4 cell count and decrease extrapulmonary TB cases. A low CD4 level can lead to the chances of death (Kamath *et al.*, 2013; Kaplan *et al.*, 2018). Additionally, children with under-threshold CD4 levels came with a 1.9-fold greater chance of developing anemia than children having CD4 counts above the threshold (Chanie *et al.*, 2021).

The presence of active tuberculosis (TB) in people with HIV is associated with two primary mechanisms, either a higher likelihood of latent TB becoming active, or a greater vulnerability to infection with *M. tuberculosis* (Bruchfeld, Correia-Neves and Källenius, 2015). Mtb-CD4+-specific Th1 cells, which are a specific type of CD4+ T cell subsets, are believed to play a protective role against TB infection. Including IFN-γ or TNF-α, these cells produce cytokines, facilitating the activation and recruitment of innate immune cells, e.g., granulocytes and monocytes. Th1 cells also play a crucial role in the activation of effector functions in macrophages, controlling Mycobacterium tuberculosis. Additionally, CD4 T cell levels in the peripheral blood in infants with HIV decrease (Prezzemolo *et al.*, 2014).

The findings of this study suggest that anemia is linked to the occurrence of co-infection between tuberculosis (TB) and HIV. The respondents with both HIV and TB had an average hemoglobin (Hb) level of 9.68 g/dl, which was lower than the average Hb level of non-TB HIV respondents (11.79 g/dl). Furthermore, in terms of the median Hb level, those with HIV-TB had a median level of 9.1 g/dl, while in non-TB HIV respondents, the level was 11.85 g/dl. It conforms to Dhurve and Dhurve (2013) who showed hematological disorders, such as pancytopenia, were common complications of HIV infection, and anemia was the most prevalent disorder. Anemia in HIV patients

could be used as a useful clinical indicator to predict and evaluate their immune status (Dhurve and Dhurve, 2013).

Children with HIV infection are at risk of developing anemia, which is further increased by a combination of factors including WHO clinical stages III and IV, CD4 levels below a certain threshold, and poor treatment adherence. Specifically, the risk of anemia is significantly higher in children experiencing WHO stages III and IV, with a 4.2-fold increase compared to those in stages I and II (Chanie *et al.*, 2021). Syphilis is a commonly co-occurring infection among individuals with HIV, particularly in men performing sexual intercourses with other men (MSM). Syphilis is a sexually transmitted disease also known as syphilitic sores. It damages mucosal barriers and escalates the risk of getting infected with HIV. The incidence rate of syphilis has ranged from 2.9 to 6.2 per hundred people in the Western world (Mahmud *et al.*, 2023).

Hepatitis B Virus (HBV) is another common co-infection experienced by people with HIV. The global prevalence of HIV co-infected with HBV is between 5-20%. Chronic HBV infection is significantly affected by HIV infection, with other effects, such as heightened HBV DNA levels, quicker advancement of liver diseases, and greater mortality due to liver-related causes. When on suppressive antiretroviral therapy, people who have both HIV and HBV infections confront an elevated liver disease risk and mortality related to liver conditions (Singh *et al.*, 2017). The findings of this study also demonstrate that the clinical stage is a confounding variable affecting the occurrence of co-infection. Clinical symptoms and the degree of immune impairment can increase the suspicion of HIV-TB co-infection (Li *et al.*, 2023).

The diagnostic approach for HIV during acute or early infection and initiating early HIV treatment quickly suppresses viremia, resulting in better clinical outcomes for individuals. This approach is highly beneficial for public health in limiting HIV transmission and suppressing the progression of clinical stages (Ulrich *et al.*, 2022). There were no reported cases of TB infection in HIV-positive patients with clinical stage 1 and 2. However, according to Roselinda's (2015) study, individuals in stage 4 of HIV infection with immunosuppression have a higher risk of developing TB infection than those without immunosuppression.

Results also show the correlation between HIV co-infection and the clinical stage. In addition, the proportion of HIV sufferers who had co-infection with pulmonary TB was more at clinical stages 3 and 4 (91.7%), while the proportion of HIV patients who did not suffer from co-infection was more at clinical stages 1 and 2. From the results of this study we can know that people with HIV with co-infection have an advanced clinical stage. When the confirmation of HIV infection through serological and/or virological evidence is achieved, clinical staging can be undertaken (WHO, 2005).

People who are HIV positive and fall into clinical stage 1 either experience a symptom-free condition or have persistent generalized lymphadenopathy for over six months. Clinical stage 2 shows symptoms of unexplained weight loss of under 10% of total body weight, recurring respiratory infections (e.g., pharyngitis, otitis media, bronchitis, and sinusitis), many different skin-related ailments (e.g., fungal nail infections, seborrheic dermatitis, pruritic papular eruptions, recurrent oral ulceration, angular cheilitis, and herpes zoster flares) (Zaongo *et al.*, 2022).

Clinical stage 3 presents more severe symptoms such as persistent diarrhea lasting for more than one month without any clear explanation, the loss of more than 10% of total body weight, severe systemic bacterial infections, e.g., bacteremia, bone and joint injections, meningitis, pyomyositis, empyema, pyelonephritis, and pneumonia. The ultimate phase, clinical stage 4 includes all

AIDS-defining diseases, such as Kaposi's sarcoma, esophageal candidiasis, chronic orolabial herpes simplex infection lasting over a month, CBS toxoplasmosis, HIV encephalopathy, extrapulmonary tuberculosis, radiological or recurring severe bacterial pneumonia, pneumocystis pneumonia (PCP), and HIV wasting syndrome (WHO, 2005; Zaongo *et al.*, 2022).

Health issues related to the immune systems and others which arise over the period of HIV infection, especially its acute and chronic phases, become considerably worse during the phase of AIDS. At this point of HIV infection, individuals may have an elevated amount of virus in the body and CD4+ T cell count which can be below 200 cells/mm^3, making him susceptible to Mycobacterium avium and Mycobacterium tuberculosis complex infections (Zaongo *et al.*, 2022). Therefore, early treatment is needed aligned with guidelines for carrying out treatments which can reduce advanced HIV and co-infection risks (Marchionatti and Parisi, 2021).

Cascading HIV care requires HIV diagnosis. Timely identification and management significantly decreases illness and enhance the chances of survival for individuals who are HIV-positives (PLWHA). Effective HIV testing services and quality HIV surveillance programs can reduce the risk of HIV co-infection (Grinsztejn *et al*., 2014; Haddad *et al*., 2019) It turns out that many people living with HIV (PLHIV) come to health facilities to access treatment at the final stage of the disease. Various factors result in treatment delay including geographic, social, economic and individual behavioral issues (Drain *et al*., 2013)

The findings of this study also demonstrate that the anemia status is a confounding variable affecting the occurrence of co-infection. HIV-AIDS infected individuals often experience anemia, a frequent hematological complication which can result in severe consequences. The implications of this occur vary from relationship with disease development to decreased survival, quality of life, to functional decline (Ageru *et al*., 2019). HIV and anemia co-infection have multifactorial causes. HIV presence in the body can have both a direct and indirect impact on the viability and operation of hematopoietic stem/progenitor cells (HSPCs) found in the bone marrow (Marchionatti and Parisi, 2021).

Drug toxicity, nutritional deficiencies, chronic diseases, and opportunistic infections are among factors contributing to anemia development in PLWHA. HIV has the ability to either directly or indirectly damage CD4+ T cells, while it tends to remain inactive in macrophages for an extended period with sporadic instances of reactivation. This is due to bacterial, viral and fungal infections in the patient's body (Ageru *et al*., 2019).

TB/HIV co-infection remains high in people living with HIV/AIDS (PLWHA). The CD4 count is the most significant predictor of increased risk for HIV-TB co-infection. It is also crucial to pay attention to the clinical stage of PLWHA, their anemia status, and other opportunistic infections. To control this co-infection, it is essential to have strict TB-HIV surveillance in place so that data sources and related information can be recorded accurately. Compliance with holistic treatment is necessary to prevent the emergence of various opportunistic infections and malignancies in PLWHA patients. Proper holistic care is crucial to improving patients' conditions (Ageru *et al.*, 2019).

Individuals who have HIV and are living with the condition are highly susceptible to anemia because of opportunistic infections and insufficient iron intake (Abioye *et al*., 2020). Among HIV-positive patients, anemia is considered an unfavorable indicator and increases the likelihood of a higher mortality rate compared to those not having anemia. This population-based

study shows that the prevalence of anemia among PLWHA varies from 1.3% to 95%, Meanwhile, the prevalence of HIV positive anemia with clinical AIDS ranges from 63-95%.A number of factors explain the variation in anemia among PLWHA, including differences in anemia criteria, HIV disease progression, and ART status (Li, Jin and Li, 2017; Ageru *et al.*, 2019)

In acute, severe, or life-threatening anemia, standard treatment is necessary, such as Standard treatments, e.g., drug therapy as well as blood transfusions are imperative for cases of life-threatening, severe, or acute anemia; therefore, it is critical to monitor the evolution of blood counts during HIV infection, to detect the development of hematological disorders and to carry out the necessary clinical interventions to avoid comorbidities. The World Health Organization recommends iron supplementation, which is considered an effective means of preventing and treating iron deficiency anemia, as a fundamental component of prenatal care and preventive measures for children in settings with a high incidence of anemia, despite their HIV statuses (WHO, 2016). The limitation of this study is that a significant number of medical records were incomplete, resulting in missing potential data, which could impact the generalizability of the results. Furthermore, this study revealed information bias due to incomplete medical records. Despite these limitations, the study's findings can serve as a foundation for implementing a co-infection control policy that is more effective. Early and consistent treatment options may help raise CD4 levels and decrease the likelihood of co-infection occurrence.

CONCLUSIONS

CD4 levels becomes the most dominant variable affecting the risk of HIV TB in people living with HIV after controlling the variable clinical stages, anemia status, and opportunistic infection.

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