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ORIGINAL ARTICLE

PREDICTOR OF ANEMIA AMONG PEOPLE LIVING WITH HIV TAKING TENOFOVIR+LAMIVUDINE+EFAVIRENZ THERAPY IN JAYAPURA, PAPUA

Prediktor Anemia pada Orang Hidup dengan HIV yang Menjalani Terapi Tenofovir+Lamivudine+Efavirenz di Jayapura, Papua

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ABSTRACT

Background: The most common hematological abnormality among people infected with Human Immunodeficiency Virus (HIV) is anemia. This is also related to high mortality risk among patients receiving Antiretroviral Therapy (ART). **Purpose:** This study aimed to identify predictors of anemia among HIV patients taking ART using a regimen of the single-tablet drug contain tenofovir, lamivudine, and efavirenz in Jayapura, Papua. **Methods:** This was a cross-sectional study conducted at Jayapura regional hospital from June to September 2017. A total of 80 HIV patients were eligible for analysis. Data collection was conducted through an interview, medical record, measurement, and laboratory assay. The significance of differences among categorical variables was analyzed using Fisher's exact test. The variables with $p < 0.25$ were then analyzed using binary logistic regression to determine predictors associated with anemia. A threshold of $p < 0.05$ indicates statistical significance. **Results:** This study showed that Body Mass Index (BMI) <18.50 ($p = 0.01$; OR = 5.63; 95% CI = 1.43 < OR < 22.19), length on ART ≤12 months ($p = 0.00$; OR = 4.90; 95% CI = 1.65 < OR < 14.53), and Cluster of Differentiation 4 (CD4+) percentage out of normal ($p = 0.02$; OR = 0.19; 95% CI = 0.05 < OR <0.77) had a significant association with anemia. **Conclusion:** BMI, length on ART, and CD4+ percentage were predictors of anemia among HIV patients taking antiretroviral therapy containing tenofovir, lamivudine, and efavirenz regimen in Jayapura.

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ABSTRAK

Latar Belakang: *Abnormalitas hematologi paling umum pada orang dengan infeksi human immunodeficiency virus (HIV) adalah anemia. Anemia juga berkaitan dengan risiko mortalitas yang tinggi pada pasien dengan terapi antiretroviral.* ***Tujuan:*** *Penelitian ini bertujuan untuk mengidentifikasi prediktor kejadian anemia pada pasien HIV yang menjalani terapi minum obat tablet-tunggal antiretroviral regimen tenofovir/lamivudine/efavirenz di Jayapura.* ***Metode:*** *Penelitian ini menggunakan desain cross-sectional yang dilaksanakan dari bulan Juni sampai September 2017 di Rumah Sakit Umum Daerah Jayapura, Papua. Sebanyak 80 pasien HIV bersedia berpartisipasi dan sesuai inklusi. Pengumpulan data dilakukan melalui wawancara, rekam medis, pengukuran, dan pemeriksaan laboratorium. Perbedaan signifikan antar variabel ditentukan menggunakan uji Fisher exact. Variabel dengan p < 0,25 kemudian diuji dengan regresi logistik untuk menentukan variabel (prediktor) yang berkaitan dengan anemia dengan p < 0,05 menunjukkan signifikansi.* ***Hasil:*** *Penelitian menunjukkan Indeks Massa Tubuh (IMT) <18,50 (p = 0,01; OR = 5,63 ; 95% CI = 1,43 < OR < 22,19), lama waktu terapi antiretroviral ≤12 bulan (p = 0,00; OR = 4,90 ; 95% CI = 1,65 < OR < 14,53), dan persentase Cluster of Differentiation 4 (CD4+) di luar batas normal (p = 0,02; OR = 0,19; 95% CI = 0,05 < OR <0,77) memiliki hubungan bermakna dengan anemia.* ***Kesimpulan:*** *IMT, lama waktu terapi antiretroviral, dan persentase CD4+ di luar batas normal merupakan prediktor kejadian anemia pada pasien HIV yang menjalani terapi menggunakan obat antiretroviral regimen tenofovir/lamivudine/efavirenz di Jayapura.*

INTRODUCTION

Anemia is the most common blood cell abnormality among people living with human immunodeficiency virus (PLHIV) (Harding et al., 2020). Anemia causes hemoglobin to be not sufficient to fulfill the individual's physiological needs. This may decrease work productivity, cause neurological development disorder, and increase mortality (1). Anemia is associated with a higher mortality risk in PLHIV receiving highly active antiretroviral therapy (2).

Anemia prevalence among PLHIV taking antiretroviral therapy (ART) has been reported, especially among those who use zidovudine in their drug regimen (3). A study in Uganda reported that the prevalence of anemia is lower among PLHIV taking a tenofovir-based regimen (11%) than those taking a zidovudine-based regimen (13%) (4). Another study in India found the anemia prevalence among PLHIV taking tenofovir lamivudine efavirenz (TLE) is lower (8%) than those taking zidovudine lamivudine nevirapine (20%) combination regimen (5). Study in Ethiopia stated that anemia prevalence among PLHIV taking tenofovir is 13.20% and among those taking zidovudine is 20.31% (6). Nevertheless, there is less information about anemia among PLHIV taking TLE therapy in Jayapura, Papua. The factors associated with anemia risk during ART initiation were female, low body mass index, WHO clinical stage 3-4 of HIV infection, and low cluster of differentiation 4 (CD4+) count (7).

Fixed dosed combination (FDC) as a single-tablet regimen containing TLE exhibits excellent efficacy and safety for first-line ART (8). Therefore, this FDC is preferred as a regimen for first-line ART programs among PLHIV in Indonesia (9), including at regional hospitals in the Papua region. Previous studies about TLE in Papua were associated with bodyweight increase (10), and CD4+ counts increase among PLHIV after taking ART (11). Nevertheless, the information regarding anemia among PLHIV taking TLE regimen in Papua is still underreported. This study aimed to identify predictors of anemia among PLHIV taking ART using a single-tablet drug-containing tenofovir+lamivudine+efavirenz (TLE) in Jayapura, Papua.

METHODS

This was a cross-sectional study. The participants were PLHIV receiving FDC therapy of TLE drugs regimen at voluntary counseling and testing (VCT) at Jayapura regional hospital in Jayapura City, Papua province of Indonesia, from June to September 2017. The participants who were male and female, aged 15 and above 15 years old, HIV positive and receiving antiretroviral therapy-naive, and agreeing to participate were included. PLHIV with severe pain (hospitalized), pregnant, and had incomplete data were excluded from the study. Participants were recruited using consecutive sampling. A total data of 80 PLHIV were eligible for analysis.

Anemia was the dependent variable in this study. The independent variables for analysis were gender (male, female), age (15-45 years old, >45 years old), body mass index (BMI <18.50, BMI ≥18.50), tuberculosis (Tb, without Tb), WHO clinical stage (stage 1-2, stage 3-4), length on ART (≤12 months, 13-24 months), adherence to ART (adherence ≤95%, adherence >95%), CD4+ percentage (normal value (30-60%), out of normal value) and total CD4+ counts (CD4+ ≤350 cells/mm³, CD4+ >350 cells/mm³).

Demographic (gender, age) and relevant clinical data information (TB status, WHO clinical stage, length on ART, adherence to therapy) from PLHIV interviews and medical record files were assessed. BMI was calculated from the measurement of PLHIV body weight and body height. Laboratory profiles of CD4+ percentage, total CD4+ counts, and Hb concentration were measured using BD facscount system (Becton Dickenson, California, USA).

Anemia was diagnosed as hemoglobin (Hb) level < 13 g/dL (men) and < 12 g/dL (women). BMI values <18.50 were categorized as underweight or malnutrition. Moderate and severe immunodeficiency were grouped as CD4+ ≤350 cells/mm³. Mild and without immunodeficiency were grouped as CD4+ >350 cells/mm³. Good adherence to ART was categorized as adherence >95% (PLHIV forgot to take antiretroviral drugs less than three doses within 30 days). CD4+ percentage is the percentage of white blood cells that are CD4+ T lymphocytes (CD4 cells). Normal CD4+ percentage was within the range of 30-60%.

Characteristics of PLHIV were presented as numbers and percentages in each variable. Prevalence of anemia was shown as percentages with corresponding 95% CIs. The significance of differences among variables was determined using Fisher's exact test. Variables with $p < 0.25$ from Fisher's exact were then analyzed using binary logistic regression and backward stepwise methods. The ORs with 95% CIs from logistic regression analysis was used to determine the variable as predictors associated with anemia among this study's participants. Two-tailed statistical tests were used where a statistical significance was indicated by the threshold of p-value < 0.05. All data were analyzed using IBM SPSS statistic 21.

This study received ethical approval from the Ethics Committee of the National Institute of Health Research and Development, Ministry of Health of Republic Indonesia, with reference number LB.02.01/2/KE.118/2017, on April 3, 2017.

RESULTS

The characteristics of this study population were presented by the sociodemographic and clinical variables. From a total of 80 PLHIV, most of them were females (61.20%), aged 15-45 years old (93.80%), had BMI ≥18.50 (81.30%), without TB (91.30%), had WHO clinical stage 3-4 (67.50%) in the early ART, already receiving therapy for 12-24 months (65.50%), had adherence >95% (53.80%), had CD4+ percentage out of normal value (81.20%), had total CD4+ counts >350 cells/mm³ (58.80%), and experienced anemia (50.00%; see Table 1).

Among 80 PLHIV, 40 (50.00%) had anemia. PLHIV with anemia were about 55.10% of females and 41.90% of males. The anemia prevalence among them with BMI <18.50 was 73.30% (p=0.08), while those with a length on ART ≤12 months was 71.40%, which was higher than those with a length on ART 13-24 months (p=0.01). The anemia prevalence among them was 44.6% (p=0.08; see Table 2).

The final regression model in this study was represented by logistic regression. The BMI <18.50, length on ART ≤12 months, and CD4+ percentage out of normal value were significantly associated with a higher risk of anemia incidence among PLHIV. The risk of BMI <18.50 on the incidence of anemia OR=5.63 ; 95% CI (1.43 < OR < 22.19); p=0.01 with α=0.05. The risk of length on ART ≤12 months on incidence of anemia was OR=4.90 ; 95% CI (1.65 < OR < 14.53); p=0.00 with α=0.05. The risk of CD4+ percentage out of normal value on anemia

incidence was OR=0.19; 95% CI (0.05 < OR <0.77); p=0.02 with α=0.05 or (see Table 3).

Table 1
Sociodemographic and Clinical Characteristics of PLHIV

Variable	Frequency	%
Gender		
Female	49	61.20
Male	31	38.80
Age groups, years		
>45	5	6.20
15-45	75	93.80
Body mass index		
BMI <18.50	15	18.70
BMI ≥18.50	65	81.30
TB status		
TB	7	8.70
Without TB	73	91.30
WHO clinical stage		
Stage 3-4	54	67.50
Stage 1-2	26	32.50
Length on ART		
≤12 months	28	35.00
13-24 months	52	65.00
Adherence to therapy		
≤95%	37	46.20
>95%	43	53.80
CD4+ percentage		
Out of normal value	65	81.20
Normal value (30-60%)	15	18.80
Total CD4+ count		
≤350 cells/mm³	33	41.20
>350 cells/mm³	47	58.80
Anemia status		
Anemia	40	50.00
Without anemia	40	50.00
Total	80	100.00

DISCUSSION

Females were the most PLHIV in this study. The HIV case among women is increasing from time to time. Women are vulnerable and often face the risky condition of HIV transmission (12). The complexity of women's biological reproductive structure and also complicated socioeconomic factors altogether could be the reasons causing women to be infected by HIV (13).

The highest number of PLHIV in our study were within the productive age of 15-45 years old. People in this age group had a higher risk to be infected by HIV. A study showed that HIV incidence was highest among the partnership of women aged 15-24 years old with men aged 30–34 years old. These play a crucial role in increasing HIV transmission (14).

Our study found that the number of PLHIV who had normal BMI or BMI ≥18.50 was higher than those with low BMI or malnutrition, although most of them already suffered from WHO clinical stage 3-4 in the early therapy. Based on WHO's guidelines, the HIV-infected individuals with WHO clinical stages 3-4 were signed by loss of body weight or wasting syndrome and opportunistic infections due to their immune deficiency system. Generally, the individual in this stage has low BMI and also commonly suffers from TB (15).

The risk factors for anemia among PLHIV include malnutrition or low BMI and disease infection (1). Good BMI and without TB among participants in our study indicated that the TB treatment and ART were effective, at least for about one year of ART. The prime concern for HIV-TB patients is to start TB treatment, followed by co-trimoxazole and ART immediately within the first eight weeks of initiating TB treatment. ART suppresses the viral load that affects immune system recovery (16).

Only 53.80% of PLHIV in our study had good adherence to therapy. Good adherence is crucial to improve the quality of life of people living with HIV and prevent mortality incidence and drug resistance events (17). Based on CD4+ measurement in our study, most of the PLHIV had mild and without immunodeficiency, shown by the CD4+ counts >350 cells/mm³, even though most of them have CD4+ percentage within out of normal value. These might indicate good recovery of the PLHIV's immune system after taking ART of TLE. The first line of antiretroviral drug works by inhibiting the virus reverse transcriptase enzyme activity, thus disturbing the HIV replication within the CD4+ cells T lymphocytes (18).

Half of the PLHIV were suffering from anemia in this study. Anemia incidence among people suffering from HIV may be caused by factors such as WHO clinical stage 3-4 of HIV infection, nutritional status, and ART regimen (19). Nutrient absorption disorder and gastro-intestinal diseases may lead to anemia, particularly in WHO clinical stages 3-4 of HIV infection. Nutritional anemia as deficiencies of iron, B12, and folic acid, also infections of parasites might contribute to the variations in the prevalence of anemia among HIV patients (20,21).

Table 2
Prevalence of Anemia and Sociodemographic-Clinical Parameters among PLHIV

Variable	Anemia		Without anemia		*p*	OR	95% CI
	n	%	n	%			
Gender							
Female	27	55.10	22	44.90	0.36	1.69	0.69–4.22
Male	13	41.90	18	58.10			
Age groups (years)							
>45	1	20.00	4	80.00	0.36	0.23	0.03–2.16
15-45	39	52.00	36	48.00			
Body mass index							
BMI <18.5	11	73.30	4	26.70	0.08*	3.41	0.98–11.58
BMI ≥18.5	29	44.60	36	55.40			
TB status							
TB	5	71.40	2	28.60	0.43	2.71	0,49–14.90
Without TB	35	47.90	38	52.10			
WHO clinical stage							
Stage 3-4	26	48.10	28	51.90	0.81	0.79	0.31–2.03
Stage 1-2	14	53.80	12	46.20			
Length on ART							
≤12 months	20	71.40	8	28.60	0,01*	4.00	1.48–10.79
13-24 months	20	38.50	32	61.50			
Adherence to therapy							
≤95%	18	48.60	19	51.40	1.00	0.90	0.38–2.18
>95%	22	51.20	21	48.80			
CD4+ percentage							
Out of normal value	29	44.60	36	55.40	0.08*	0.29	0.08–1.02
Normal value	11	73.30	4	26.70			
Total CD4+ count							
≤350 cells/mm³	17	51.50	16	48.50	1.00	1.11	0.46–2.70
>350 cells/mm³	23	48.90	24	51.10			
Total	40	100.00	40	100.00			

Table 3
Predictors of Anemia among Participants in the Logistic Regression Model

Risk factor	*p*-value	OR	95% CI
Body mass index			
BMI <18.50	0.01*	5.63	1.43–22.19
BMI ≥18.50			
Length on ART			
≤12 months	0.00*	4.90	1.65–14.53
13-24 months			
CD4+ percentage			
Out of normal value	0.02*	0.19	0.05–0.77
Normal value			

*significant if p-value < 0.05 (α=0.05

More female PLHIV had anemia in this study. In line, the prevalence of anemia was higher among women, both in non-pregnant women of reproductive-age 18–44 years old and women aged <51 years old (22). Women of reproductive age are commonly suffering from iron deficiency because of menstrual blood loss, and need a high demand for iron during pregnancy and lactation but experience malnutrition. Low socioeconomic status, such as less source of drinking water and unimproved toilet facility, also had an impact on anemia incidence among them (23).

Anemia was higher among PLHIV within the age group of 15-45 years old in this study. Another

study found that the mild anemia prevalence increases with age, but moderate and severe anemia is associated inversely with age increases. The majority of the cells in mild anemia are normocytic, in moderate anemia are microcytic, while most of the cells in severe anemia are macrocytic. Normocytic was the most common anemia, which was mostly experienced by the elderly aged 61-85 years old (24). Anemia in the elderly was associated with increasing age, hospitalization, and chronic diseases such as diabetes than malnutrition (25).

Our study showed there are more PLHIV with TB who were suffering from anemia than without anemia, but this TB status is not related significantly to anemia. A study reported that cotrimoxazole prophylaxis treatment on PLHIV with TB coinfection was the factor associated with anemia incidence. The possible explanation could be that trimethoprim, one of the cotrimoxazole ingredients, is a weak inhibitor of dihydrofolate reductase which can inhibit folic acid metabolism through increasing folate catabolism or inhibiting folate absorption. High doses of trimethoprim have been implicated in megaloblastic changes, especially in HIV-TB patients who have experienced malnutrition or are not on folate supplementation (6).

Megaloblastic is drug-induced anemia. This disease is characterized by abnormal hematopoietic cell morphology and unproductive hematopoiesis. However, patients with adequate stores of folate or vitamin B12 are not at risk for drug-induced megaloblastic (26). Based on Fisher's exact test, only the length on ART was associated significantly with anemia incidence among PLHIV in this study. However, the final logistic regression showed not only the length on ART but also BMI and CD4+ percentage out of normal value were significantly related to anemia incidence among them.

The PLHIV with length on ART ≤12 months had 4.90 times higher risk for suffering from anemia than those who had already taken ART 13-24 months. This study showed that anemia incidence was higher among them with a length on TLE therapy of less than one year. Another study reported that a quick start of HAART might help to decrease the prevalence of anemia and its subsequent complications. This was significantly associated with reducing anemia comorbidity in pediatric HIV patients. The ability of ART to prevent opportunistic infections can reduce the negative impact of retroviral infections on bone marrow cells by increasing the growth of hematopoietic progenitor cells (21).

ART using the TLE regimen in this study might have the beneficial effect of reducing the frequency of anemia, the opposite of zidovudine (ZDV)-based ART regimens. Another study reported that severe anemia or macrocytic among HIV patients was related to ZDV. ZDV plays a role by inhibiting viral reverse transcriptase and mammalian cellular DNA polymerase. It competes with natural deoxynucleoside triphosphates to bind reverse transcriptase and deoxynucleoside triphosphates for incorporation into newly synthesized DNA viral strands. Thus, it disturbs DNA replication and the cell division of erythroblasts, causing macrocytosis in mature erythrocytes (27).

We found that PLHIV with a BMI value less than 18.50 had 5,63 times higher risk for suffering from anemia. BMI value less than 18.50 among them in this study was associated with malnutrition (28). Another study found that both weight loss and wasting were seen in those who had failed ART, and those who were ART-naïve. The primary cause for weight loss in PLHIV is inadequate calorie intake, while wasting is associated with low serum albumin levels and deficiency of essential micronutrients like iron, B12, folic acid, zinc, and selenium. Various causes of anorexia include oral and or esophageal candidiasis, and ART adverse effects also lead to HIV wasting. These may impact anemia incidence among them (29).

The PLHIV with normal CD4+ percentage had a 5,26 higher possibility to have not experienced an anemia incidence than those who had CD4+ percentage out of normal value. The prevalence of PLHIV with a CD4+ percentage out of normal value suffering from anemia was higher than those whose CD4+ percentage was within the normal value. Another study found that white blood cells <5.0 x 109/L and CD4+ <200.0 cells/µL were found to be associated with an increase in anemia among PLHIV (30). TLE regimen is preferred as one of the regimens in the ART program for PLHIV. This regimen is safer than other regimens consisting of ZDV and disturbs the cell division of erythroblasts which causes anemia. However, the anemia among PLHIV taking the TLE regimen should be countered by developing the PLHIV body mass index value through improved nutrition intake during the ART program, also in conducting early detection of HIV tests for an individual with a high risk of HIV transmission, then supporting

them to take ART regimen as quickly as possible. These actions may recover the CD4+ count to normal and delay the worst infection by the WHO clinical stage 3-4 of HIV infection that contributes to anemia incidence among PLHIV.

CONCLUSION

The predictors of anemia among people living with HIV taking antiretroviral therapy containing fixed dosed combination of single-tablet TLE regimen drug in Jayapura were body mass index value, length on antiretroviral therapy, and CD4+ percentage.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

SA: Conceptualization, writing-original draft preparation, methodology, software, reviewing. TNK: Data curation, validation, writing-reviewing. MW: Methodology, writing- reviewing, supervision. TW: Visualization, editing.

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