

Original Article

THE IMPACT OF ANTIRETROVIRAL THERAPY ON HEMOGLOBIN LEVELS OF HIV/AIDS PATIENTS AT MERPATI CLINIC, WANGAYA HOSPITAL, DENPASAR, BALI, INDONESIA

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ABSTRACT

Objective: Anemia is responsible for poor outcomes in HIV/AIDS patients. It's related to disease progression, morbidity, and mortality. Antiretroviral therapy (ART) agent, zidovudine (ZDV) is also known to trigger anemia in the early initiation. However, studies found improved hemoglobin (Hb) levels of HIV/AIDS patients several months after ART routinely taken. This study aims to find the impact and correlation of ART on the hemoglobin level of HIV/AIDS patients.

Methods: A retrospective cohort study was done at Merpati Clinic, Wangaya Hospital, Denpasar-Bali, Indonesia. Data were collected from medical records and laboratory results. A total sample of 64 HIV/AIDS patients with at least 6 mo on ART was included in this study.

Results: Anemia was found in 34 (53.1%) of patients before ART initiation. After taking ART for 6 mo, we observed a significant improvement in patients' hemoglobin levels, 48 (75%) shows increased hemoglobin levels. The paired t-test revealed a correlation between ART and Hb level ($p < 0.001$). Fourteen (43.8%) patient taking ZDV shows no improvement, even declining of Hb level. Chi-square analysis performed with $p = 0.001$ to ZDV and lower or no improvement of hemoglobin level. Both results considered statistically significant (p -value less than 0.05) with a confidence interval (CI) of 95%. Relative risk (RR) of no improvement or decline in Hb level is 7 folds higher in the ZDV group than the non-ZDV group.

Conclusion: This study concludes that ART affects hemoglobin levels in HIV/AIDS patients. Zidovudine regimen is more prone to lower or no increase of Hb.

Keywords: Antiretroviral therapy, Anemia, Hemoglobin, HIV/AIDS

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INTRODUCTION

Anemia is considered as a frequently found hematological problem affecting more than one-third of HIV patients [1, 2]. Previous researches have reported that the prevalence of anemia in HIV naïve patients varies between 25.8-34.6% [2-4]. However, other studies found a higher prevalence of anemia in 71-86.4% of HIV/AIDS patients. Anemia in HIV patients correlates strongly to disease progression, morbidity, and mortality. Routine screening of anemia should be done and anemia should be properly addressed in HIV patients [5-7].

Human Immunodeficiency Virus is known to lead inflammatory cytokines discharge, erythropoiesis disturbance, depletion of hematopoietic growth factors, with malabsorption and ineffective iron recycling and eventually causing anemia [3, 6]. Several drugs in the standard regiment of Antiretroviral Therapy (ART) such as zidovudine (ZDV) affect hematopoiesis, thus contributes to anemia. The decrease of CD4 counts also strongly associated with the severity of anemia [8, 9]. Anemia can be classified into a few groups, based on the severity (mild, moderate, and severe anemia). Mild anemia is described as a hemoglobin level of 11-11.9 g/dl. Moderate anemia is when the hemoglobin level 8-10.9 g/dl. The diagnosis of severe anemia is made if the hemoglobin level is <8 g/dl [7, 10].

Antiretroviral therapy (ART) should be initiated as soon as the diagnosis of HIV infection was made. This early administration of ART aims to suppress the viral load, restore the immune system, and improve the clinical outcome in HIV patients. From a medical perspective, ART has turned the HIV diagnosis to chronic disease instead of terminal disease [9, 11]. Yesuf T *et al.* reported that ART initiation reduces the prevalence of anemia in HIV patients after 6 mo and 12 mo [1]. The same result also comes from another study in Ethiopia. They found that after 6 mo of ART initiation, the hemoglobin level increased significantly [7]. Another study reported

that ZDV triggers anemia in HIV patients, especially 1 to 3 mo after initiation. Tamir *et al.*, compared anemia on two groups of HIV patients. The first group is taking non-zidovudine ART and second group on ART with zidovudine. It was later found that there was a higher risk of anemia in the zidovudine group [12]. More researches should be done to establish a clear role of ART in anemic HIV patients. This study aims to find the impact of ART on the hemoglobin level of HIV patients visiting Merpati Clinic, Wangaya Hospital, Denpasar-Bali, Indonesia.

MATERIALS AND METHODS

Research design

A retrospective cohort study was done in May 2020 at Merpati Clinic, Wangaya Hospital, Denpasar, Bali, Indonesia. The data for this study were collected from the patients' medical records. This study was granted an ethical clearance: 02/RSUDW/litbang/2020 from local Ethical Committee.

Population and sample of the study

The study was held at Merpati Clinic, Wangaya Hospital, Denpasar, Bali, Indonesia in May 2020. Consecutive sampling was done, and we obtained a total of 64 HIV/AIDS patients as participants. All of the participants of this study fulfilled the inclusion and exclusion criteria. The inclusion criteria are HIV/AIDS patients with the age of 18 y old and above, with minimum Antiretroviral therapy duration of 6 mo with a complete medical record. Pregnant and lactating women, patients with chronic renal disease, and patients with thalassemia were excluded from this study.

Variables and data sources

Beside demographic characteristic (age, sex, weight, education, marital status), variables used on this study are; HIV/AIDS staging,

types of anemia: mild (Hb level 11-11.9 d/dl), moderate (Hb level 8-10.9 d/dl), severe (Hb level <9 g/dl); hemoglobin level (before ART initiation and after ART initiation), types of regimen taken: tenofovir+lamivudine+efavirenz (Fixed Drug Combination/FDC or TDF/3TC/EFV), tenofovir+lamivudine+nevirapine (TDF/3TC/NVP), zidovudine+lamivudine+efavirenz (ZDV/3TC/EFV), and zidovudine+lamivudine+nevirapine (ZDV/3TC/NVP). Included also: CD4+level of <200 or \geq 200: and opportunistic infection. We collected patient's data from the medical record.

Data analysis

Patients' hemoglobin and ART initiation data were taken from the medical record and the laboratory result of the hematologic panel. The hemoglobin levels of the patient before starting ART and after taking ART for 6 mo were compared. Demographic characteristics such as gender, age, CD4 count, the severity of anemia, opportunistic infection, and regimen. The association between hemoglobin value before and after ART was analyzed using a paired t-test, while the correlation of zidovudine and lower hemoglobin level after ART were analyzed with the chi-square test. With a p-value of <0.05 and a 95% confidence interval considered statistically significant in both tests.

RESULTS

Before ART initiation

As shown in table 1, from 64 HIV/AIDS patients included in this study, the mean age is 43.88 y old, with a standard deviation (SD) of 9.667. The mean weight of the samples is 57.64 kilograms, with an SD of 9.037. Thirty-five males (54.7%) and 29 (45.3%) women were

included in this study. The overall prevalence of anemia was 34 (53.1%). Initial Hb level (before ART) mean \pm SD was 11.645 \pm 1.6768 g/dl. The CD4 count before ART started divided into two group, 51 (79.7%) patients with CD4<200 cell/mm³ and 13 (20.3%) patients with CD4 \geq 200 cell/mm³. Seventeen patients (26.6%) experienced opportunistic infection, and 62 patients (96.9%) of the sample were in the HIV stage. The most regimen used is the Fixed Drug Combination (TDF/3TC/EFV) of tenofovir, lamivudine, and efavirenz, account to 27 (42.2%) of the patients, followed by zidovudine, lamivudine, and nevirapine regimen (ZDV/3TC/NVP) taken by 22 (34.4%) patients.

After ART initiation

We found 48 (75%) of the patient shows improvement in hemoglobin levels. The other 16 (25%) didn't show improved hemoglobin levels or even decreased. The mean \pm SD of Hb value after ART is 12.756 \pm 1.7750 g/dl. Initial hemoglobin value (Mean = 11.645, SD = 1.6768) and Hemoglobin value after 6 mo of ART (Mean = 12.756, SD = 1.7750) were tested using paired t-test. Data on the hemoglobin level was normally distributed from the Kolmogorov-Smirnoff test, and the value of skew and kurtosis were estimated at 0.084 and -0.306, respectively. We also found that the correlation between the condition was estimated at $r = 0.350$, $p = 0.005$. This indicates a paired t-test is appropriate to use. From the analysis, it was found that there is a correlation between the initiation of ART and hemoglobin value in HIV patients, with a p-value <0.001 (table 2). Zidovudine containing regimen and risk of anemia (or lower Hb level) is also observed in table 3 with p-value = 0.001. Relative risk (RR) of the ZDV group compared to the non-ZDV group is 7 folds higher than in those without the ZDV regimen.

Table 1: Demographic characteristic of the participant before starting ART

Variables	n (%)	mean \pm SD	Median (min, max)
Age		43.88 \pm 9.667	42 (28,68)
Weight		57.64 \pm 9.037	56 (40,82)
Hb before ART initiation		11.645 \pm 1.6768	11.9 (8.1,15.1)
Hb after ART initiation		12.756 \pm 1.7750	12.7 (9.0,16.6)
Sex			
Male	35 (54.7)		
Female	29 (45.3)		
Education			
Elementary school	10 (15.6)		
Junior High School	9 (14.1)		
Senior High School	39 (60.9)		
University	6 (9.4)		
Marital			
Unmarried	2 (3.1)		
Married	49 (76.6)		
Widowed/Divorced	13 (20.3)		
HIV/AIDS staging			
HIV	62 (96.9)		
AIDS	2 (3.1)		
ART regimen			
TDF/3TC/EFV(FDC)	27 (42.2)		
TDF/3TC/NVP	5 (7.8)		
ZDV/3TC/EFV	10 (15.6)		
ZDV/3TC/NVP	22 (34.4)		
Anemia before ART			
Yes	34 (53.1)		
Mild Anemia	13 (20.3)		
Moderate Anemia	21 (32.8)		
No	30 (46.9)		
Hb improvement after ART			
Yes	48 (75)		
No	16 (25)		
CD4+count			
<200 cell/mm ³	51 (79.7)		
\geq 200 cell/mm ³	13 (20.3)		
Opportunistic infection			
Yes	17 (26.6)		
No	47 (73.4)		

Table 2: Mean hemoglobin (Hb) value

Variables	Mean±SD		Mean difference (95% CI)	t-statistic (df)	p-value
	Before ART initiation	After ART initiation			
Hemoglobin (g/dl)	11.645±1.6768	12.756±1.7750	-1.1109 (-1.6027, -0.6191)	-4.514 (63)	<0.001*

n=64, SD = standard deviation, CI= confidence interval, df = degree of freedom, *paired t-test

Table 3: Correlation of ZDV containing ART regimen with hemoglobin (Hb) level

Variables	No increase of Hb (%)	Increase of Hb (%)	N	χ^2 statistic (df)	p-value
ART with ZDV	14 (43.8)	18 (56.3)	32	12 (1)	0.001**
ART without ZDV	2 (6.3)	30 (93.8)	32		

**chi-square, RR (Relative Risk) = 7

DISCUSSION

Anemia is dubbed as a marker of disease progression in HIV/AIDS and associated with poor outcomes. The initiation of ART is believed to reverse this condition, marked by an increase in hemoglobin level and associated with better survival (prognosis) [14, 15]. Anemia prevalence in HIV/AIDS patients varies greatly. In this study, we found the prevalence of anemia of 53.1%. Panwar A *et al.* reported that 86.4% of HIV patients experience anemia, while other studies found a 38.8% prevalence of anemia in HIV patients [6, 14]. Among the anemia prevalence, a study in Ethiopia declares that 84.1% of HIV patients had mild anemia, and 15.9% had moderate anemia [7]. While we found about 20.3% had mild anemia, and 32.8% had moderate anemia.

Based on the statistical analysis of this study, we found that the mean hemoglobin level increased after the patient taking ART at least for 6 mo. This finding accompanied by the p-value of <0.001, which shows there was a significant correlation of hemoglobin level and ART. Previous researches also reported similar findings in which ART was found to increase the Hb level of HIV patients [1, 8, 13]. The mean value of Hb before ART is 11.645±1.6768, and after ART is 12.756±1.7750. Similar research conducted by Woldeamanuel GG *et al.* reported the mean value of Hb before and after ART was 12.8 ± 1.99 g/dl versus 14.34 ± 1.89 g/dl, respectively [7]. Both studies met the same conclusion that ART initiation can improve Hb levels in HIV patients.

Zidovudine (ZDV/AZT) is found to cause anemia among patients as its adverse effect [8, 9, 13, 16]. Three different studies reported that the prevalence of anemia as a side effect of zidovudine therapy found on 10.6%, 34.6%, and anemia after administration of ART regimen (not specified) in 46.15% patients [17-19]. In this study, we found that 14 (43.8%) patients receiving ZDV based regimen didn't show improvement of Hb level. These patients' Hb levels even reduced. Statistical significance of p-value = 0.001 which shows there's an association between ZDV takers and no increase of Hb level or lower in Hb level. Patients taking zidovudine containing regimens are also developing a risk of no increase of Hb or lower Hb level by 7 times more than the non-zidovudine group. Tamir Z *et al.*, also reported that the patients taking regimen with zidovudine are in 3.34 folds risk than patients taking non-zidovudine ART [11]. Therefore, routine screening of anemia in patients with ART treatment is important, especially for the regimen with zidovudine.

CONCLUSION

Anemia in HIV/AIDS patients is constituted by many factors, including the disease itself and side effects of the regimen of medication. Antiretroviral therapy (ART) initiation in HIV patients can lead to the improvement of hemoglobin levels, especially after 6 mo. However, a regimen containing zidovudine had more risk to develop anemia or a decrease in Hb level. Routine hematologic panel monitoring, especially for anemia (Hb) should be done, even in patients without symptoms, because it's related to the disease progression and patient's prognosis. Other causes of anemia must be sought and excluded before treating the patients and regimen change should be considered in patients with anemia.

STUDY LIMITATION

The limitation of this study was the small sample size.

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Nil

AUTHORS CONTRIBUTIONS

Putu Dewinta Darmada contributes to research planning, data collection and data management, logical interpretation of the results, literature review, and construction of the manuscript. Ketut Suryana contributes to research planning, idea construction, supervising the course of the project and research article, logical interpretation of the result, reviewing and approving the article before submission.

CONFLICT OF INTERESTS

The authors reported there was no conflict of interest in this study.

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