Effect of Art Increasing Hemoglobin in Human Immunodeficiency Virus-Infected Patient with Anemia at Wangaya Hospital in 2018-2020

I Made Bayu Surya Dana[1], Lisa Anggriani Susanto[2], Ketut Suryana[3]

[1, 2]General Practitioner, Wangaya Regional Hospital, Denpasar, Bali, Indonesia

[3]Internist, Wangaya Regional Hospital, Denpasar, Bali, Indonesia

Abstract: *Background: Anemia is most common hematologic abnormalities among people living with HIV/AIDS (PLWHA) is frequently associated with poor quality of life and poor prognosis. It has been well described who taking ART dan non ART regimens. In addition, we have discussed on relationship between PLWHA with anemia with before taking ART and after taking ART. Methodology: We conducted observational analitic with follow up study design use medical record data during 2018 to 2020 from PLWHA with anemia at Wangaya Hospital, in Denpasar, Bali, Indonesia taking ART for at least 3 months. We excluded PLWHA with impaired hemoglobin level causes renal failure, thalassemia, aplastic anemia, bleeding, pregnant woman. The data were analyzed using SPSS software for windows version 24.0. McNemar test was done, with p value of < 0.05 was considered statistically significant. Results: A total of 426 PLWHA, the overall effectiveness of ART 318 (74.6%) samples were reported increasing hemoglobin level but 108(25.4%) samples with decreasing hemoglobin level. There is significant association statistically between patient's anemia status before and after ART (p < 0.001). Conclusion: This study has shown that PLWHA with anemia before taking ART and after taking ART significant increasing hemoglobin level. A statistically significant association was observed between ART therapy and increasing hemoglobin level.*

Keywords: Anemia, HIV, ART, observational analitic

1. Introduction

Hematologic abnormalities are the most common manifestations of advanced Human Immunodeficiency Virus (HIV) infections and Acquired Immune Deficiency Syndrome (AIDS).[1-3] Of these abnormalities, anemia is the most common hematologic manifestation, affecting 60% to 80% of HIV-infected patients in last-stage disease and has been associated with disease progression and poor clinical outcomes.[1,4,5] Study of the pathophysiology of anemia in HIV has been recognized as an important step forward improving therapeutic option and disease management. A large epidemiological study of worldwide about 35 million people live with HIV, meanwhile Indonesia is in order 5th country risk factor HIV/AIDS infection in Asia.[6] In 2005 until 2019data Indonesia ministry of health PLWHA was 121.101 cases.[7]

The estimated number PLWHA in 2019 was 365.496, 270.802 patients who had received Anti Retroviral Therapy (ART), and 127.613 patients on treatment with ART.[2]According to the Bali Provincial Government Health Office, HIV cases from 1987 to March 2019 found 21.018 cases, of which 12.678 cases were in the HIV phase and 8.340 cases in the AIDS phase.[3]

Anemia is also one of the strongest predictors of HIV mortality and anemia that does not resolved, is associated with shorter survival of PLWHA.[8,9] Reduction of anemia is one of the key components of medical care for PLWHA. The cause of anemia in PLWHA is multifactorialin origin. Infiltrations of the bone marrow by neoplasm or infection, use of myelosuppressive medications, decrease production of endogenous erythropoietin, hemolysis is that may result from RBC auto antibodies and HIV infection itself are some of the causes of anemia in PLWHA.[10,11]The risk factors of HIV associated anemia in developing countries might differ from developed countries due to high prevalence of malnutrition, tuberculosis and helminthic infection.[12]HIV itself produces chronic immune activation and inflammation, under this inflammatory conditions, dietary iron is blocked from enterocyte release, whereas circulating iron is redistributed into cellular storage locations including macrophages including suppression of several hematopoietic cells and opportunistic infections. Pro-inflammatory factor (IL-6) is host defense and dominant regulator of hepatic hepcidin production in bacterial infections and other inflammatory conditions, but IL-6 concentrations are often only slightly increased in viral infections.[13]The virus itself, immune dysregulation, opportunistic infection, and medication result in anemia.[14]Alterations of iron homeostasis are common in chronic inflammatory and infectious diseases.[15]Prevalence of PLWHA with anemia is high and it is frequently improved after cART initiation.[16,17]

The goal of this study, we have discussed on relationship between PLWHA with anemia before taking ART and after taking ART. Based on this, research on the effect of ART therapy in improving hemoglobin in PLWHA with anemia at Wangaya Regional General Hospital in Denpasar, Bali, Indonesiawas conducted.

2. Methodology

Study Population and Design
A hospital-based observational analitic with follow up study design was conducted using medical record data from PLWHA with anemia at Wangaya Regional General

Hospital in Bali, Indonesia during 2018 to 2020. Study participant were adults (age ≥ 18 years) anemia with PLWHA who had not received ART regimen (first line or second line); initiated ART had at least three months follow-up. We excluded PLWHA with impaired hemoglobin level causes renal failure, thalassemia, aplastic anemia, bleeding, pregnant woman. Figure 1.
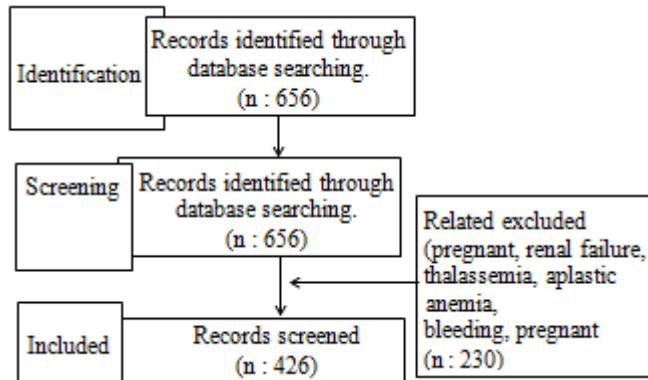

Figure 1: Flow Diagram for Study Participants, Inclusion, and Exclusion in This Riview.

Variables
The WHO hemoglobin concentrations for the diagnosis of anemia and assessment of severity were used to define anemia as hemoglobin (Hb) < 13.0 g/dl for men and Hb < 12.0 g/dl for non-pregnant women. Anemia was further classified as mild (11-12.9 in men, 11-12.9 in non-pregnant women), moderate (8-10.9 g/dl both sexes) and severe (< 8 g/dl both sexes).

Statistical Analysis
The data were collected and analyzed using Statistical Package for Social Sciences (SPSS). Statistics for windows version 24.0.The categorical variables sex, age, education, marital status, zidovudine, opportunistic infection PLWHA with anemia before taking ART and after taking ART were analyzed by McNemar test, with p value of <0.05 was considered statistically significant.

Ethical Clearance
The study research was approved by ethical committee of Wangaya Regional General Hospital in Denpasar, Bali, Indonesia with register number : 069/XII/KEP/RSW/2020. We collect the data from medical record Wangaya Regional General Hospital, Denpasar, Bali.

3. Results

Characteristics of the Study Samples
This study's goal is to assess the effect of ART increasing hemoglobin level among PLWHA at Wangaya Hospital, Denpasar, Bali, Indonesia. The effect of ART in increasing hemoglobin level was assess by medical record, history of hemoglobin before ART was compared by hemoglobin at least 3 month after ART. In this study, 426 participants analyzed, the overall effectiveness of ART 318 (74.6%) samples were reported increasing hemoglobin level but 108 (25.4%) samples with decreasing hemoglobin level. Data characteristics are shown in Table 1.

In Table 1, we found that 54 (12.7%) samples were in the group age 18 – 25, 204 (47.9%) samples were in group age 26 – 40, 84 (19.7%) samples were in group age 41 – 50, and 84 (19.7%) samples were in group age >50. They are 276 (64.8%) male and 150 (35,2%) female. There are no uneducated sample, 108 (25.4%) samples graduated from elementary and junior high school, 240 (56.3%) graduated from senior high school, and 78 (18.3%) graduated from university. We also found 330 (77.5%) samples were married, and 96 (22.5%) samples were unmarried. There are 198 (46.5%) samples who use zidovudine and 228 (53.5%) samples do not use zidovudine. There are 90 (21.1%) samples with opportunistic infection and 336 (78.9%) samples without opportunistic infection.

Table 1: Characteristic of the Study Samples

Variable	n (%)
Age	
18 – 25	54 (12.7)
26 – 40	204 (47.9)
41 – 50	84 (19.7)
>50	84(19.7)
Sex	
Male	276 (64.8)
Female	150 (35,2)
Education	
Uneducated	0 (0)
Elementary – junior high school	108 (25.4)
Senior High school	240 (56.3)
University	78 (18.3)
Marital Status	
Married	330 (77.5)
Unmarried	96 (22.5)
Zidovudine	
Yes	198 (46.5)
No	228 (53.5)
Opportunistic Infection	
Yes	90 (21.1)
No	336 (78.9)

Table 2: HIV- infected patients with Anemia Before and After ART.

Variable	Before ART (%)	After ART (%)	p-value
Anemia			
Noanemia	0 (0)	114 (26.8)	
Mild	348 (83.1)	288 (67.6)	<0.001
Moderate	72 (16.9)	24 (5.6)	
Severe	0 (0)	0 (0)	

In table 2, we found that before ART there are348 (83.1%) patients with mild anemia, 72 (16.9%) patients with moderate anemia. After ART, there are 114 (26.8%) patients without anemia, 228 (67.6%) with mild anemia, and 24 (5.6%) patients with moderate anemia. There is significant association statistically between patient's anemia status before and after ART (p < 0.001).

4. Discussion

Hematologic changes are frequent complications in PLWHA.[18]Whether the person is on ART or not, the presence of anemia predicts poor clinical outcomes such as death, clinical progression to AIDS, morbidity and a poor

quality of life.[19]Previous studies have reported an estimated one-year mortality of 30–55% in severely anemia, compared to 3.7% in non-anemia, PLWHA in resource limited settings.[20] However, individuals who recover from anemia have better clinical outcomes and reducing anemia is a key component of care in PLWHA.[19]

Total of 426 participants in this study was showed that 318(74.6%) samples in ART were reported increasing hemoglobin level, but 108(25.4%) samples with decreasing hemoglobin level. An increased number of viruses along with the development of HIV was followed by the release of inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1, and interferon gamma.The cytokines have been shown to inhibit red cell production (erythropoiesis) and myelosuppression.TNF levels were found to be consistently elevated in HIV infection, and this condition is correlated with viral load. On the other hand HIV disease progresses, the severity of anemia also increases.[21] A report demonstrates that molecular mimicry between erythropoietin (EPO) and the HIV-1 p17 protein can lead to circulating auto-antibodies against endogenous EPO in some HIV patients, blunting the normal physiologic cytokine response to anemia.[22]

The previous study have reported 81% of participants were suffered from anemia on chronic disease or inflammatory anemia and 19% of participants were suffered from iron deficiency anemia.[19]We found anemia is slightly more common in women than men. Wills *et al.* and Diallo *et al.* showed that anemia was more frequent in women than in men.[23,24]Mildvan*et al.* studied prevalence of anemia in 9690 PLWHA receiving ART were anemia. They found anemia was more prevalent among men and patients with CD4<200 cells/mm^3.[25]CD4+ T lymphocyte count, viral load is a marker that predisposes to the development of anemia. Thus, ART while suppressing the individual's viral load, may indirectly improve hemoglobin level because it improves that erythropoietic dysfunction resulting from the increase viral load.[26,27,28]

Several studies have also demonstrated a direct effect of HIV on hematopoietic progenitor cells and EPO responsiveness. HIV-2 infection of BM progenitor cells in the in vitro setting has been shown previously to inhibit erythropoiesis. BM analysis demonstrated that HIV+ patient anemia have a decreased number of both CD34+ progenitor cells and primitive erythroid progenitors compared with HIV-patient with anemia. Studies evaluating hematopoiesis in patients undergoing HIV treatment also support a direct role for the virus in inducing anemia. At the molecular level, BM from PLWHA receiving cART but without adequate response so-called immunologic nonresponders demonstrated reduced clonogenic ability and a decrease in the number of the more multipotent primitive progenitor cells compared with those with response to therapy. Actively replicating virus thus appears to suppress the normal physiologic response to anemia and the complex network of regulatory cytokines that maintain normal hematopoiesis. Intriguingly, the cytokine profile produced by the BM cells from patients without immunologic response to cART was notable for decreased IL-2 and increased TNF-α and IL-7, consistent with a proinflammatory milieu.[22]

The Statistically significant association between zidovudine usage with hemoglobin outcome (p = 0.047). Johannessen, et.al (2011) reported that the mean hemoglobin increased significantly in patients who received ART, but one third were still anemia 12 months after ART initiation indicating that additional interventions to treat HIV-associated anemia in rural Africa might be warranted, particularly in patients with microcytosis and those treated with zidovudine.An initial zidovudine-containing ART regimen was also associated with persistent anemia in our study, increasing the risk by nearly 3 times compared to regimens containing stavudine. The potential myelosuppressive effect of zidovudine has been known for more than two decades.[29]Kiragga AN, et.al (2010) reported that in Uganda did not find an increased risk of early severe anemia (hemoglobin≤8 g/dL within 6 months of ART initiation) in patients on zidovudine, and concluded that zidovudine - in the absence of better alternatives - should not be withheld even in patient with a hemoglobin below 8 g/dL at the time of ART initiation. However, the same study reported that PLWHA with anemia (hemoglobin≤9.5 g/dL) who started a stavudine-containing regimen had a significantly larger hemoglobin increase than those who started zidovudine (3.1 g/dL vs 2.5 g/dL).[30]

This study found that there is no association between hemoglobin outcome with age, sex, education, social status, and opportunistic infection. In contrast, Huibers, et.al (2020) Tuberculosis patients was a common co-infection with HIV (41%), the prevalence is comparable to previous reports on Tuberculosis prevalence (43%) among severely PLWHA with anemia in Africa.[29]

5. Conclusion

In Conclusion, mostly this study has shown that PLWHA with anemia before taking ART and after taking ART significant increasing hemoglobin level. Astatistically significant association was observed between ART therapy and increasing hemoglobin level.

6. Limitations of Study

The limitations of this study included its small sample size. This study conducted at Wangaya Regional General Hospital in Denpasar, Bali, Indonesia during January 2018 – November 2020. Since this is a hospital-based study which only included PLWHA who attended Wangaya Regional General Hospital in Denpasar, Bali, Indonesia during the study period, so the result cannot be generalized to all HIV-infected patients in Bali.

8. Author Contribution

All author made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; took part in drafting the article or revising it critically

for important intellectual content, gave final approval of the vision to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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