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Hemoglobin Levels in Patients with Human Immunodeficiency Virus Naïve Therapy Containing Zidovudine in the First Three Months

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ABSTRACT

Background: Zidovudine, one of the combination antiretroviral used to treat HIV/AIDS, is the most common cause of anemia in HIV patients. Anemia related to zidovudine in HIV can worsen HIV infection. This study determined the hemoglobin level and effect of zidovudine therapy on HIV naïve patients in the first three months initiation therapy.

Methods: Observational analytic study with longitudinal prospective approach was carried out all new HIV patients who received zidovudine therapy. Hemoglobin examination was done at the beginning of the examination and every month for the first three months of zidovudine therapy.

Results: Thirteen (38.23%) subjects developed a decrease in hemoglobin levels. The highest incidence of decreased hemoglobin levels in month 2 was in 11 (84.6%) subjects. The mean hemoglobin levels before the initiation of zidovudine ARV and after 3rd month therapy were 12.75±1.57 and 11.94±2.23 g/dl, respectively. The mean decrease in hemoglobin levels of zidovudine therapy was 2.24±1.99 g/dl. There was an effect of three months of zidovudine therapy on decreasing hemoglobin levels in HIV naïve patients with a statistical significance (p = 0.006).

Conclusion: There was an effect of zidovudine therapy on decreasing hemoglobin levels in the first three months of ARV therapy HIV naïve patients.

Keywords: HIV/AIDS, naïve, zidovudine, hemoglobin.

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INTRODUCTION

HIV/AIDS, one of life-threatening infectious diseases, is caused by the Human Immunodeficiency Virus (HIV). HIV is a rapidly growing, progressive, chronic, and serious illness compared to other diseases.[1,2] Antiretroviral (ARV) therapy is a widely used strategy worldwide to prevent transmission of HIV.[3] ARV therapy requires high adherence and monitoring to suppress viral replication, prevent transmission in the blood, and improve immunology and clinical outcomes.[4,5] Thus, ARV therapy should only begin when the patient is committed to long term treatment.[6]

In patients with HIV, hematological abnormalities often occur that manifest as anemia. Anemia in HIV patients is caused by various factors, one of which is zidovudine related to HIV treatment.[7,8] Zidovudine, one of the first-line ARV used in combination for HIV/AIDS therapy, is the most common cause of anemia in HIV patients.[9,10] Zidovudine-related anemia in HIV can worsen HIV infection, reduce the effectiveness of treatment, and affect the adherence to treatment and quality of life of patients.[7,8] The survival time of HIV patients can increase after anemia is corrected, but HIV patients often come in a condition of severe anemia.[8] Based on various information above, anemia has a big influence in reducing the quality of life and progression of the disease; it is necessary to have a deeper understanding of anemia related to zidovudine as first-line ARV in patients with HIV/AIDS infection.

The prevalence of zidovudine-related anemia in HIV patients is 22.6%.[11] A retrospective study showed that 16.2% of HIV patients had zidovudine-related anemia, with peripheral smears showed normochromic normocytic anemia. In the study, females were more prone to develop anemia, but age, weight, WHO clinical stage and CD4+ counts had no relation to development of anemia.[12] CD4 count was the most important biomarker of disease stage and progression in patients with an HIV infection.[13] Another study presented 14.6% of patients on zidovudine regimen developed anemia for 1 year therapy. Mean decline hemoglobin was 6.4±1.2 g/dl. Patients with low CD4+ count were more prone to developed anemia, but age, sex, weight, WHO clinical stage had not relation development of anemia.[14] Previous studies in Indonesia retrospectively for 6 months therapy showed zidovudine-associated anemia at 70.5% at CD4+ 200-350 cell/mm3 levels and anemia at CD4+ >350 cell/mm^3 at 72.2%.[10] Several studies have shown low hemoglobin (Hb) levels associated with higher mortality rates in HIV patients despite improvements in CD4+ counts and a decrease in viral load. Patients with advanced HIV stage and low CD4+ levels had a higher incidence of anemia.[7,8]

There is still controversy about the incidence of anemia in HIV patients, especially the effect of zidovudine therapy. This study aimed to determine the hemoglobin level of HIV naive patients receiving zidovudine-containing therapy in Dr. Soetomo Hospital, Surabaya at the beginning of the initiation of the first 3 months of therapy.

METHODS

This observational analytic study with a longitudinal prospective approach took place in the Installation of Intensive Care Infectious Diseases, Outpatient Clinic, Dr.Soetomo Hospital Surabaya from December 2018 to May 2019. Data on general characteristics such as age, sex, risk factors, Body mass index (BMI), WHO clinical stage, CD4 cell count and viral load were recorded. The study involved all new case HIV patients who received zidovudine therapy and were confirmed positive by three methods examination, aged 18 - 60 years, Hb ≥10 g/dl at the start of therapy, and agree to follow the study by sign informed consent. Pregnant

HIV patients, a history of malaria infection, patients with malignancy, patients with hematological abnormalities, patients with macroscopic bleeding and patients with decreased renal function with serum creatinine ≥2.5 mg/dl were excluded in this study.

Hemoglobin examination is performed at the beginning of therapy and every month for three months of observation of zidovudine therapy. During the three-month evaluation, hemoglobin levels were monitored; if there was a decline in hemoglobin level to grade 1 (Hb ≥8.5 g/dl), zidovudine was continued, if the decrease was to grade 2, 3, and 4 (Hb <8.5 g/dl), based on the WHO guidelines, zidovudine was replaced with another ARV, and blood transfusion was added according to the patient's Hb level. If during monitoring the patient experienced an adverse event or serious adverse event so that the patient could not continue zidovudine therapy, lost to follow up, the patient died and the patient refuses to continue the study, the patient was declared drop out.

Statistical Analysis

Statistical analysis was done using the EZR (Easy R) program version 1.40. Data on age, sex, and risk factors for transmission were presented descriptively, namely frequency and percentage for categorical data types (nominal and ordinal), while the mean standardized intersection for continuous data types (intervals and ratios). The independent variable was the therapy of ARV zidovudine. The dependent variable was the hemoglobin level every month. The dependent and dependent variable analysis was performed using the repeated Anova test if the data were normally distributed, or the Friedman test if the data were not normally distributed. It was stated as statistically significant if p <0.05 and 95% confidence intervals.

RESULTS

The total number of new patients during the December 2018-January 2019 period was 111 patients, of which 44 patients received zidovudine. Ten patients met the exclusion criteria where 3 patients refused to participate in the study, 3 patients were pregnant and 4 patients with renal abnormalities with serum creatinine ≥ 2.5 g/dl. The total number of subjects in this study were 34 new cases of HIV patients who were confirmed positive by examining 3 methods that met the inclusion criteria and did not meet the exclusion criteria.

The general characteristics of subjects are shown in Table 1. Research subjects were dominated by male sex with 28 (82.4%) persons, while for female sex there were 6 (17.6%) persons. The mean age of the subjects of this study was 30.44±7.15 years, with the youngest age being 19 years and the oldest being 49 years. Heterosexual was the highest risk factor for transmission in this study subjects with 19 (55.9%), followed by homosexual risk factors as many as 10 (29.4%). The lowest BMI was 15.15 kg/m^2, and the highest was 31.14 kg/m^2, with an overall mean of 21.16±3.57 kg/m^2. Research subjects with BMI <18.5 kg/m^2 were 7 (20.6%) persons, and BMI ≥ 18.5 kg/m^2 were 27 (79.4%) persons. Of our 34 subjects, WHO clinical stage characteristics showed clinical stage 1 as many as 14 (41.2%) persons, clinical stage 2 as many as 6 (17.6%) persons, clinical stage 3 as many as 13 (38.2%) persons, and stage clinical 4 only 1 (2.9%) person.

In Table 2, the mean hemoglobin level before the initiation of zidovudine ARV was 12.75±1.57 g/dl, with the highest value of 16.4 g/dl and the lowest of 10.2 g/dl. The first month the lowest hemoglobin level was 8.6 g/dl and the highest was 15.3 g/dl, with an mean of 11.87±1.97 g/dl. After 2 months of zidovudine ARV therapy the mean hemoglobin of the study subjects was 11.01±2.45 g/dl, with the lowest of 4.4 g/dl and the highest of 14.7 g/dl. At the end of the 3rd month evaluation, the lowest hemoglobin level was 4.9 g/dl, the highest was 15.0 g/dl, and mean was 11.94±2.23 g/dl.

The mean decrease hemoglobin levels in 1, 2 and 3 months was 0.94±0.88 g/dl, 0.95±1.12 g/dl, 0, and 35±0.94 g/dl, respectively. The mean decrease in hemoglobin levels in all study subjects during the 3-month evaluation was 2.24±1.99 g/dl. Decrease in hemoglobin level effect of zidovudine therapy in the initial 3 months of therapy showed that the highest in the second month was 11 (84.6%), followed by the first month of therapy which was as many as 7 (53.8%) research subjects had decreased hemoglobin levels (Table 3).

Figure 1 shows the hemoglobin level in all study subjects for 3 months on zidovudine therapy. In month 0 or the beginning of the study, a total of all subjects were 34 (100%) persons. In the first month, the total study subjects were 31 (91.2%) persons, 3 patients had dropped out because 1 patient had an allergy to ARV so it could not be continued, and 2 patients did not come to control (lost to follow up). Based on WHO, subjects who experienced a decrease in Hb in the first month with a grade 1 Hb level with Hb 8.5-10.0 g/dl were 7 (20.6%) persons.

In the 2nd month of zidovudine therapy, out of a total of 28 study subjects (82.4%), 3 people died. There was a decrease in Hb with news of Hb grade 1 by 4 (11.8%) persons, grade 2 by 1 (2.9%) person, grade 3 by 2 (5.9%) persons, and grade 4 by 1 (2, 9%) person. A total of 4 study subjects with hemoglobin levels <8.5 g/dl (grade 2 - grade 4) underwent a change in the NRTI ARV regimen to tenofovir because zidovudine therapy could not be continued. The patient also received blood transfusion to increase the Hb level.

Total research subjects in the third month were 23 (67.6%) persons. As many as 5 patients dropped out, with 1 patient dying and 4 patients experiencing a decrease in Hb levels <8.5 g/dl, so zidovudine ARV therapy could not be continued and replaced with another NRTI, tenofovir, so monitoring in these patients was not continued. The level of Hb reduction in the 3rd month showed that each of 1 (2.9%) person was in grades 1, 2, and 4. No study subjects experienced a decrease in grade 3 Hb in the third month of zidovudine therapy. Research subjects with a decrease in grade 2 and grade 4 Hb got a change in the NRTI ARV regimen to tenofovir because they were unable to continue since zidovudine therapy resulted in the patient's Hb reduction. Patients also receive blood transfusion to increase hemoglobin levels.

Table 4 shows analysis of Hb levels of HIV patients who received zidovudine therapy during the three-month evaluation using the Friedman test showed a p-value of 0.006, which was smaller than the 5% significance level. Analysis continued with post hoc Wilxocon because there were at least two different measurements obtained. Wilxocon post hoc analysis results obtained consecutively Hb month 0 vs Hb month 1 p = 0.02; Hb month 0 vs Hb month 2 p = 0.007; Hb

month 0 vs Hb month 3 p = 0.277; Hb month 1 vs Hb month 2 p = 0.214; Hb month 1 vs Hb month 3 p = 1.00; Hb month 2 vs Hb month 3 p = 1.00. Through these results, it can be concluded that there was an effect of zidovudine therapy on hemoglobin levels at the beginning of the first 3 months of therapy.

DISCUSSION

The effect of zidovudine-containing therapy on decreasing hemoglobin levels in this study was statistically significant. Followed by the Wilxocon post hoc test, there was an effect of zidovudine therapy on hemoglobin levels at the start of therapy with the first month, beginning of therapy with the second month. Whereas, therapy at the beginning of therapy with the third month, the first month with the second month, the first month with the third month, and the second month with the third month showed no significant differences. Of these, the concern is that the monitoring of hemoglobin from the beginning of therapy to the second month of therapy is more important because in this study, the hemoglobin level was significant until the second month evaluation.

The mean decrease in hemoglobin during three months of therapy containing zidovudine in the subjects of this study was 2.24±1.99 g/dl. This was similar to a previous study retrospectively for 6 months in Surabaya, Indonesia which presented mean decrease in hemoglobin of 3.2±2.11 g/dl. This equation can be caused by the characteristics of research subjects that are almost the same despite the different time of observation. This study conducted observations for three months because anemia often occurs at week 4 through week 12 of the initiation of zidovudine therapy.[10]

However, in contrast to studies in India, the mean decrease in the influence of zidovudine hemoglobin was 6.4±1.2 g/dl in a prospective cohort study in 1221 new patients who received zidovudine ARV drugs with a mean hemoglobin reduction time of 3.56±2.43 months, and other reports revealed decreased retrospectively of 6.3±1.4 g/dl. This difference can be due to different monitoring times where in India observations were made for 1 year, and in the second study retrospectively data were taken based on medical records, which involved all HIV patients who had received zidovudine therapy not only naïve patients, whereas in this study, the observations was done for three months of first therapy in HIV naïve patients. Another difference is the cut-off of hemoglobin levels, in which studies in India patients were said to be anemic when Hb <8 g/dl, whereas in this study referring to the WHO toxicity-grade toxicity level of <10 g/dl.[12,14]

There was an effect of zidovudine-containing therapy on decreasing hemoglobin levels in this study. Similar results to this study also occurred in a retrospective study of 1256 patients in India, where the patient was evaluated monthly for 12 months, the patient anemic if the Hb level was <8 g/dl. Statistical analysis was performed with an unpaired t-test between the zidovudine-related anemia group and the non-anemic group. There was an effect of zidovudine therapy on decreasing hemoglobin levels.[12]

Another report which conducted retrospectively for 6 months in Surabaya, Indonesia based on medical data record, involving 97 patients, showed that there was an influence of the incidence of anemia with the use of Zidovudine therapy.[10] This study divided the study subjects into two groups: HIV patients with CD4 levels of 200-350 cells/mm^3 and patients with CD4 levels >350 cells/mm^3. The results showed that the incidence of anemia increased significantly after zidovudine treatment in both groups, but there was a Hb level before treatment with zidovudine significantly associated with the incidence of anemia. Our study was different from previous studies. We did not differentiate groups of patients based on CD4 because ARV initiation therapy based on Indonesian Ministry of Health Regulation 2014 did not look at CD4 data and prerequisites for zidovudine therapy with Hb levels ≥10 g/dl.[15] Our study evaluated the Hb levels every month in the first three months, whereas previous studies only examined the initial Hb levels and six months after therapy based on medical data record so that changes in Hb levels were evident in the monthly evaluations within the first 3 months of initiation of ARV therapy.[10]

Anemia in HIV patients can be caused by various factors, infiltration of the bone marrow due to malignancy (lymphoma) or infections[16], HIV infection itself, opportunistic infections, malnutrition, drug-related myelosuppression anemia, such as zidovudine, and cytopenia related to drugs in HIV patients, such as Ganciclovir, Zidovudine, Trimethoprim-sulfamathoxazole, Dapsone, Sulfadiazine, Pyrimethamine, Amphotericin B, 5-Flucytosine, Antineoplastic Interferon-alpha, Cidofovir.[17–19] In this study, the greatest suspicion of a decrease in hemoglobin levels could be related to zidovudine therapy. Zidovudine is the most common ARV to cause anemia in HIV patients. Decreasing hemoglobin levels which ultimately causes anemia is related to the mechanism of action of zidovudine, which suppresses the production of red blood cells in the bone marrow.[12] Subanalysis was done where sex, age, risk factors, BMI, CD4 and viral load did not show a significant effect on hemoglobin levels. Whereas, the clinical stage showed an influence on the hemoglobin levels of HIV-naïve patients who received zidovudine therapy for the first three months. Clinical stages 3 and 4 were more at risk of decreasing hemoglobin levels than clinical stages 1 and 2. It was in accordance with previous study where the prevalence of anemia was higher in patients with advanced HIV.[20] This is of concern to HIV patients with clinical stages 3 and 4 who receive zidovudine-containing therapy requiring more rigorous Hb monitoring every month for the initial three months of therapy.

Limitations in this study are Bone marrow aspiration (BMA) was not examined to determine the exact cause of anemia, and there was no control group (non zidovudine), so there were still several other factors that can influence the decrease in hemoglobin levels in HIV patients.

CONCLUSION

There was an effect of zidovudine-containing therapy on decreasing hemoglobin levels in the first three months of therapy with a statistical significance of p-value of 0.006. ARV therapy of zidovudine requires close monitoring in the first two months because of a decrease in hemoglobin levels, especially in HIV patients with clinical stages 3 and 4.

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CONFLICT OF INTEREST

The authors in this study declared that they do not have any conflict of interest with respect to this manuscript

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Table 1: General characteristics

Characteristic	N (%)	Mean± SD	Median (Range)
Sex	34 (100%)		
Female	6 (17.6%)		
Male	28 (82.4%)		
Age	34 (100%)	30.44±7.15	30 (19-49)
18 - 30 years	19 (55.9%)		
31 – 45 years	13 (38.2%)		
46 – 60 years	2 (5.9%)		
Risk Factors			
Homosexual	10 (29.4%)		
Heterosexual	19 (55.9%)		
Homosexual+ Heterosexual	3 (8.8%)		
IVDU	2 (5.9%)		
Body Mass Index (BMI)	34 (100%)	21.16±3.57	20.82 (15.15-31.14)
< 18.5 Kg/m^2	7 (20.6%)		
≥ 18.5 Kg/m^2	27 (79.4%)		
WHO stage	34 (100%)		
Stage I	14 (41.2%)		
Stage II	6 (17.6%)		
Stage III	13 (38.2%)		
Stage IV	1 (2.9%)		
CD4	34 (100%)	214.74±166.38	180 (7-734)
≤200	19 (55.9%)		
> 200	15 (44.1%)		
Viral Load	34 (100%)	264,019.35±590,547.56	55,243.5 (164 – 3,283,661)
< 100,000	21 (61.8%)		
≥ 100,000	13 (38.2%)		

Table 2: Hemoglobin level per-month

Month	n (%)	Hemoglobin level	
		Mean± SD	Median (Range)
0	34 (100%)	12.75±1.57	12.6 (10.2-16.4)
1	31 (91.2%)	11.87±1.97	12.0 (8.6 – 15.3)
2	28 (82.4%)	11.01±2.45	11.55 (4.4 – 14.7)
3	23 (67.6%)	11.94±2.23	12.5 (4.9 – 15.0)

Table 3: The incidence of hemoglobin reduction is based on the time of therapy

Month	n (%)	Cumulative n (%)
1	7 (53.8%)	7 (53.8%)
2	4 (30.7%)	11 (84.6%)
3	2 (15.3%)	13 (100%)

Table 4: Effect of zidovudine on hemoglobin levels

Hemoglobin Levels	Median (Minimum – Maximum)	P value
Month 0 (n=34)	12.6 (10.2-16.4)	0.006
1st Month (n= 31)	12.0 (8.6 – 15.3)	
2nd Month (n= 28)	11.55 (4.4 – 14.7)	
3rd Month (n= 23)	12.5 (4.9 – 15.0)	

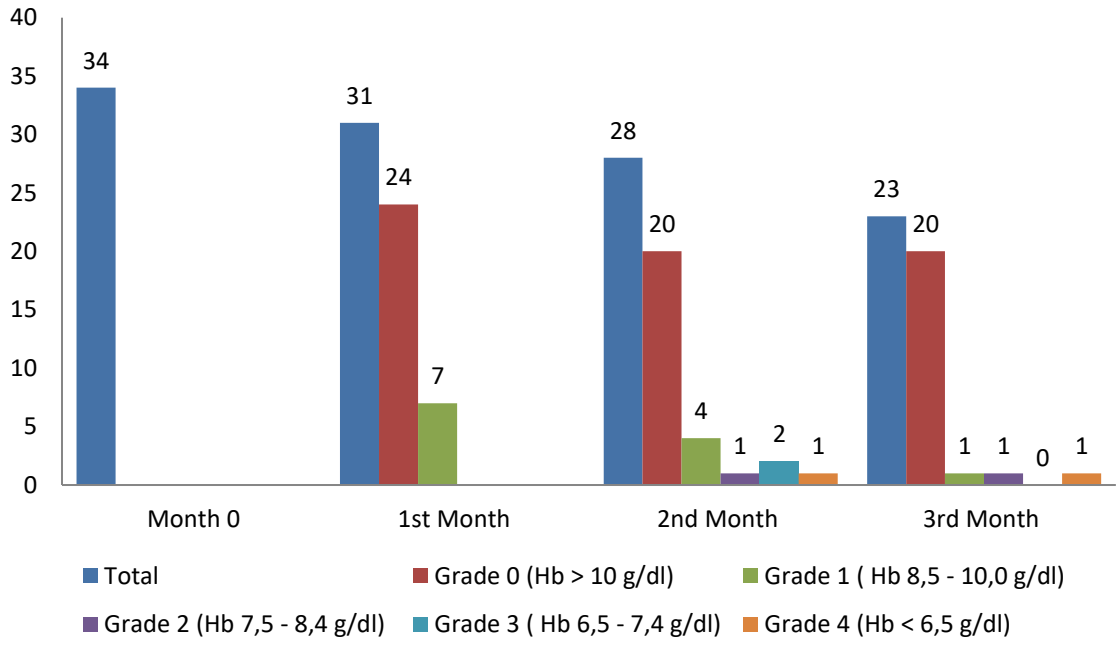

Figure 1: Levels of hemoglobin every month.