

## Contributing Factors of Zidovudine-Induced Anaemia in Hiv/Aids Patients (A Case Study in Dr. Kariadi Hospital Semarang, Indonesia)

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### ABSTRACT

**Background:** The administration of Zidovudine (ZDV) has an important role in decreasing the number of mortality on HIV/AIDS patients, despite the side effect of anaemia. The incidence of anaemia can be influenced by several factors, e.g. age, sex, duration of treatment, CD4 count, and ALT level.

**Aims:** This research aimed to determine factors contributing to the incidence of anaemia in HIV/AIDS patients with Zidovudine treatment in Dr. Kariadi Hospital Semarang Indonesia and see the correlation between those determinant factors to the incidence of anaemia.

**Methods:** This research was an analytic observational with cohort-retrospective method used. The study was taken in VCT Clinic, Dr. Kariadi Hospital Semarang, Indonesia. The data was collated among HIV/AIDS patients' medical records from April 2014 to May 2015. 70 out of over 300 patients on Zidovudine were eligible: 35 belonged to case group, the other 35 as control. The data was analyzed by Chi-square and Fischer test.

**Results:** The average age of patients with and without anaemia in this study were 33.65 years old and 38.02 years old, respectively. However, age did not have any significant relation with the incidence of anaemia ( $p=0.075$ ). A statistically significant relation was shown between sex and incidences of anaemia ( $p=0.027$ ); indicated by 18 female HIV/AIDS patients (51.4%) suffered from anaemia. Duration of treatment (2.1 months average) was the most influential factor towards occurrences of anaemia ( $p=0.000$ ). No significant relationship between low CD4 count ( $<200$  cells/mm<sup>3</sup>) and ALT level to the occurrence of anaemia ( $p=0.055$  and  $p=1.000$  respectively).

**Conclusion:** The incidence of anaemia on HIV/AIDS patients from Dr. Kariadi Hospital Semarang Indonesia was related to sex (gender) and duration of treatment as the influencing factors; Age, CD4 count, and ALT level did not appear to have any significant relation with it in response to the administration of Zidovudine.

### Keywords

HIV/AIDS, Zidovudine, Anaemia.

### Introduction

Acquired Immunodeficiency Syndrome (AIDS) has been a prolonged debate since first discovered in 1981, and a worldwide epidemic disease ever since [1]. World Health Organization (WHO) released the data up to December 2013 that the disease caused by Human Immunodeficiency Virus (HIV) has infected 35.0 million people in the world [2]. The Joint United Nations

Programme on HIV and AIDS (UNAIDS) data stated that in 2013, Indonesia was ranked thirteen (13) highest incidence rate of HIV/AIDS in the world [3]. Directorate General of Centers for Disease Control and Environmental Health (CDC & EH) of the Ministry of Health of the Republic of Indonesia reported in the period of April to June 2014, there were 6.626 and 308 cases of HIV and AIDS respectively. The incidence of HIV/AIDS cases has decreased compared to the first quarter (January to March) of 2014, which recorded 8.908 HIV cases and 1.392 AIDS cases in Indonesia. As in the province of Central Java, up to June 2014, 8.368 and 3.767

cases of HIV and AIDS were recorded respectively [4].

The expanding access to Anti-Retroviral Therapy (ART) has changed the HIV global epidemic significantly in order to reduce the number of AIDS disease-related mortality [5]. Several clinical condition or appearance may arise when a person is HIV-infected at various stages of AIDS, one of which is anaemia.

Anaemia is a condition where a person has a low Haemoglobin (Hb) level in the erythrocytes [6]. According to the latest data from WHO, the prevalence of anaemia in patients with HIV/AIDS is 24.8% globally, where as much as 22% of these patients suffered from anaemia caused by the administration of various drugs, including the ART [7].

Zidovudine, a Nucleoside Reverse Transcriptase Inhibitors (NRTIs) among Anti-Retroviral (ARV), is a first-line treatment regimen for HIV/AIDS, according to WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection 2013. Nevertheless, the administration of Zidovudine is proven to suppress the bone marrow affecting the red blood cells production [8-9].

A study in Ethiopia showed a considerable-high number of the Zidovudine-induced anaemia in HIV/AIDS patient, about 201 out of 616 patients (33%) were positive. Several independent predictors found in line towards this issue: age, chronic diarrhea, HIV treatment regimens, CD4 count, and Alanine Aminotransferase (ALT) level [10].

By 2015, there were 540 HIV/AIDS patients who received ARV regularly every month in Voluntary Counseling and Testing (VCT) clinic of Dr. Kariadi General Hospital, Semarang. However, there has not been any research of Zidovudine induced-anaemia and its contributing factors. Therefore, this research is to answer the problem: to determine the factors influencing incidence of anaemia in HIV/AIDS patients with Zidovudine treatment.

## Methods

This retrospective cohort study was conducted in the VCT clinic, Dr. Kariadi General Hospital, Semarang from March 2015 to May 2015. Subjects were selected based on consecutive sampling method. We obtained the secondary data: age, sex, duration of treatment, CD4 count, and ALT level from medical records.

The subjects were classified into two big groups: 35 patients in the control group (HIV/AIDS without anaemia) and 35 patients in the case group (HIV/AIDS with anaemia). The inclusion criteria for the case group were history of treatment with Zidovudine, anaemia, and age  $\geq 18$  years old; while the inclusion criteria for the control group were history of treatment with Zidovudine, no indications of anaemia, and age  $\geq 18$  years old. The exclusion criteria for case and control groups included history of anaemia prior to treatment, chronic kidney failure, and haematological malignancies. Meanwhile, the independent variables for this study were Zidovudine administration and anaemia; while the dependent

variables were age, sex, CD4 count, ALT level, and duration of treatment. We used the WHO criteria for anaemia:  $<13$  g/dL for men,  $<12$  g/dL for women, and  $<11$  g/dL for pregnancy. All statistical calculations were performed using SPSS (version 20) software. Data analysis used chi-square (to find out significant association for qualitative variable used) and Fischer Exact tests. A p value  $<0.05$  was considered as statistically significant.

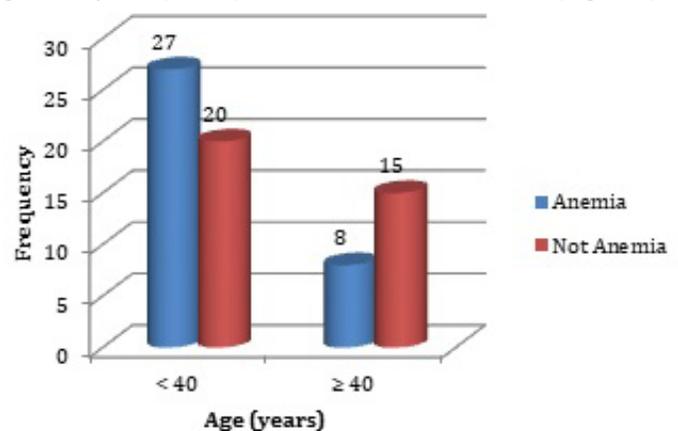
## Results

Among seventy (70) samples, 47 patients (67.1%) aged  $<40$  years, while the others were  $>40$  years. The majority of patients were male: 43 (61.4%). Thirty-nine patients (55.7%) had  $\geq 12$  months duration of treatment; while thirty-eight patients (54.3%) had a CD4 count  $<200$  cells/mm<sup>3</sup>. There were only four patients (5.7%) with ALT level  $>2$ -fold while 66 patients (94.3%) had normal ALT level.

Variable	Frequency	%	
Age	$< 40$ years	47	67.1
	$\geq 40$ years	23	32.9
Sex	Female	27	38.6
	Male	43	61.4
Duration of treatment	$< 12$ months	31	44.3
	$\geq 12$ months	39	55.7
CD4 count	$< 200$	38	54.3
	$\geq 200$	32	45.7
ALT level	$> 2$ -fold	4	5.7
	Normal	66	94.3

**Table 1:** Data frequency.

Age was not considered as statistically significant ( $p=0.075$ ) among HIV/AIDS patients suffered and not suffered from anaemia. Most patients were aged  $<40$  years. A total of 27 patients aged  $<40$  years (77.1%) and 8 patients aged  $>40$  years (22.9%) had anaemia. In the control group, 20 patients aged  $<40$  years (57.1%) and 15 patients aged  $>40$  years (42.9%) did not suffer from anaemia (Figure 1).



**Figure 1:** Age in HIV/AIDS Patients with Anaemia.

Sex was considered as statistically significant ( $p=0.027$ ) among HIV/AIDS patients suffered and not suffered from anaemia.

Among patients with anaemia, female were higher with 18 patients (51.4%), a slight difference to male of 17 patients (48.6%). In the control group, 9 female patients (25.7%) and 26 male patients (74.3%) were not suffered from anaemia (Figure 2).

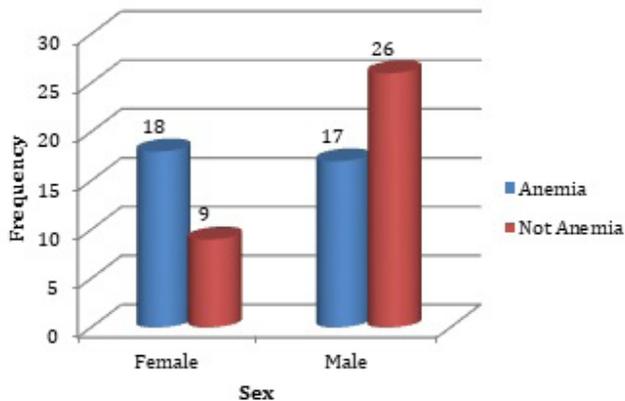


Figure 2: Sex in HIV/AIDS Patients with Anaemia.

Duration of treatment was considered as statistically significant ( $p=0.000$ ). Twenty-six patients (74.3%) had anaemia in <12 months of treatment and 9 patients (25.7%) had anaemia in >12 months of treatment. In the control group, 5 patients (14.3%) with duration of treatment <12 months and 30 patients (85.7%) with >12 months of treatment did not suffer from anaemia (Figure 3).

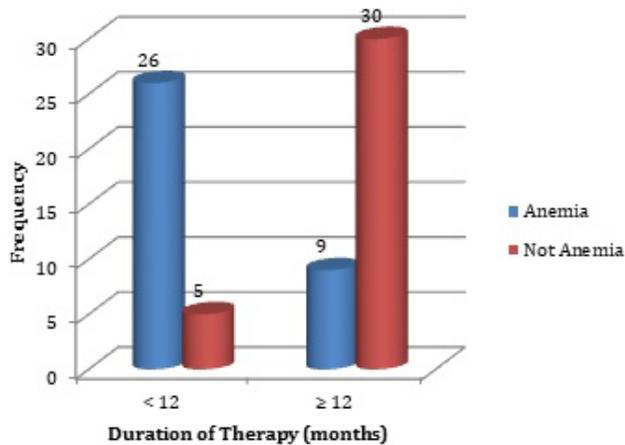


Figure 3: Duration of Therapy in HIV/AIDS Patients with Anaemia.

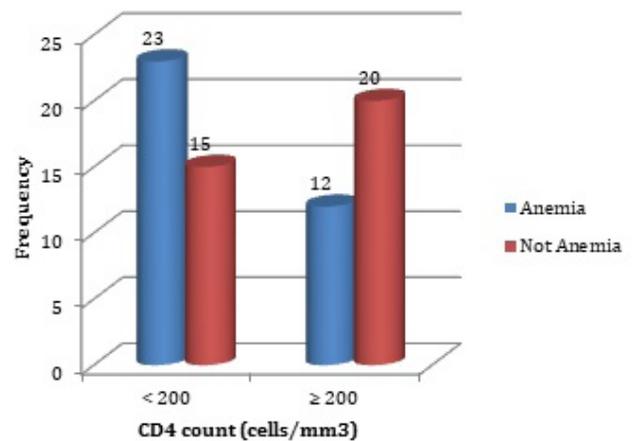


Figure 4: CD4 Count in HIV/AIDS Patients with Anaemia.

CD4 count was not considered as statistically significant ( $p=0.055$ ). Twenty-three patients (65.7%) had CD4 <200 cells/mm<sup>3</sup> were prone to be anemic, rather than patients had CD4 >200 cells/mm<sup>3</sup>: 12 patients (34.3%). In the control group, 15 patients (42.9%) with CD4 <200 cells/mm<sup>3</sup> and 20 patients (57.1%) with CD4 >200 cells/mm<sup>3</sup> were non-anemic (Figure 4).

ALT level was not considered as statistically significant ( $p=1.000$ ). Both case and control group showed only 2 patients (5.7%) had >2-fold ALT level while 33 patients (94.3%) had normal ALT level for each group (Figure 5).

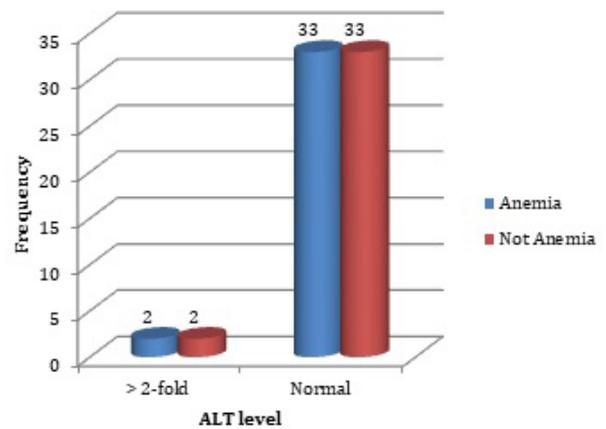


Figure 5: ALT Level in HIV/AIDS Patients with Anaemia.

Variable		Anaemia				P	OR	CI 95%
		Yes		No				
Age	< 40 years	27	77,1	20	57,1	0,075§	2,531	0, 899 – 7,124
	≥ 40 years	8	11,5	15	42,9			
Sex	Female	18	51,4	9	25,7	0,027*§	3,059	1,117 – 8,373
	Male	17	48,6	26	74,3			
Duration of therapy	< 12 months	26	74,3	5	14,3	0,000*§	17,333	5,154 – 58,291
	> 12 months	9	25,7	30	85,7			
CD4 count	< 200 cells/mm <sup>3</sup>	23	65,7	15	42,9	0,055§	2,556	0,972 – 6,722
	≥ 200 cells/mm <sup>3</sup>	12	34,3	20	57,1			
ALT level	> 2-fold	2	5,7	2	5,7	1,000‡	1,000	0,133 – 7,527
	Normal	33	94,3	33	94,3			

**Table 2:** Bivariate chi-square test in accordance to incidence of anaemia. Remark: \* Significance  $p < 0.05$ ; ‡ Fisher's Exact test; § Pearson Chi Square test.

## Discussion

Anaemia appears to be a frequent complication of HIV-infected patients, whereas this finding could be clinically important. The average age of patients with and without anaemia in this study are 33.65 years old and 38.02 years old, respectively. Previous study in Iran showed that the average age of patients with and without anaemia were 36.8 years old and 35.6 years old, respectively [11]. However, in this study, we found out that age did not have any significant relation with the occurrence of anaemia ( $p=0.075$ ). We proposed the variability between different studies performed in various countries as the reason behind differences in the outcome of the study. In addition to this, our study set the baseline of age was to be below 40 or above 40 years of age, yet there has not been any reference to set the baseline for age; thus we propose to set the baseline to be higher or lower and see whether it is considered as statistically significant or not.

In agreement with previous studies in Ethiopia and India [10,12], we demonstrated a statistically significant relation between sex and occurrences of anaemia; indicated by 18 female HIV/AIDS patients (51.4%) who suffered from anaemia. It is possible that it is because of the menstrual cycle of female which may disrupt homeostatic mechanism and decrease haemoglobin level. Nonetheless, Jabbari et al. reported borderline relationship between female sex and anaemia, while Mata-Martin et al. in a cross-sectional study in the Mexican population found anaemia and severe anaemia higher in men [11]. There was not any particular performance to determine direct cause of anaemia in men, but it is our belief that any gastrointestinal bleeding and hypogonadism might be followed for they should be considered in the evaluation of HIV-infected patients with anaemia. Hypogonadism is relatively common in HIV-infected men, and the associated symptoms and problems (e.g. fatigue, weight loss, sexual dysfunction) may also include anaemia. We realised one of the limitations in our study include lack of evaluation in the clinical symptoms occurred that might lead to any possible cause for anaemia.

Our findings showed that duration of treatment was the most influential factor towards occurrences of anaemia ( $p=0.000$ ). Patients who had been treated for less than 12 months (average duration of treatment: 2.17 months), were more susceptible to anaemia compared with patients who had been treated for more than 12 months. A similar study in India also showed statistically significant result for patients with average duration of Zidovudine treatment 3.2 months [12]. We believe that this average duration was due to the life cycle of erythrocyte spanning 100 to 120 days (3 to 4 months), hence the average result of below 6 months to develop anaemia. From these findings, we recommend Hb examination prior to consumption of antiretroviral medications with observation in the first three months of treatment.

We did not find any significant relationship between low CD4

count ( $CD4 < 200$  cells/ $mm^3$ ) and occurrences of anaemia ( $p=0.055$ ). Contrary to our findings, previous experiment showed that patients with CD4 count less than 200 cells/ $mm^3$  had 5.91-fold higher risk to suffer from anaemia ( $p=0.001$ ) compared with patients with CD4 count more than 200 cells/ $mm^3$  [3,10]. However, similar with our findings, Mugisha, et al. also demonstrated no significant relation between CD4 count and occurrences of anaemia [13]. The fact that our study is more related to prevalence rather than incidence might be the cause of our different findings from previous studies. Variability in sample sizes and sample types may also cause variability of the results. In addition to this, we believe that the low CD4 count was due to the administration of Zidovudine, leaving anaemia to be independent for the issue. It is possible that Zidovudine could cause a reduction in both red blood cells (leading to anaemia) and white blood cells (leading to the dropping of CD4 count, as they are a subset of white blood cells) due to bone marrow suppression by AZT.

Finally, in our study, we did not find any significant relation between elevated ALT level and occurrences of anaemia ( $p=1.000$ ) since there were only two patients with 2-fold elevation of ALT level from all of our samples. A study conducted in Ethiopia by Wolde, et al. showed approximately 38% higher risk of anaemia among patients with abnormal ALT level compared with patients with normal ALT level. Nevertheless, this study also did not show statistically significant relationship between ALT level and occurrences of anaemia (Unadjusted Hazard Ratios/UHR=1.38, 95% CI=0.9601–1.9802) [10]. Limited number of patients with abnormal ALT level may be one of the reasons on why our results showed no significant relation between ALT level and occurrences of anaemia.

To conclude, we demonstrated that occurrence of anaemia in HIV/AIDS patients from Dr. Kariadi Hospital, Semarang, Indonesia, was related to sex and duration of treatment; while age, CD4 count, and ALT level did not appear to have any significant relation with it.

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