Old Relationship Getting Antiretrovirals with The Event of Anemia in HIV Infected Children

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Abstract

Anemia is one of the most common hematological complications found in children with HIV infection. The causes of anemia in patients with HIV are multifactorial including the duration of ARV administration, age at the time of ARV administration, administration of cotrimoxazole and Isoniazid drugs. The purpose of this study was to determine the relationship between the length of time receiving ARVs and the incidence of anemia in HIV-infected children at H. Adam Malik Hospital, Medan . The design of this study used observational analytic with retrospective cross-sectional method from medical records to determine the relationship between the length of ARV therapy and the incidence of anemia in HIV children at H Adam Malik Hospital as many as 32 samples were taken from medical records. The results showed that the moderate degree of anemia was 56.3 % , the severe degree was 28.1%, and the mild degree was 15.5%. Bivariate analysis There is a relationship between anemia and early age of ARV administration p value 0.0 44 , duration of ARV administration p value 0.0 13 , cotrimoxazole administration p value 0.0 29 . and administration of isoniazid p value 0.020 . Multivariate analysis found that the duration of ARV administration with p value 0.043, OR = 10,899 (95 % CI = 1.073-110.668) was the most influential risk factor in influencing the onset of anemia, which means the longer the administration ARV drugs , the greater the incidence of anemia . There is a relationship between the initial age of ARV administration, duration of ARV administration, administration of cotrimoxazole and isoniazid on the incidence of anemia in HIV-infected children.

Key Words: Anemia, HIV, Children, ARV, cotrimoxazole, Isoniazid

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Introduction

Human Immunodeficiency Virus attacks the body's immune system by infecting and destroying T lymphocyte cells. Untreated HIV infection will lead to an immune deficiency syndrome called Acquired Immune Deficiency Syndrome (AIDS). AIDS is characterized by a variety of clinical symptoms, including severe immune deficiency accompanied by opportunistic infections, malignancy, and degeneration of the central nervous system. As many as 2.9% of people with HIV are from the age of 15 to 19 years and 1.5% are under 4 years of age. Finally, the lowest reported percentage of HIV sufferers is between the ages of 5 and 14 years at 0.8% (Zubairi 2014).

World Health Organization (WHO) until 2019, in the world there are 1.8 million children living with Human Immunodeficiency Virus (HIV) , 95,000 children died, and there were 150,000 new cases. Data in Indonesia shows the HIV infection rate is 0.17 per 1000 population k. Basic Health Research Data (RISKESDAS) in 2018 reported a total of 377,449 people infected with HIV and 74.2 % were aged 15-24 years n.

Anemia is one of the most common hematological complications found in children with HIV infection (Zubairi, 2014). The causes of anemia in patients with HIV are multifactorial. The etiopathogenesis of anemia in HIV infection can be divided into four, namely (Meidani et al., 2012). Decreased production of red blood cells, namely infiltration into the bone

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marrow by malignancy, infection, use of myelosuppressive drugs (antibiotics, ARV and chemotherapy drugs), HIV infection itself, decreased production erythropoietin. 2) Increased destruction of red blood cells immaturity occurs in the spleen or the circulatory system. Hemolytic anemia can be caused by auto antibodies in red blood cells, hemopagocytosis syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura , glucose-6-phosphate dehydrogenase deficiency , the use of various drugs. 3) Production of ineffective red blood cells caused by nutritional deficiencies (iron, folic acid or vitamin B12) . 4) Bleeding may occur in some malignancies such as Kaposi's sacroma in the gastrointestinal tract or bleeding from gastrointestinal lesions such as cytomegalovirus infection (Meidani et al., 2012).

Research on ARV administration is important because side effects occur in some people, one of which is a decrease in hemoglobin (Hb) which is influenced by the duration of therapy and CD4 levels . The decrease in hemoglobin associated with ARVs in HIV/AIDS-infected patients is most likely due to bone marrow infiltration caused by HIV, neoplasms or infection, decreased endogenous erythropoietin, hemolytic anemia, use of myelosuppressive drugs such as zidovudine, nevirapine, cotrimoxazole and isoniazid (Ministry of Health, 2015).

Antiretroviral therapy was administered by Elena et al. (2012) The results showed that 22.2% (50/225) of the children received an ARV regimen and 52.0% (26/50) had a CD4 + T lymphocyte percentage > 25%. At the last examination, during the regimen, 80% (40/50) of the patients had undetectable VL, and 90% (45/50) of them had a CD4+ T lymphocyte percentage > 25%. The most widely used drugs were: dolutegravir/ abacavir/ lamivudine (16%; 8/50), emtricitbine/ tenofovir disoproxil (22%; 11/50), lopinavir/ ritonavir (20%; 10/50) and elvitegravir /cobicistat/ emtricitabine/tenofovir alafenamide (10%; 10/50).

The prevalence of anemia in HIV infection ranges from 1.3% to 95%, influenced by the clinical stage of the disease . The prevalence of anemia in children with HIV at the Sanglah Central General Hospital in 2015 was 34%. In Jakarta , 13.7% of anemia was reported in patients receiving zidovudine 22 . In Hasan Sadikin Hospital, Bandung , there were 41.6 % of anemia sufferers, 21.3% of whom were moderate-severe anemia due to the use of zidovudine. In RSUP HAM Medan in 2013 the incidence of anemia was reported to be 7%, and in 2013 in Asia it was reported that there were 2.9% severe anemia that occurred after six months of taking ARV containing zidovudine (Sumantri et al., 2008).

Based on the above review, the researchers conducted a study on how the relationship between long time receiving ARV and the incidence of anemia in HIV-infected children at H. Adam Malik Hospital Medan.

Methodology

This study is an analytic observational study with a retrospective cross-sectional method from medical records to determine the relationship between the length of ARV therapy and the incidence of anemia in HIV children, carried out in outpatient and outpatient clinics, Division of Allergy Immunology, Pediatric Health Sciences, RSUP HAM Medan, data taken from medical records. patients diagnosed with HIV and receiving antiretroviral drugs before January 2022. The population in this study were HIV-infected children who received ARV therapy and suffered from anemia in the inpatient and outpatient polyclinic Allergy Immunology pediatric RSUP HAM Medan as many as 102 people. Sampling using consecutive sampling technique amounted to 32 subjects. Data analysis consisted of univariate, bivariate with Chi-square, and multivariate with logistic regression.

Results and Discussion

Univariate Analysis

Table 1. Characteristics of Research Subjects

Subject Characteristics	N = 32
Gender, n (%)	
- Man	11 (34.4)
- Woman	21 (65.6)
Source of Transmission, n (%)	
- Mother	31 (97)

- Etc	1 (3)
Birth History, n (%)	
-Normal	26 (81.3)
- Sectio	6 (18.7)
Age at ARV study , n (%)	
- Toddler	6 (18.7)
- Childhood	16 (50)
- Early adolescence	10 (31.3)
Initial age of ARV administration, n (%)	
- Toddler	8 (25)
- Childhood	21 (65.6)
- Early adolescence	3 (9.4)
Nutritional Status, n (%)	
- Good Nutrition	26 (81.2)
- Malnutrition	3 (9.4)
- Malnutrition	3 (9.4)
Opportunistic Infections, n (%)	
- Yes	17 (53.1)
- Not	15 (46.9)
-trimoxazole administration , n (%)	
- Ada	27 (84.4)
- None _	5 (15.6)
Administration of isoniazid, n (%)	
- Ada	28 (87.5)
- None _	4 (12.5)
Degree of prevalence of anemia	
- Mild - Medium	23 (71.9)
- Heavy	9 (28,1)

Subjects were female 21 (65.6%) . The most common source of transmission was 31 (97.0 %), with a history of normal birth 26 (81.3%). Age at the time of research ARV most categories were childhood 16 people (50, 0 %) followed by early adolescence 10 people (31, 3 %). Most of the early age subjects who were given ARV were in the childhood category, 21 people, then 8 people under five. The nutritional status is generally good with a total of 26 (81.2 %). The most opportunistic infections were 17 (53.1 %), 27 people were given cotrimoxazole (84.4%) and 28 people were given isoniazid (87.5%). Most of the prevalence degrees of anemia were in the mild to moderate category as many as 23 (71,9 %).

Bivariate Analysis

Table 2. Frequency Distribution of Anemia Prevalence in HIV-Infected Children

Subject Characteristics	**Degree of Anemia**		**P *value***
	Mild – Medium	**Heavy**	
Gender, n (%)			
- Man	8 (25)	3 (9.4)	1,000
- Woman	15 (46.9)	6 (18.8)	
Initial age of ARV administration, n (%)			
- Toddler	5 (21.7)	3 (33,3)	0.044
- Childhood	1 8 (56.2)	6 (1 8.8)	
Duration of ARV drug administration, n (%)			

- < 6 months	14 (43,8)	2 (6,2)	0.013
- > 6 months	9 (28,1)	7 (21.9)	
Co-trimoxazole administration, n (%)			
- There isn't any	5 (1 5,6)	0 (0)	0.029
- There is	1 8 (56.2)	9 (28,1)	
Administration of isoniazid, n (%)			
- There isn't any	3 (9.4)	1(3.1)	0.020
- There is	2 0 (62.5)	8 (7.9)	

Subjects were male with severe anemia 3 people (9.4 %), and female sex with severe anemia 6 people (18.8%) Based on the *chi - square test* obtained p *value* 1,000 , so there is no sex relationship with the incidence of anemia at H. Adam Malik Hospital.

Subjects under five with severe anemia were 3 people (33,3 %), and 6 people in childhood with severe anemia (1 8.8 %) . Based on the *chi - square . test* obtained p *value* 0.044 , so that there is a relationship between the initial age of ARV administration and the incidence of anemia at H. Adam Malik Hospital.

ARV administration < 6 months with severe anemia 2 people (6.2 %), and ARV administration > 6 months with severe anemia 7 people (21.9%) Based on the *chi - square test* obtained p *value* 0.013 , so that there is a relationship between ARV administration and the incidence of anemia at H. Adam Malik Hospital.

Drug cotrimoxazole category is not present with severe anemia 0 people (0%), and the drug cotrimoxazole is categorized as having severe anemia 9 people (28.1 %) Based on the *chi - square test* obtained p *value* 0.029 , so there is a relationship between the administration of cotrimoxazole drug with the incidence of anemia at H. Adam Malik Hospital.

There is no category of isoniazid drug with severe anemia 1 person (3.1%), and isoniazid drug category is present with severe anemia 8 people (7.9%) Based on the chi - *square test* obtained p *value* 0.020 , so there is a relationship between the administration of isoniazid drug with the incidence of anemia at H. Adam Malik Hospital.

Multivariate Analysis

Table 3. Results of the Final Stage of Logistics Regression Analysis

Variable	B	p *value*	Exp(B) OR	95% CI For Exp (B)
Early age	-1,694	0.166	0.184	0.017-2.020
The duration of ARV drug administration	2,389	0.043	10,899	1.073-110.668

In table 3 in above, it can be seen that the last stage of logistic regression analysis resulted in one of the most dominant variables with the incidence of anemia at H. Adam Malik Hospital, namely the variable duration of ARV drug administration with p *value* 0.043 , OR = 10,899 (95% CI = 1.073 - 110.668) means that giving ATV drugs > 6 months has a chance of 10.899 experienced anemia in the severe category with a B coefficient value of 2,389 which was positive, the longer the administration of ARV drugs , the greater the incidence of anemia

ARV therapy is the most effective HIV therapy effective at this time to suppress viral replication. Any individual with HIV infection have vulnerabilities and factors that influence the occurrence of anemia . In this research obtained 32 respondents, most of the respondents were female as many as 21 (65.6 %). Of 21 respondents There were 2 (6.2 %) respondents with mild anemia, 13 (40.6%) respondents with moderate anemia, and 6 (18.8%) respondents with severe anemia. Male sex as much as 1 1 (34,4 %) . Of the 11 respondents there is 3 (9.4%) respondents with mild anemia, 5 (15.6 %) respondents with moderate anemia, and 3 (9.4%) respondents with severe anemia. Based on the results of statistical test calculations of gender obtained p value 0.405 (> 0.05), so it can be concluded that there is no relationship between sex with the incidence of anemia at H. Adam Malik Hospital .

Cahyani, et al (2015) shows that in terms of the sex of the child, It is known that men with HIV/AIDS have anemia more than men female (69 %:31%). Leite et al in (2013) reported that boys men show a low risk of anemia higher than women (PR 1.06; 95% CI 1.01-1.13). On some research, it can be seen that the types of gender with the incidence of anemia have inconsistent relationship, where there are several studies which reveal a relationship and some also don't show the relationship between these variables.

Based on the initial age of ARV administration in this study, most of the respondents were in childhood, namely 21 (65.6%), with 1 respondent (3.1%) with a mild degree of anemia, 15 (46.9%) respondents with a mild degree of anemia. moderate anemia and 5 respondents (15.6%) with severe anemia. By using statistical test calculations obtained p value 0.016 (<0.05), so it can be concluded that there is a relationship between the initial age of ARV administration and the incidence of anemia. at H. Adam Malik Hospital.

ARV therapy as effective treatment to prevent anemia by how to suppress the amount of HIV virus replication where the HIV virus can infect the bone marrow and cause process disorders hematopoiesis which can lead to anemia. Z idovudin is an element of first-line ARV regimens for the treatment of HIV infection in countries with low resources , but identified as the cause of anemia. Mechanism of causing anemia by ZDV with -inhibition hemoglobin synthesis, globin gene transcription and proliferation blood cell progenitors depend on time and dose of administration (Peterson et al., 2013; Techane et al., 2020).

A research that conducted in the United States comparing the incidence of anemia in patients treated with antiretroviral drugs containing ZDV and those not containing ZDV found that patients who started antiretrovirals containing ZDV had a greater risk for anemia to occur.

Zidovudine has been reported as cause of hematological disorders, especially anemia, since the first was introduced as an ARV therapy. In the ARV therapy guidelines by WHO also it has been said that ZDV is a NRTIs with marrow suppression toxicity bone. Previous research has reported nucleoside analogue genotoxicity lead to mutations, deletions and DNA damage that results in damage high cells occur in bone marrow and cells peripheral blood. This toxicity is related to Zidovudine dose (Makubi et al., 2012).

Neviral ® the capsules contains a class of drugs The NNRTI (nevirapine) was 22%. For AZT 3FDC tablets usually used for antiretroviral therapy for children with a usage of 7%. Based on treatment guidelines Antiretrovirals on Ministerial Regulation Health No.87 year 2014 it is stated that the main combination in the first line of treatment with ARVs for children 5 years to on which recommended alternative combinations are zidovudine + lamivudine + efavirenz (or nevirapine) and tenofovir + lamivudine (or emtricitabine) + nevirapine for first-line ART in children < 5 years (Anggriani et al., 2019). Somali, et al research in 2017 Nevirapine can cause anemia, the incidence of anemia due to the use of the drug nevirapine is 1-10% and ratilgivir <1%. In the 2014 study of Wipasa et al. in Africa, infants who received nevirapine compared to zidovudine did not find a difference in the incidence of anemia.

Based on the results of this study, from 32 respondents studied, the duration of ARV drug administration > 6 months was 16 (50.0%), and obtained 9 (28.1%) respondents with moderate degree of anemia, and 7 (21.9%) respondents with severe anemia. Meanwhile , there were 16 (50,0 %) ARV drugs given for < 6 months 5 (15.6 %) respondents with mild degree of anemia and 9 (28.1%) respondents with moderate degree of anemia, and 2 (6.2 %) respondents with severe degree of anemia . Based on the results of statistical test calculations obtained p value 0.020 (<0.05) , so there is a relationship between the duration of ARV drug administration with the incidence of anemia. at H. Adam Malik Hospital.

In general, this study shows that there was a difference in the prevalence of anemia, the level of severity and characteristics , when starting before six months and after six months of ARV follow-up at among participants starting a drug regimen that containing ZDV and those without ZDV. That ZDV had a side effect of severe anemia in six the first month of the term , which is mostly anemia. With However, monitoring of hemoglobin levels should still be monitored during the first six months of taking ARVs (Kebede et al., 2021).

On Liza 's study who received ZDV < 6 months had a 2,779 times (95% CI 1,428-5409) risk of developing anemia compared with those who received ZDV > 6 months. The results are the same as the Kaibalaya study, where the average duration of Hb reduction is 3.56 ± 2.43 month (Salawati, 2021).

ARV initiation among HIV/AIDS patients significantly reduced the prevalence of anemia. HB levels increased at the three visits after starting ARVs (from baseline 12.87 ± 2.16 to 13.61 ± 2.07 to 14.1 ± 2.1 to 15.34 ± 0.11) among patients who starting ARV drugs, supported by Adane A et al . and Maskew M et al.

Of the 32 respondents in the study , 27 (84.3 %) respondents were accompanied by the administration of cotrimoxazole 17 (53.1 %) respondents with moderate degree of anemia , and 9 (28.1 %) respondents with severe anemia degree. Based on the results of statistical test calculations obtained p value 0.000 (<0.05) , so it can be concluded that there is a relationship with the incidence of anemia with cotrimoxazole administration. at H. Adam Malik Hospital .

Proportion of the number of children who receiving more cotrimoxazole therapy more anemia than with those who don't accept cotrimoxazole (92 % : 8%) 30 . Co-trimoxazole administration with HAARV (Highly Active Antiretroviral) therapy) can increase the risk haematological toxicity reported in Sub-Saharan, Africa in adolescent population and in infants given long-term cotrimoxazole as prophylaxis, it will be more prone to cause a decrease in concentration hemoglobin and has the potential to cause anemia. Based on this description, it is expected that Co-trimoxazole administration in pediatric patients should be balanced with giving vitamins and micronutrients (Makubi et al., 2012).

The results of the 32 respondents from this study, 28 (87.5 %) respondents were given Isoniazid drugs , obtained 20 (62.5 %) respondents with mild to moderate anemia , and 8 (7.9 %) respondents with severe anemia. Based on the results of statistical test calculations obtained p value 0.02 0 (< 0.05) , so it can be concluded that there is a relationship with the incidence of anemia with isoniazid administration. at H. Adam Malik Hospital.

Isoniazid is one of the drugs of choice for first-line tuberculosis drugs. Its function is to inhibit the production of mycolic acid, an important cell wall component in bacteria. INH prophylaxis is given to HIV-exposed children with adult TB for 6 months . Types, combinations, and doses of antituberculosis drugs given to pediatric patients with AIDS were given according to the reference. Drug problems encountered were side effects of nausea and abdominal pain (41%), itching (23%), and an increase in SGOT and SGPT (9%) due to the use of isoniazid (Goddess, 2015). In addition, Isonizide can cause an increase in the excretion of pyrodoxine (vitamin B6). Vitamin B6 is required for heme synthesis, so vitamin B6 deficiency causes anemia with anemia incidence reported to be <1% (Katzung, 2018).

Several opportunistic infections can cause anemia through direct infiltration of the bone marrow, such as infection with cytomegalovirus, parovirus B19, Mycobacterium and Cryptococcus neoformans (Mangunatmadja et al., 2021).. Research in Ethiopia found an association between the presence of opportunistic infections and the incidence of anemia (P=0.001). The results of the study by Sumantri et al (2008) at Hasan Sadikin Hospital in Bandung, where tuberculosis infection did not cause anemia (p = 0.83) . In contrast to Masresha's study in Ethiopia, tuberculosis infection had a 2.1 times higher risk of developing anemia compared to those without tuberculosis (OR = 2.1, 95% CI; 1.4, 3.3) (Goddess, 2015; Anggriani et al., 2019).

The cause of anemia in TB is suppression of erythropoiesis by inflammatory mediators, namely IL-6, IFN-γ, IL-1β, TNF-α. The pathogenesis of anemia due to inflammation occurs due to the invasion of microorganisms, malignant cells or autoimmune reactions leading to activation of T cells (CD3+) and monocytes. These cells induce immune effector mechanisms by producing cytokines such as interferon-γ from T cells and TNF-, Interleukin-1, Interleukin-6 and Interleukin-10 (from monocytes or macrophages). These proinflammatory cytokines cause inhibition of proliferation and differentiation of erythroid progenitor cells and trigger suppression of erythropoietin in the kidney. Interleukin-6 and lipopolysaccharide stimulate the expression of the acute phase protein hepcidin, which reduces the absorption of iron in the duodenum. Hepcidin is elevated during inflammation and infection. This results in iron dysregulation with hypoferremia and inflammatory anemia (Weiss & Goodnough, 2005)

Conclusion

Based on the results of this research and discussion, it can be concluded that most of the prevalence degrees of anemia are in the mild to moderate category as many as 23 (71.9%). There was a relationship between the initial age of ARV administration (p= 0.044 < 0.05) , there was a relationship between the duration of ARV administration (p= 0.013 < 0.05), the administration of cotrimoxazole (p= 0.029 < 0.05) and administration of isoniazid (p = 0.0 20 < 0.05) with the incidence of anemia in HIV - infected children at H Adam Malik Hospital Medan. There is no relationship between gender with the incidence of anemia in HIV-infected children with p value = 1,000> 0.05.

Suggestion

It is hoped that this research can be a reference in considering the selection of ARVs , the use of cotrimoxazole and isoniazid drugs in HIV-infected children and minimizing the side effects of anemia in order to achieve optimal management of HIV infection in children.

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