

## Original Article

# Age and CD4 count are dominant factors in the prediction of anaemia in Javanese HIV patients

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**Background and Objectives:** Anaemia in Human Immunodeficiency Virus (HIV) infection is multifactorial and an increasingly important variable to consider in the management. This is the first study of anaemia in HIV infection in the Javanese population, which constitutes the largest ethnic group in Indonesia. The aim of this study was to determine the factors which are associated with anaemia in Javanese patients with HIV infection. **Methods and Study Design:** This study applied a cross-sectional design involving HIV patients in Dr Kariadi Hospital and Balai Kesehatan Paru Masyarakat (BKPM), Semarang, Indonesia. The characteristic data of the subjects were age, gender, BMI, duration of therapy and antiretroviral (ARV) drugs. Haematology tests were conducted using flow cytometry. **Results:** The prevalence of anaemia in HIV-infected patients was 21 (38.88%). Macrocytic anemia was found as a majority (12; 57.1 %) in anaemic patients. The risk factors which were found to be associated with increase of anaemia were white blood cells (WBC)  $<5.0 \times 10^9/L$  and CD4  $<200.0$  cells/ $\mu L$  ( $p < 0.05$ ). A correlation between anaemia and age ( $r=0.49$ ,  $p < 0.01$ ), duration of treatment ( $r=0.35$ ,  $p < 0.01$ ), CD4 count ( $r=-0.42$ ,  $p < 0.01$ ), total bilirubin ( $r=-0.28$ ,  $p < 0.05$ ), and unconjugated bilirubin ( $r=-0.29$ ,  $p < 0.05$ ) was identified. Age ( $p=0.023$ ) and CD4 count ( $p=0.07$ ) were the dominant factors in the multivariate analysis. **Conclusion:** Age and CD4 count are the dominant factors in determining of anaemia in Javanese patients with HIV infection.

**Key Words:** age, CD4, anaemia, HIV, Javanese

## INTRODUCTION

According to 2015 Global UNAIDS data, 5.1 million people in the Asia Pacific region are living with HIV.<sup>1</sup> Anaemia is a common feature of HIV infection and is reported as a prognostic marker of progressivity and death, independent of CD4 count and viral load.<sup>2-4</sup> Anaemia in HIV-infected patients is multifactorial and regarded as an increasingly important variable in monitoring management, particularly in resource-limited settings.<sup>5</sup>

Age and sex are reported to account for the variations in anaemia prevalence in HIV infection.<sup>6,7</sup> The multifactorial conditions involved in anaemia in HIV infection complicate diagnosis of the underlying cause and appropriate therapy.<sup>8</sup> The mechanisms involved in the pathophysiology of anaemia in HIV infection are related to bone marrow infiltration, nutritional status, and drug side effects, which can cause decreased red blood cell (RBC) production, increased RBC destruction, and ineffective RBC production.<sup>9</sup> Anaemia due to nutritional status has been reported to involve iron,<sup>10,11</sup> vitamin A, B-12, and folate deficiencies.<sup>12,13</sup> Anaemia caused by the adverse

effect of long-term use antiretroviral therapy (ART) is associated with treatments involving a Zidovudine (AZT) regimen.<sup>14-16</sup> The use of AZT for patients with HIV infection has yielded revolutionary results in restraining viral growth.<sup>17</sup> However, the risk of anaemia in the use of AZT is reported higher than when using other ARV drugs such as Stavudine (d4T) and Tenofovir (TDF).<sup>18,19</sup>

Heterogeneity of population and different study settings influence haematological abnormality in patients with HIV infection.<sup>20</sup> Anaemia is an important issue in public health and is monitored routinely worldwide. Effective reduction of anaemia in Indonesia has been

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reported, with estimates being consistent with those for Southeast Asia. Monitoring anaemia prevalence in different populations is necessary to better understand the changing burden over time.<sup>21</sup> Few studies of anaemia in HIV-infected patients in Indonesia have been conducted.<sup>22</sup> This is the first study of anaemia in patients with HIV infection focusing only on the Javanese population, which constitutes the largest ethnic group in Indonesia.

The aim of this study was to determine factors that are associated with anaemia in Javanese patients with HIV infection.

## PARTICIPANTS AND METHODS

### *Population and samples*

This study was a cross-sectional design involving HIV patients in Dr Kariadi Hospital and BKPM, Semarang, Indonesia. The inclusion criteria for the samples were being an adult, being Javanese (for three continuous generations), and having undergone HIV therapy for more than 6 weeks. Secondary data were obtained from anamnesis and medical records. This study was approved by the Medical Ethics Committee, Faculty of Medicine, Diponegoro University, Dr Kariadi Hospital, Semarang (No. 513/EC/FK-RSDK/2015), and informed consent was obtained from the samples. The characteristic data of the subjects included were age, gender, BMI, duration of therapy, and type of ARV drugs. Fifty-four samples met these criteria, consisting of 21 (38.9%) male and 33 (61.1%) female subjects.

### *Haematology examination*

The blood of eligible subjects was collected by competent medical personnel and placed in three separate vacutainer tubes (two EDTA tubes, and one plain tube). Haematology examinations using flow cytometry were performed to assess levels of Hb, reticulocytes, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), platelets, WBC, CD4, total bilirubin, and unconjugated bilirubin.

### *Definition of variables and statistical analysis*

ARV drugs regimens were classified into regimens with and without AZT. According to the World Health Association (WHO) classification, BMI <18.5 kg/m<sup>2</sup> indicates underweight and ≥18.5 kg/m<sup>2</sup> indicates non-underweight.<sup>23,24</sup> The Hb findings were used to diagnose anaemia in adults according to the WHO guidelines. The classifications of Hb concentration are non-anaemic (≥12.0 g/dL; ≥13.0 g/dL) and anaemic (<12.0 g/dL, <13.0 g/dL) for female and male patients, respectively.<sup>21,25</sup> WBC counts <5.0 × 10<sup>9</sup>/L are regarded as being indicative of low WBC levels. Platelet counts <150 × 10<sup>9</sup>/L indicate low platelet levels.<sup>26</sup> MCV >96.0 fL and <80.0 fL are indicative of macrocytic and microcytic anaemia, respectively. MCH <1.68 fmol/cells constitutes hypochromia.<sup>11</sup> Progression of infection, as indicated by Center for Disease Control and Prevention guidelines, involves CD4 counts <200 cells/μL.<sup>27,28</sup>

The data are presented in tables and graphs. The statistics analyses were performed using IBM SPSS Statistics v.23 software. The chi-square test was applied to analyze the categorical variables, and the independent t-test was

employed to assess numerical variables. Results were viewed as statistically significant if the observed  $p < 0.05$ . The relationship between risk factors and anaemia was calculated through univariate analysis, applying odds ratios and 95% confidence intervals. Pearson's correlation coefficient was obtained to investigate the strength of the relationship. A logistic regression model was developed to identify the dominant factor in anaemia prediction for Javanese HIV patients.

## RESULTS

A total of 21 (38.88%) HIV patients in Dr Kariadi hospital and BKPM Semarang exhibited anaemia. Haematology examination revealed that the mean Hb concentration was 10.7±1.65 g/dL in samples with anaemia and 12.6±1.26 g/dL in the normal group. The male subjects exhibited a higher mean Hb concentration than did the female group (13.2±2.08 g/dL and 12.0±1.80 g/dL, respectively).

MCV in patients with anaemia was >96.0 fL, 80.0-96.0 fL, and <80.0 fL in 12 (57.1%), 6 (28.6%), and 3 (14.3%) samples, respectively. An MCH level <1.68 fmol/cells was observed in 4 (19%) samples with anaemia and associated with MCV <80.0 fL ( $p=0.000$ ). Reticulocyte count <2% was found in 19 (35.2 %) patients with anaemia (Table 1). The distribution of MCV level (>96.0, 80.0-96.0, and <80.0 fL) stratified by reticulocyte status in patients with anaemia was 11 (57.9 %), 5 (26.3 %) and 3 (15.8 %), respectively. Regarding ARV drugs type, 43 (79.6%) patients received regimens with AZT and 11 (20.4%) patients received regimens without AZT (d4T and TDF-containing regimen).

Risk factors were analysed using a univariate analysis to investigate their relationship with anaemia prevalence. The associated risk factors ( $p < 0.05$ ) were identified as being WBC <5.0 × 10<sup>9</sup>/L (OR 4.09, 95% CI [1.2-13.5]) and CD4 <200 cells/μL (OR 5.44, 95% CI [1.4-21.1]) (Figure 1). Compare means of age, duration of treatment, CD4, total bilirubin, and unconjugated bilirubin to anaemia were statistically significant ( $p < 0.05$ ) in this study (Table 1).

The strength of the relationship between factors that were significant to Hb status was analysed. There was a moderate positive correlation between age and anaemia ( $r=0.49$ ,  $p < 0.01$ ), a moderate positive correlation between duration of treatment and anaemia ( $r=0.35$ ,  $p < 0.01$ ), a moderate negative correlation between CD4 counts and anaemia ( $r=-0.42$ ,  $p < 0.01$ ), a weak negative correlation between total bilirubin and anaemia ( $r=-0.28$ ,  $p < 0.05$ ), and a weak negative correlation between unconjugated bilirubin and anaemia ( $r=-0.29$ ,  $p < 0.05$ ). The age ( $p=0.023$ ) and CD4 ( $p=0.07$ ) count were identified as being the dominant factors in anaemia prediction for Javanese HIV patients in the multivariate analysis (Table 2).

## DISCUSSION

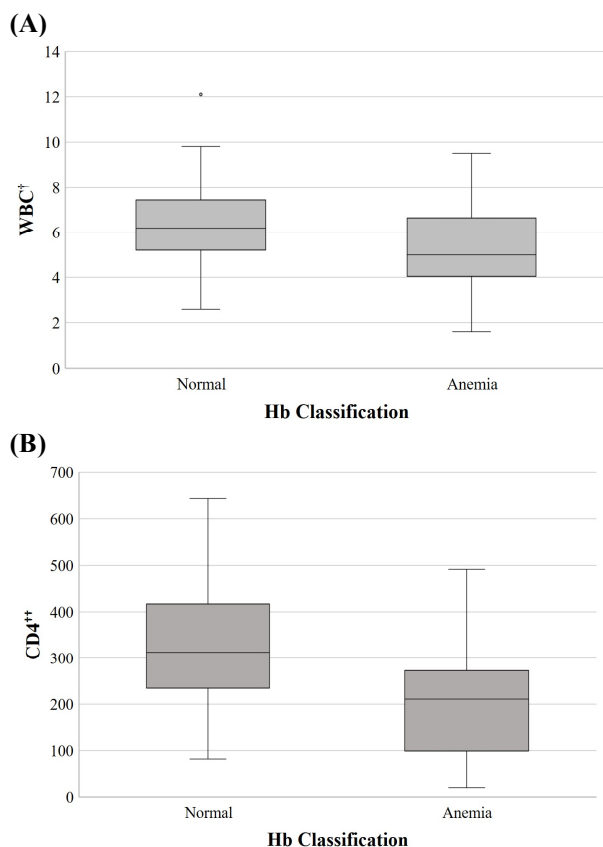
The pathophysiology of anaemia in HIV is considered to be an important factor in disease management and prevention from death and morbidity.<sup>29</sup> Further study of anaemia in HIV patients in Indonesia is necessary in order to achieve better management and outcome. The

**Table 1.** Subject description

Characteristics	Hb status (n, % or mean±SD)		p-value
	Normal (n=33)	Anemia (n=21)	
Age (years)	34.3±7.2	44.1±10.7	<0.0001 <sup>†</sup>
Sex			
Male	10, 18.5	11, 20.4	0.105
Female	23, 42.6	10, 18.5	
BMI			
Underweight	11, 20.4	4, 7.4	0.253
Non-underweight	22, 40.7	17, 31.5	
Drugs			
Containing AZT	26, 48.2	17, 31.5	0.847
Without AZT	7, 12.9	4, 7.4	
WBC (10 <sup>9</sup> /L)			
<5.0	7, 13	11, 20.4	0.018 <sup>†</sup>
≥5.0	26, 48.1	10, 18.5	
Platelets (10 <sup>9</sup> /L)			
<150	33, 61.1	18, 33.3	0.054
≥150	0	3, 5.56	
Reticulocyte (%)			
<2.0	31, 57.4	19, 35.2	0.638
≥2.0	2, 3.7	2, 3.7	
CD4 (cells/μL)			
CD4 <200	4, 7.4	9, 16.7	0.010 <sup>†</sup>
CD4 ≥200	29, 53.7	12, 22.2	
Duration of treatment (month)	29.5±18.9	46.4±26.7	0.009 <sup>‡</sup>
MCV (fL)	103±12.7	101±18.5	0.568
MCH (fmol/cells)	2.2±0.3	2.2±0.5	0.533
Total bilirubin(μmol/L)	7.4±2.1	5.9±2.4	0.040 <sup>‡</sup>
Unconjugated bilirubin (μmol/L)	4.5±1.7	3.4±1.7	0.030 <sup>‡</sup>

<sup>†</sup>Chi square test significant  $p < 0.05$ .

<sup>‡</sup>t-test significant  $p < 0.05$ .



**Figure 1.** WBC and CD4 count as risk factor of anemia. (A) Low WBC (OR 4.09, 95% CI [1.2-13.5]) and (B) low CD4 count (OR 5.44, 95% CI [1.4-21.1]) increased the risk of anemia. <sup>†</sup> $\times 10^9/L$ . <sup>‡</sup>cells/ $\mu L$ .

prevalence of anaemia observed in this study (38.8%) was lower than that of a study conducted in East Java, Indonesia (41.6%)<sup>22</sup> and Ethiopia (70.1%).<sup>30</sup> The prevalence of anaemia identified in this study is higher than that observed in other studies using cross-sectional designs that were conducted in Mexico (20.3%).<sup>28</sup> No statistical differences were noted between anaemia prevalence in male (20.4%) and female (18.5%) subjects ( $p=0.105$ ). This finding is similar to that of a study conducted in Brazil but contrasts with that of another study which found more frequent anaemia in female patients with HIV infection.<sup>4,20</sup>

Reticulocyte counts did not differ between patients with and without anaemia ( $p=0.638$ ). However, reticulocyte count is an indicator of bone marrow activity corresponding to the aetiology of anaemia. Active or suppressed bone marrow responses are indicated by reticulocyte count  $\geq 2\%$  and  $< 2\%$ , respectively. Patients with low reticulocyte counts ( $< 2\%$ ) and notable MCVs may suggest the aetiology of anaemia. Patients with  $MCV < 80.0$  fL may have iron-deficiency anaemia as secondary factor in chronic blood loss or thalassemia. Patients with  $MCV 80.0-96.0$  fL may have anaemia caused by chronic disease, drug side effects, or bone marrow abnormalities.<sup>8</sup> The mean of MCV for groups with and without anaemia was found to be higher than 96.0 fL, which is indicative of macrocytic red blood cells. Macrocytic anaemia was found in a majority of patients (12; 57.1%); however, this finding has no statistical significance. Macrocytic anaemia may be caused by ineffective RBC production as a result of nutritional deficiencies of folic acid or vitamin

**Table 2.** Logistic regression for correlates factors of anaemia

Factors	$\beta$ -value	<i>p</i> -value
Age	0.128	0.023
Duration of treatment	0.030	0.117
CD4 counts	-0.010	0.007
Total bilirubin	-5.717	0.397
Unconjugated bilirubin	2.201	0.817

B-12. Macrocytic anaemia is commonly reported in patients on ART.<sup>8,9,13</sup> Gastrointestinal complications are also common in HIV infection, leading to increased inflammation and decreased mucosal repair, as well as producing massive depletion in the lamina propria due to viral replication. This pathological change may cause malabsorption of vitamin B12 and folate.<sup>31</sup>

This study observed no statistical difference in the prevalence of anaemia between groups receiving drug regimens with or without AZT. However, the duration of treatment was found to have a moderate positive correlation with anaemia ( $r=0.35$ ,  $p<0.01$ ). Long-term use of ART was shown to increase toxicity, especially when involving AZT. The use of AZT as a nucleoside analogue reverse transcriptase inhibitor has been reported to cause hematologic toxicity, including anaemia, following its implementation in 1987. A number of drugs which are often used in combination with AZT have been demonstrated to have similar toxicities.<sup>32</sup> AZT-induced anaemia has been reported to occur in 24% of patients.<sup>33</sup> AZT is employed as a first-line drug in HIV therapy in many countries. Because of AZT's toxicity, alternative drugs are employed as first-line treatments in India (2011)<sup>34</sup> and Indonesia (2014).<sup>35</sup> Hence, routine monitoring for anaemia should be considered in relation to the duration of treatment of HIV in patients prescribed regimens with or without AZT.

Unconjugated bilirubin has both cytotoxic and cytoprotective activities. Unconjugated bilirubin is oxidized to biliverdin or binds to human albumin when it neutralizes peroxy radicals. Low unconjugated bilirubin is indicative of a physiological state which contributes to endogenous antioxidant activity.<sup>36,37</sup> Unconjugated bilirubin was found to have a weak negative correlation with anaemia ( $r=-0.29$ ,  $p<0.05$ ). This finding may indicate endogenous response to oxidative stress play role in anaemia of HIV patients.

The relationship between HIV and old age in the pathophysiology of anaemia has been postulated, as has the role of anaemia in age-related chronic disease. Anaemia in elderly patients with HIV infection is associated with a lower proinflammatory state, increased mortality, and poor quality of life.<sup>5,38</sup> This study found a moderate positive correlation between age and anaemia ( $r=0.49$ ,  $p<0.01$ ). Anaemia in HIV infection was considered with respect to the mean age  $44.1\pm 10.7$  years ( $p<0.0001$ ) of Javanese patients. In America, a tailored medicine has been recommended for older patients with HIV owing to the different consequences of the immune state leading to higher comorbid illnesses in elderly patients.<sup>39</sup>

The pathogenesis of low CD4 was reported to be independently associated with anaemia.<sup>20</sup> It was suggested

that the viral load and progression of HIV infection produce haematological abnormality as a consequence of cytokine-mediated myelosuppression.<sup>5</sup> CD4 count is easy technology and cost effective rather than viral load examination in monitoring management in HIV-positive patients.<sup>40</sup> In this study, CD4 count was observed to be a risk factor for anaemia (OR 5.44, 95% CI [1.4-21.1]), which is consistent with a previous study conducted in Nigeria.<sup>41</sup> Low CD4 counts and age were associated with anaemia after multiple regression analysis ( $p<0.05$ ). The association between CD4 counts and Hb level, producing lower concentrations in older people with HIV, was also reported in a large cohort in the UK.<sup>42</sup> The limitation of this study was that it did not assess opportunistic infections that may cause lower CD4 counts and increase the prevalence of anaemia.

### Conclusion

Routine monitoring for anaemia related to the duration of treatment for HIV infection should be considered for Javanese patients receiving treatment with or without AZT. Age and CD4 counts are dominant factors in determining of anaemia in Javanese patients with HIV infection. A tailored medicine may be necessary for older patients regarding CD4 counts.

### AUTHOR DISCLOSURES

The authors declare no conflict of interest. This work was supported by the Directorate General of Higher Education (BPPS), Ministry of Research, Technology, and Higher Education, Indonesia.

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