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# Correlation between Blood Sodium and CD4 Level in Pediatrics with Human Immunodeficiency Virus Infection

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## ABSTRACT

**Background:** Electrolyte disorders such as hyponatremia are often found in human immunodeficiency virus (HIV) patients. It is closely correlated with HIV morbidity and mortality. Sodium levels have also been reported to correlate with cluster of differentiation 4 (CD4) in adult subjects, but it is not yet known how in children with HIV infection.This study conducted to analyze the correlation between electrolyte levels, especially sodium, and CD4 levels in children with HIV infection.

**Subjects and Method:** Descriptive analytical study with a cross-sectional design. The subjects were 42 pediatric HIV patients aged 0-18 years who were willing to undergo sodium and CD4 level examinations. Subjects with liver cancer, liver cirrhosis and cardiovascular disease and opportunistic infections in HIV were excluded. Subjects were selected by consecutive sampling. The dependent variables was blood sodium levels, while the independent variables was CD4 counts, and the confounding variables were age, and ARV duration use. Sodium levels were measured using the Cbs400, Jokoh ex-d and smarlyte devices while CD4 levels were measured using the BD FACSCount device by flow cytometry. The correlation between sodium and ARV duration use on CD4 levels analyzed by Pearson test, while correlation between patient's age and CD4 levels analyzed by Spearman rank test. The multiple linear regression used to control the confounding variables.

**Results:** The average sodium level in pediatric HIV patients at Dr. Moewardi Surakarta Regional General Hospital (Mean= 131.19; SD= 5.68 mEq/L), while the average CD4 level (Mean= 940.40; SD= 464.81 cells/µL). Pearson test showed a positive and weak correlation between sodium levels and CD4 counts (r= 0.32; p = 0.040), meaning that the higher the sodium level, the higher the CD4 count. There was a negative and very weak correlation with the duration of ARV use (r= -0.18; p= 0.254), meaning that the higher the sodium level, the lower the CD4 count. Spearman Rank test showed a correlation between age and CD4 count (r= -0.52; p<0.001), meaning that the older the person, the lower the CD4 count. The results of linear regression showed that there was a significant influence between sodium levels on CD4 count (b= 24.99; p= 0.029) and patient age (b= -55.21; p=0.003).

**Conclusion:** Sodium levels have a moderate positive correlation with CD4 levels in pediatric patients with HIV infection. Examination of sodium levels can be an additional parameter in routine monitoring of the immunodeficiency status of pediatric HIV patients.

**Keywords:** Sodium, CD4, HIV.

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## BACKGROUND

Human immunodeficiency virus (HIV) is a viral infection that attacks and damages the human immune system. Acquired immunodeficiency syndrome (AIDS) is the final stage of HIV infection when the immune system has been severely damaged. Therapy that can completely cure HIV infection has not yet been found. The available treatment is antiretroviral therapy (ART) which aims to inhibit viral replication in the body. This therapy is long-term and must be taken regularly throughout the patient's life (Sharp and Hahn, 2011).

The availability and increasing use of combined ART (cART) has changed the clinical spectrum of HIV-related illness. HIV-infected patients, and especially those with AIDS, are prone to a variety of water, electrolyte, and acid-base disorders, due to modified renal physiology and exposure to a variety of infections, inflammations, endocrinology, and oncology that can worsen the clinical condition (Musso et al., 2016). Electrolyte disorders that are often experienced by HIV patients include sodium deficiency (hyponatremia) (Braconnier et al., 2017). This deficiency occurs due to hypovolemia due to renal sodium loss, also occurs due to diarrhea or vomiting, and syndrome of inappropriate antidiuretic hormone (SIADH) associated with pulmonary and intracranial disease (Kumar and Gupta, 2013).

Hyponatremia is common in HIV-infected individuals with a prevalence of around 30-60% in hospitalized patients, especially in outpatients with AIDS- related complex (ARC) . Hyponatremia is strongly correlated with HIV morbidity and mortality, because very low serum sodium levels (usually 115 mEq/L) can cause intracerebral osmotic fluid shifts and brain edema (Shu et al., 2018). HIV patients with low serum sodium levels at the time of admission can be considered for follow-up to improve patient outcomes (Braconnier et al., 2017).

Sodium is recognized as a factor that can influence inflammatory and autoimmune diseases through direct and indirect effects on immune cells (Wilck et al., 2019). Chronic hyponatremia ($Na^+$ <135 mEq/L) can disrupt CD4+ cell homeostasis through decreased serum and glucocorticoid-inducible kinase 1 (SGK1) activity that reduces Treg differentiation and memory T cell responses and creates osmotic stress. T cells exposed to a hypotonic environment experience edema, metabolic disorders, and decreased viability (Dumitru et al., 2018).

In hyponatremia, Th1/Th17 Subset decreases because TonEBP/NFAT5 is not activated so that Treg function weakens, increasing the risk of autoimmunity or infection (Wilck et al., 2019). HIV infection plays a significant role in decreasing the number of CD4 T cells which are the main indicator of a person's immune status (Okoye and Picker, 2013). Previous studies have shown a positive correlation between sodium concentration and CD4 in adult subjects aged (27-51 years) (Braconnier et al., 2017), but have never been done in children. CD4 is a type of white blood cell, namely T helper cells, which are the main target of the HIV virus. HIV infects and destroys CD4 cells, decreasing their number and weakening the immune system. Low CD4 count is a significant indicator of HIV infection and its development with levels ≤200 cells/mm3 indicating AIDS (Adrian et

al., 2021; Aurelina, 2020; Kandel et al., 2021).

Research on the correlation between blood sodium levels and CD4 levels in pediatric patients with HIV infection needs to be conducted considering that the correlation between both is expected to be an additional reference in the management of pediatric patients with HIV.

## SUBJECTS AND METHOD

### 1. Study Design

This was a descriptive analytical research using a cross-sectional design. It conducted between March to September 2024 at outpatient department of dr. Moewardi General Hospital Surakarta.

### 2. Population and Sample

The target population of this study is pediatric patient with HIV, meanwhile the accesibble population is pediatric HIV outpatient at dr. Moewardi General Hospital Surakarta. Subject were selected by consecutive based on specific criteria such as: aged 0-18 years, had complete laboratory test results consisting of electrolyte examinations, sodium levels and CD4, and agreed to be research subjects were selected as research subjects while pediatric patients with liver cancer, liver cirrhosis and cardiovascular disease and opportunistic infections in HIV were excluded. A minimum sample size required of 38 subjects, obtained from the correlation analysis sample formula for numeric data at type I and II errors of 10% and 20% with a minimum correlation coefficient considered significant of 0.40.

### 3. Study Variables

Variable study consists of sodium and CD4 level as independent and dependent variable respectively. Counfonding variable consists of gender, age and duration of ARV uses.

### 4. Operational Definition of Variables

Sodium level defines as amount of blood sodium level in pediatric HIV patient that measured by the Cbs400, Jokoh ex-d and smarlyte devices, while CD4 levels are amount of CD4 in pediatric HIV patient that measured by FACSCount device by flow cytometry. Duration of ARV use count in year, gender and age of patients obtained from anamnesis and electronical medical record.

### 5. Study Instruments

The measurement tools of this study consists of Cbs400, Jokoh ex-d and smarlyte devices to measure blood sodium level and FACSCount device by flow-cytometri to count of CD4 levels.

### 6. Data analysis

The collected research data were analyzed univariately to see the description in the form of frequency and distribution values for patient gender, and in mean and standard deviation to describe age, duration of ARV use, sodium and CD4 levels. Other analysis is Pearson test to analyze the correlation between use of ARV and sodium level with CD4 level, and Spearman rank test to see the correlation between age and CD4 level. Previously, the normality of data distribution that tested by Shapiro Wilk were conducted. Another analysis is a linear regression test to determine the predictive value of sodium levels and duration of ARV use on CD4 levels. The analysis was carried out at a significance level of $p < 0.05$ with the help of SPSS software version 22.

### 7. Research Ethics

The research was conducted after receiving ethical approval recommendations from the Research Ethics Committee of Dr. Moewardi Surakarta Hospital. Surakarta, Indonesia, No. 893/4.735/2025, on 28 april, 2025.

## RESULTS

### 1. Sample Characteristics

The number of subjects obtained from the screening results was 42 pediatric patients with the characteristics that the majority (54.8%) were male (Table 1). The average of patient age was 11.48, and SD = 4.26 years with an average use of ARVs of 7.52, and SD = 3.65 years, an average sodium level of 131.19, and SD= 5.68 68 mEq / L and an average absolute CD4 level of 940.40, and SD= 464.81 cells / µL (see Table 2). The p-value listed in Table 2 is the result of the analysis of the normality of data distribution using the Shapiro Wilk test, which found that the use of ARVs, sodium levels and absolute CD4 levels all had normal data distribution.

### 2. Bivariate Analysis

The results of the correlation test of subject characteristics with absolute CD4 levels presented in Table 3, shows that age (r=-0.52; p=<0.001) is significantly negatively correlated with CD4 levels. The younger the age, the higher the CD4 test results. The r square value for age is 0.274, which means that the variance of the absolute CD4 variable can be influenced by the age variable by 27.4%. The variable that is positively and significantly related to CD4 is sodium (r= 0.32; p=0.040), the higher the sodium, the higher the CD4 test, the r square value for sodium is 0.101, which means that the variance of the Absolute CD4 variable can be influenced by the sodium variable by 10.1%. The duration of ARV use is negatively correlated with absolute CD4 levels but not significant (r=-0.18; p=0.254), with an explanatory power of only 3.2% for CD4 levels.

**Table 1 Characteristics of subject's gender**

| Gender | Frequency (n) | Percentage (%) |
|---|---|---|
| Male | 23 | 54.8 |
| Female | 19 | 45.2 |

**Table 2. Characteristics of HIV Patient**

| Variables | Mean | SD | p |
|---|---|---|---|
| Age | 11.48 | 4.26 | 0.021 |
| Use of ARV | 7.52 | 3.65 | 0.073 |
| Sodium levels | 131.19 | 5.68 | 0.127 |
| CD4 levels | 940.40 | 464.81 | 0.085 |

**Table 3. Bivariate analysis (Pearson correlation and Rank spearman) of patient characteristivs and CD4 levels**

| Variables | CD4 Levels | |
|---|---|---|
| | r | p |
| Age* | -0.52 | <0.001 |
| Use of ARV ** | -0.18 | 0.254 |
| Sodium** | 0.32 | 0.040 |

Note: * (Rank spearman); ** (Pearson correlation)

### 3. Multivariate analysis

Multivariate analysis conducted by multiple linier regression, showed that age and sodium level were independent predictors of CD4 levels with p values of 0.003 and 0.029, respectively. Age had a significant negative effect while sodium levels had a significant positive effect on CD4 levels.

Both predictors were able to explain CD4 levels by 37.8%, meaning that there are still many other factors (62.2%) that affect CD4 levels but have not been included in this study (Table 4).

**Tabel 4. Multivariate analysis of age and sodium level on the CD4 level**

| Variables | 95%CI | | | p |
|---|---|---|---|---|
| | b | Lower limit | Upper limit | |
| Age | -55.20 | -90.12 | -20.30 | 0.003 |
| Sodium | 24.99 | 2.75 | 47.22 | 0.029 |
| Adj R Square= 37.8% | | | | |

## DISCUSSION

The results of the bivariate study showed that age affects CD4 levels, the younger the age the higher the CD4 levels, this result is supported by research by the CDC reporting that CD4 and lymphocyte levels in children have higher levels and will decrease with age until adulthood (Selik et al., 2014). HIV-infected children experience changes in the immune system similar to those in HIV-infected adults. The absolute decline in CD4 cells may not be as dramatic as in adults because infants normally have a relative lymphocytosis (Hayes, 2024).

Research conducted by Zhang showed similar things children under 18 months of age had higher absolute numbers of T and B lymphocytes compared to older children and adults. The percentage of B lymphocytes was also higher in younger children, The absolute numbers of CD4 and CD8 lymphocytes decreased with increasing age of the child. The percentage of CD4 lymphocytes decreased significantly with increasing age, while the percentage of CD8 increased, although not as much as the decrease in CD4 (Zhang et al., 2022). Basically, young children have higher lymphocyte levels compared to adolescents and adults. These levels decrease with age, accompanied by significant changes in the percentage and absolute number of CD4 and CD8 lymphocytes. Age is an important factor in analyzing the results of CD4 and CD8 lymphocyte examinations in children.

Blood sodium levels were found to be positively correlated with CD4 test results, this finding is in line with research by Ritarwan who reported that HIV patients with hyponatremia had significantly lower CD4 levels than HIV patients without hyponatremia (Mean= 208; SD= 198/µL compared to Mean =404.4; SD= 277/µL), approximately twice the HIV viral load, and prevalence approximately four times higher (Ritarwan et al., 2022). The same research results were obtained in Belgium in 2017 that hyponatremia was positively correlated with a decrease in CD4 count (r= 0.30; p<0.001) (Braconnier et al., 2017).

Sodium plays a crucial role in regulating the body's fluid balance, controlling blood pressure, influencing blood volume, maintaining heart rhythm, and supporting brain and nervous system function. Blood sodium levels in healthy people, usually ranges between 135-145 mEq/L. The findings of this study are in line with research conducted by Braconier et al. (2017) which revealed variations in the optimal sodium range, where lower than normal sodium levels before therapy were correlated with an increase in the number of CD4 cells above the average value. This condition is thought to occur due to changes in osmotic pressure between the fluid outside and inside the cell which is influenced by

sodium levels during active viral infection before treatment (Braconnier et al., 2017). The results of this study are in line with previous research that patients in advanced stages with lower CD4 counts have lower sodium levels, while patients with higher CD4 counts have higher sodium levels ($F = 7.004$; $p < 0.001$). The significant positive correlation between serum sodium and CD4 cell counts suggests that sodium levels can be used as an indicator of HIV/AIDS progression (Xu et al., 2014). Although not a specific marker of AIDS, hyponatremia is considered relevant in relation to serious complications that increase mortality in AIDS patients (Hayes, 2024).

Recommendations regarding surrogate parameters for CD4+ counts, predictors, and pre-treatment assessment options have previously been shown to have potential to be used as control factors to influence long-term CD4+ cell responses in HIV-positive patients. For example, close monitoring of sodium levels has been reported to improve clinical outcomes (Braconnier et al., 2017), because sodium levels positively affect CD4+ counts, and early treatment of sodium imbalance has been shown to contribute to the survival rate of HIV-positive patients (Xu et al., 2014).

Blood lymphocyte levels also correlate with CD4 levels in patients with HIV. Gao's study revealed a significant relationship between lymphocyte and hemoglobin levels with CD4+ levels in HIV patients. Multivariate logistic regression analysis showed that an increase The number of lymphocytes and hemoglobin were significantly associated with CD4+ levels, with odds ratio (OR) values of 3.170 and 2.545, respectively. This finding was supported by neural network modeling, which suggested that both parameters could act as predictors of CD4+ levels (Gao et al., 2023). Gao's research also identified a specific CD4+ range as a high-risk warning indicator, namely when lymphocyte levels are between 3–3.6 x $10^9$/L and hemoglobin between 150–200 g/L. This range can be a clinical reference in monitoring the condition of HIV patients related to decreasing CD4+ levels (Gao et al., 2023).

Previous study with 56 patients undergoing treatment at Prof. Dr. IGNG Ngoerah General Hospital found that CD4+ T lymphocytes had a close relationship with the number of total lymphocytes and the CD4+/CD8+ ratio in HIV patients. Meanwhile, hemoglobin levels and NLR values also showed a correlation with CD4+, although the relationship was not as strong as other lymphocyte parameters. These findings indicate that monitoring total lymphocytes and the CD4+/CD8+ ratio may be a more effective approach in assessing the immune status of HIV patients, while hemoglobin and NLR may have additional roles in clinical evaluation (Prianggandanni et al., 2023). Further research on the correlation between lymphocytes and CD4 levels needs to be conducted, which is expected to become another recommendation in replacement parameters other than sodium as a predictor of CD4 levels.

Positive correlation between sodium and CD4 lymphocytes by Yi et al. in a longitudinal observational study in healthy men with well-controlled variations in salt intake for a total of 205 days showed that when dietary salt intake was fixed at 12 g, 9 g, or 6 g for a period of 50, SD= 10 days, the absolute number of blood monocytes was positively correlated with salt intake and revealed an interesting correlation between salt consumption and the immune system. Healthy volunteers who consumed a high-salt diet (≥15 grams NaCl/day) for a week experienced a significant increase in pro-

inflammatory CD14hiCD16+ monocytes. These changes were reversible – when participants switched to a low-salt diet (≤5 grams NaCl/day), the levels of inflammatory monocytes returned to normal (Yi et al., 2015).

The results of this study are in line with the research of Luo et al, that there is a correlation between sodium and CD4 levels. Further monitoring using longitudinal flow cytometry techniques revealed significant changes in the composition of T cells. As salt intake increased, a progressive increase in CD4 + cells producing IL-17 - a pro-inflammatory cytokine - was observed. On the other hand, there was a simultaneous decrease in the population of regulatory T cells (Treg) which play a role in suppressing the immune response. This imbalance in immune regulation has the potential to influence the development of various pathological conditions, especially those related to autoimmune disorders and chronic inflammatory processes (Luo et al., 2016).

The analysis shows how variations in salt levels can modulate the subtle balance between pro- and anti-inflammatory immune components. These changes in the ratio of TH17 to Treg cells are of particular interest because of their association with the pathogenesis of various diseases involving immune dysregulation. These findings provide new insights into the influence of electrolyte factors on the body's immunological homeostasis (Luo et al., 2016).

Normal CD4 values in healthy individuals are 500–1500 cells/mm³. The average CD4 in this study was 940.40, still within the normal range, although there was wide variation, some patients were very low, namely 32 cells/mm³, indicating severe immunosuppression. This indicates the heterogeneity of the immune response in HIV patients, possibly related to the length of ARV use (average 7.52 years) or adherence to therapy.

This study has limitations that do not calculate molecular relationships such as decreased SGK1 expression and calculation of proinflammatory molecules IL-23 and TGF-β as the main pathway for sodium to affect CD4 levels. This study also did not analyze nutritional status in patients that may be related to sodium levels.

## AUTHORS CONTRIBUTION

Shahdan Taufik Maulana is the main author who conducted the research, conducted data analysis and wrote the manuscript. Husnia Auliyatul Umma examined the background and discussion of the research, while Hari Wahyu Nugroho examined the research framework.

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## CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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