



# Correlation between Hyponatremia and Cluster of Differentiation 4 in Response to Highly Active Antiretroviral Therapy Treatment in Patients with Human Immunodeficiency Virus Cerebral Toxoplasmosis

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## Abstract

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**BACKGROUND:** The proportion of HIV patients with hyponatremia was significantly higher in hospital compared to those without hyponatremia. HIV patients with hyponatremia had significantly lower CD4 cell counts, about twice the HIV viral load and an approximately four-fold higher prevalence. Hyponatremia was positively correlated with a decrease in CD4 cell count.

**AIM:** The aim of this study was to determine the correlation between hyponatremia and CD4 cells in response to HAART treatment in patients with HIV cerebral toxoplasmosis.

**METHODS:** The design of this study was correlative analytic with retrospective data collection method with secondary data sources obtained from the medical records of HIV-toxoplasma cerebral patients with hyponatremia at Haji Adam Malik Hospital Medan who met the inclusion and exclusion criteria and were included in this study. The research started from December 2021 to January 2022.

**RESULT:** This study was conducted on 30 samples of medical records consisting of 24 males and six females with a mean (min-max) age of 36.1 (23–53). There were 28 subjects (83.3%) with an effective response to treatment and two subjects (6.6%) with a less effective response to treatment. There was a significant correlation between hyponatremia and CD4 cells in response to HAART treatment ( $p < 0.005$ ;  $r = 0.0462$ ). There was a significant correlation between hyponatremia and CD4 cell count before receiving HAART treatment ( $p < 0.005$ ;  $r = 0.0526$ ).

**CONCLUSION:** There is a significant correlation between hyponatremia and CD4 cells in response to HAART treatment in patients with HIV cerebral toxoplasmosis.

## Introduction

Human immunodeficiency virus (HIV) is an infection that attacks the immune system, specifically white blood cells called cluster of differentiation 4 (CD4) cells. HIV destroys CD4 cells, weakening immunity to infection such as tuberculosis and some cancers [1].

Cerebral toxoplasmosis is an infection caused by the protozoan *Toxoplasma gondii* that occurs primarily due to the reactivation of latent tissue cysts. Primary infection can cause acute encephalitis that can be disseminated [2].

*Toxoplasma gondii* can cause serious illness in immunocompromised patients such as HIV patients. In most cases, central nervous system involvement can lead to encephalitis, which is one of the most important causes of death in patients with HIV. *Toxoplasma* encephalitis occurs in the advanced stages of HIV due to the reactivation of latent tissue cysts after a primary infection that causes focal lesions in the brains of HIV/AIDS patients [3].

Cluster of differentiation 4 synchronizes the immune system's response to pathogens. In people who are not infected with HIV, a CD4 count shows a picture of the immune system, with a higher CD4 count usually signaling a better immune system [4].

Hyponatremia is defined as plasma sodium levels  $<135$  mmol/L, a breakdown in the balance of body fluids and electrolytes most commonly found in clinical practice. Hyponatremia occurs in 15–20% of emergency care in hospitals and in nearly 20% of patients who are in critical condition. Clinical manifestations of hyponatremia can be found in a broad spectrum, ranging from asymptomatic to severe or life-threatening conditions and are associated with increased mortality, morbidity, and length of hospitalization with these conditions [5].

Highly active antiretroviral therapy (HAART) is a treatment regimen that usually consists of a combination of three or more antiretroviral drugs. HAART can also be called ARVs or combination antiretroviral therapy (cART). The main cornerstone of ARVs is the joint use of various drugs that inhibit

viral replication through several mechanisms so that the spread of viruses resistant to one agent becomes hampered by the work of the other two agents [6].

The proportion of HIV patients with hyponatremia was significantly higher hospitalized (72.3%) compared to without hyponatremia (20.0%). HIV patients with hyponatremia had significantly lower CD4 levels ( $208 \pm 198/\mu\text{l}$  vs.  $400.4 \pm 277/\mu\text{l}$ ), about twice the viral load of HIV and a roughly four-fold higher prevalence. Hyponatremia positively correlates with a decrease in CD4 count (Pearson cholera coefficient = 0.2993;  $p < 0.0001$ ) [7].

## Methods

### Study population

The research was conducted at the Polyclinic Center for Special Services and medical records of Adam Malik General Hospital, Medan from December 2021 to January 2022. The research will be conducted after being approved by the Research Ethics Committee for Health Faculty of Medicine, Universitas Sumatera Utara/Adam Malik General Hospital, Medan. A total of 30 research subjects were taken from the medical records of hospital patients Adam Malik Genera Hospital, Medan. Determination of research subjects is done according to non-random sampling methods consequently. All cerebral toxoplasma HIV-positive patients with hyponatremia were treated with anamnesa, physical examination, and support who received HAART treatment for 12 months.

### Study method

All populations of cerebral toxoplasma HIV patients with hyponatremia at Adam Malik General Hospital, Medan upheld their diagnosis with anamnesa, clinical symptoms, laboratory, head CT-Scan as seen from the medical records of Adam Malik General Hospital, Medan taken consequently that meets the inclusion criteria and no exclusion criteria. Assessment of hyponatremia and CD4 before the administration of HAART. Hyponatremia and CD4 assessment before and administration of HAART and after 12 months of HAART. Response to treatment assessed with CD4 levels after 12 months of HAART treatment.

### Statistical analysis

The data were analyzed statistically with the help of the SPSS (Statistical Product and Science Service) computer program. To find out cholera correlation between hyponatremia and CD4 in the treatment response of HAART patients with cerebral

toxoplasma HIV by conducting Pearson correlation test to find out the significance and r correlation. From the correlation coefficient obtained, it can be used to measure the degree of correlation between the two variables. When the data are not normally distributed, Spearman correlation tests are performed.

## Results

This study was conducted on 30 samples of medical records consisting of 24 males and six females with a mean (min–max) age of 36.1 (23–53). There were 28 subjects (83.3%) with an effective response to treatment and two subjects (6.6%) with a less effective response to treatment. Serum sodium levels before receiving HAART treatment showed a mean (min–max) of 122.9 (112–130). Serum sodium levels post-treatment HAART showed a mean (min-max) 139.4 (130–148). CD4 levels before receiving a response to HAART treatment obtained a mean (min–max) of 53.8 (7–89). After receiving HAART treatment, the mean (min–max) of CD4 cells was 341 (209–482). The baseline characteristics of the patients in the study group are indicated in Table 1.

**Table 1: Baseline characteristics**

Characteristics	Mean (Min–Maks)	N (30)	Percentage
Age	36.1 (23–53)		
Sex			
Male		24	80
Female		6	20
Work			
Unemployment		5	16.6
Civil servants		1	3.3
Private employees		15	50.0
Self-employed		8	26.7
Farmers		1	3.3
Status of education			
High school		21	70.0
Bachelor		9	30.0
Marital status			
Married		18	60.0
Unmarried		12	40.0
Treatment response			
Effective		28	93.3
Less effective		2	6.6
Levels of Na serum before treatment	122.9 (112-130)		
Na levels after treatment	139.4 (130-148)		
CD4 levels before treatment	52.8 (7-89)		
CD4 levels after treatment	341 (209-482)		

Based on spearman correlation tests in this study, there was a significant correlation between hyponatremia and CD4 before receiving HAART treatment ( $p < 0005$ ). The value of correlation obtained is 0.526 with moderate correlation strength. This is shown in Table 2.

Pearson's correlation test on this study found that there was a significant correlation between

**Table 2: Correlation between hyponatremia and CD4 before HAART treatment**

CD4 levels before HAART treatment	
Hyponatremia	$r = 0.526$ $p = 0,003$ $n = 30$

\*Spearman correlation test. HAART: Highly active antiretroviral therapy.

hyponatremia and CD4 in the HAART treatment response ( $p < 0.05$ ). The value of correlation obtained is 0.462 with moderate correlation strength. This is shown in Table 3.

**Table 3: Correlation between hyponatremia and CD4 in HAART treatment response**

CD4 levels after HAART treatment	
Hyponatremia	$r = 0.462$ $p = 0.010$ $n = 30$

\*Pearson correlation test. HAART: Highly active antiretroviral therapy.

## Discussion

In this study, the sex characteristics of cerebral toxoplasmosis HIV were mostly male as many as 24 subjects (80%). The results of this study are relevant to a previous study conducted by Ismayani *et al.*, in 2012, which reported that cerebral toxoplasmosis in HIV-positive patients was more experienced by men (94.3%) compared to women (5.7%) [8]. The results are almost the same as well. It was reported in the research of Achappa *et al.*, in 2011, that cerebral toxoplasmosis in HIV-positive patients was more common in men (87.9%) than women (12.1%) [9].

The most marital status of HIV cerebral toxoplasmosis patients was married as many as 18 subjects (60%). The results of this study are relevant to a previous study conducted by Sow *et al.* in 2019 at the Donka National Hospital, Conakry, Guinea which reported cerebral toxoplasmosis in HIV-positive patients more in married status (65.5%) compared to unmarried (25.3%) [10] that someone has been sexually active and if there are feelings of dissatisfaction with their partner it will trigger that person to look for another ideal man or other ideal woman [11].

In this study, of 30 study subjects with HIV toxoplasmosis cerebral with hyponatremia, the serum sodium value before receiving HAART treatment with a mean (min–max) of 122.9 (112–130). This study is relevant to the previous study by Liboro *et al.*, in 2012 which stated that 46.7% of HIV cerebral toxoplasmosis patients with hyponatremia had serum sodium levels of less than 125 mEq/L, with a range from 116–139 mEq/L [12]. This is close to the average value of serum sodium levels in a previous study by Barconnier *et al.*, in 2017, which stated that the average sodium level of HIV cerebral toxoplasmosis patients was 132.0 (130.0–134.0) [7].

The most common opportunistic infections in HIV patients are pulmonary tuberculosis, cerebral toxoplasmosis, hepatitis B, and hepatitis C. Infections of the lungs and central nervous system (such as meningitis, encephalitis, and abscesses) can cause excessive ADH release, known as SIADH and cerebral salt wasting syndrome (CSWS). The underlying

pathophysiological mechanisms involved in CSWS are decreased sympathetic nervous system outflow during intracranial disease, leading to decreased proximal tubular sodium reabsorption, inhibition of the renin-angiotensin-aldosterone system, and release of several natriuretic factors, such as Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), and other natriuretic proteins. This altered effect is the induction of natriuresis, leading to polyuria and a decrease in effective circulating volume [13], [14], [15], [16].

Based on spearman correlation tests in this study, there was a significant correlation between hyponatremia and CD4 before receiving HAART treatment ( $p < 0.005$ ). The value of correlation obtained is 0.526 with moderate correlation strength. This is in line with Braconnier *et al.*, 2017 study that the proportion of HIV patients with hyponatremia is significantly higher in hospitalization (72.3%) compared to without hyponatremia (20.0%). HIV patients with hyponatremia had significantly lower CD4 levels ( $208 \pm 198/\mu\text{l}$  vs.  $404.4 \pm 277/\mu\text{l}$ ), about twice the viral load of HIV and a roughly four-fold higher prevalence. Hyponatremia positively correlated with decreased CD4 count (Pearson coefficient correlation = 0.2993;  $p < 0.0001$ ) [17].

Sodium plays an important role in the regulation of water balance, blood pressure, blood volume, heart rhythm, brain, and nerve function. Under normal circumstances, between 135 mEq/L and 145 mEq/L. These results also show that there is a shift in the optimal range of sodium, where measurements below the normal range during the pre-treatment phase are associated with an increase in above-average CD4 counts. This may indicate a change in the osmotic gradient between the extracellular and intracellular fluids in the cells due to sodium in the presence of a viral infection before treatment [17].

Pearson's cholera test on this study found that there was significant cholera between hyponatremia and CD4 in the HAART treatment response ( $p < 0.05$ ). The value of correlation obtained is 0.462 with moderate correlation strength. This is in line with a 2014 study by Xu *et al.* that this study describes patients at an advanced stage with lower CD4 counts as having lower sodium concentrations, while patients with higher CD4 levels have higher sodium levels ( $F = 7,004$ ,  $p < 0.001$ ). Significant positive correlation between serum sodium and CD4 cell counts suggests that sodium concentrations may be used as an indicator of the development of HIV/AIDS. Although, not a specific marker of AIDS, hyponatremia is recognized as relevant to the serious complications of increased mortality of AIDS patients [18].

After the suppression of the virus during HAART treatment, there is a direct relationship between sodium counts and CD4. Similar positive correlation was observed in HIV-positive patients but without considering the phase of infection. In some

literature, it is revealed that positive correlation during HAART administration ends at approximately serum sodium >140 mEq/L, but still influences CD4 counts to achieve above-average values [8]. Determination of sodium concentration is an available, objective, and simple reference in clinical practice. Very little is known about the relationship between sodium concentration and CD4 count in the severity of HIV/AIDS patients. Further, investigation is needed to explain the relationship between sodium concentration and CD4 counts and whether hyponatremia is an independent risk factor for the severity of HIV/AIDS patients. The effect of serum sodium concentrations on the long-term survival of AIDS patients is currently unknown [18].

### Limitation

Assessments of the etiology and other comorbidities that cause hyponatremia of patients with toxoplasmosis cerebellum HIV before receiving HAART treatment are not all listed in the medical record so not all are removed.

### Conclusion

There is a significant correlation between hyponatremia and CD4 cells in response to HAART treatment in patients with HIV cerebral toxoplasmosis.

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