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# The Difference of CD4 Count Between HIV Positive Patients With Cognitive Decline and Without Cognitive Decline

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**ABSTRACT**

The relationship between low absolute CD4 lymphocyte count and neurological complications is well established in the era preceding highly active antiretroviral therapy (HAART). The aims of this study to assess the proportion of cognitive decline among HIV outclinic patient Sardjito General Hospital Yogyakarta and to determine whether the difference of CD4 count between HIV positive patients with cognitive decline and without cognitive decline. A cross sectional study with consecutive sampling. Subject eligible were 15-50 years of age, without a history of stroke, brain injury, CNS tumor and Parkinson's disease wich devided into 2 groups (CD4 > 200 cel/mm3 and d"200 cel/mm3). Cognitive function was measured by using MMSE and specified for each domain. Digit span and Trail Making Test B were added to further analyze short term memory and motor processing speed and they perform CD4 count in their blood. Ninety six patients fulfill inclution and exclution criteria. Proportion of cognitive decline was 33.3% among HIV patient. Univariate analysis showed significant difference of CD4 count between HIV positive patients with cognitive decline and without cognitive decline (p=0.02). CD4 count was significantly different in the decline of all cognitive domain on MMSE, also in the decline of short term memory and processing speed. There are high of cognitive decline among HIV outclinic patient Sardjito General Hospital Yogyakarta. CD4 count are difference between HIV positive patients with cognitive decline and without cognitive decline.

**Keywords:** Low CD4 lymphocyte count, Cognitive decline, HIV patient.

## INTRODUCTION

Worldwide development of infection of human immunodeficiency virus-1 (HIV-1) and acquired immune deficiency syndrome (AIDS) is the dangerous stage, with an estimated growth of more than 35 million infections in 2001 to 38 million in 2003, and more than 20 million deaths since 1981.[1]

At first, most serious neurological symptoms occur at the stage of systemic disease of HIV-1 and the prevalence of HAD estimated 20-30% in individuals with T-cell cluster of differentiation 4 (CD4) count is low. In addition, anemia associated with HIV-1 infection presents itself as an early predictor of high risk of neuropsychological disorders.[2]

Data from the HIV Neurobehavioral Research Center (HNRC) indicates that the asymptomatic subject has a level of neuropsychological disorders as much as two-fold compared with seronegative control have risk subjects (35.3% vs. 17.0%), and the level of disturbance increases associated with the worsening of disease (55.8% for individuals with minor infections, or the stage of the Center for Disease Control [CDC] B; 58.1% for individuals with an opportunistic infection such as AIDS). Among individuals who were classified as having

neuropsychological disorders, domains most commonly affected is the attention and speed of information processing, learning, verbal ability (especially smoothness), and motor function.

There are no specific laboratory findings for neuropsychological disorders and minor cognitive motor disorder (MCMD). CD4 lymphocyte count has only a very weak correlation with cognitive dysfunction, although the speed of CD4 cell decline may be associated with worsening of neuropsychological disorders.[3] The other immunological indicators (such as beta-2 microglobulin serum) also has only a weak correlation with the neuropsychological ability. Neuropsychological function also did not appear closely related to the amount of virus (HIV RNA) in the blood. However, a person with AIDS, a higher viral load in the cerebrospinal fluid associated with a greater tendency towards neuropsychological abnormalities, although this relationship does not seem to apply to a person who does not immunocompromise significantly (who have a CD4 count of over 200).[4]

Examination by using high-resolution MRI, in patients with AIDS was found in the primary sensory cortex are thinning, motoric and premotor by 15%. Frontopolar thinning and cortical language associated with the deterioration of the immune system can be assessed with blood levels of CD4 lymphocytes. The loss of prefrontal and parietal tissue associated with cognitive/motoric deficits. MRI results showed that HIV selectively damage the brain cortex.[5]

Highly active antiretroviral therapy (HAART) has improved the life expectancy of people infected with HIV-1 and produce at least a temporary decline in the incidence of HAD to as low as 10.5%.[6]

HIV seems to penetrate into the central nervous system rapidly after infection of peripheral, and then settled primarily within perivaskuler macrophages and microglia,[7] the current therapeutic guidelines for AIDS propose to start HAART when $CD4^+$ T cell counts began to decline. Because it may happen within a few years after peripheral infection, HAART is not likely to prevent the entry of HIV-1 into the CNS. As a result, as people are living longer with HIV-1 and AIDS prevalence of dementia may be increased and in recent years the incidence of HAD as a disease that confirms the AIDS actualy increase.[8]

Thus the need to know a good marker of clinical and laboratory-related with deterioration of complications especially neurocognitive complications in patients with HIV so that it can do the proper precautions and efficient.

This study aims to determine the proportion of cognitive decline in patients with HIV and determine whether there are differences in the numbers of CD4 lymphocytes of HIV patients with cognitive decline and without cognitive decline function.

## MATERIALS AND METHODS

This study uses cross-sectional study design as a descriptive survey to determine the proportion of cognitive impairment in patients with HIV and assess whether the difference in the number of CD4 lymphocytes in HIV patients with cognitive decline and without cognitive decline.

The population in this study were HIV positive patients are undergoing treatment at the Dr. Sardjito Hospital. As a sample of this study were all HIV positive patients were still undergoing treatment at the Dr. Sardjito Hospital and conform of the eligibility criteria. Criteria for inclusion in this study are: 1) People with HIV positive, 2) Aged less than 50 years, 3) Cooperative and able to read and write, 4) Willing to participate in research. Exclusion criteria in this study are: 1) Patients with a history of neurological disorders such as stroke, head trauma, or Parkinson disease, 2) Having a risk factor for cognitive decline such as hypertension or diabetes, heart disorders, smoking, and dyslipidemia. The number of samples to determine the relationship CD4 count in two proportion groups with cognitive decline in HIV patients with cross-sectional analytical design with no pairs of data based on samples formula are 48 people each group.

The dependent variable in this study is a cognitive decline. While the independent variables

are gender, age, education, mode of transmission, duration of suffering from HIV, anti retoviral treatment, depression, anemia and thrombocytopenia.

**Neurocognitive assessments**

Practical tools and brief to assess cognitive decline is MMSE with the maximum score is 30, and patients with cognitive decline if MMSE scores <24.[9] In addition cognitive decline detailed in each cognitive domain are;[10] 1) Orientation: disrupted if the item scores on the MMSE <10, 2) Memory Recall: interrupted when the score memory recall items on the MMSE <3, 3) Attention/ calculation: disturbed when scores of items of attention / calculation on the MMSE <5, 4) Registration: disrupted if the registration item scores on the MMSE <3, 5) Language: disrupted if the language items on the MMSE score <8, and 6) Visuospatial: disturbed when visuospatial item scores on the MMSE <1. Digit span forward: disturbed when item scores on digit span <5 and Trail Making Test B to asseses motor processing speed: disturbed when item scores >180 secons.[10] The centre for epidemiologic studies depression scale (CES-D) were used to assess depression in the subjects.

This study uses structured interview questionnaire regarding of confounding factors the occurrence of cognitive decline, completed blood counts and results of CD4 lymphocyte. This study has received a recommendation from the Ethics Committee on human research, Faculty of Medicine, Universitas Gadjah Mada. Written consent was obtained from each subject after they understood the purpose and agreed to join the study.

Analysis of the data in this study is a descriptive, univariate test using chi square test were carried out using SPSS version 16 to analyze the data.

## RESULTS

The research was conducted from December 2008 to April 2009 at Edelweiss Clinic Dr. Sardjito Hospital, Yogyakarta, Indonesia. During this period the number of people living with HIV were receiving treatment and routine control of each month is 212. Of this amount, based on inclusion and exclusion criteria obtained 96 patients as a sample study, selected sequentially and were divided into two groups; ie patients who have a CD4 lymphocyte numbers d"200 cells/mm$^3$ and lymphocyte CD4 >200 cells/mm$^3$. The number of samples of this research has met the minimum amount based on the calculation that 96 people.

**The basic characteristics of research subjects**

The results were obtained from 96 HIV patients who underwent outpatient Edelweiss Clinic Dr. Sardjito Hospital between December 2008 until April 30, 2009. Most subjects aged between 25-29 years is 37 people (37.5%). The gender ratio between male and female is 2: 1. All subjects underwent a formal education from elementary to university level, with the highest percentage of high school education is 49%. And the marital status, 63.5% are married and 36, %% not married.

Most modes of transmission through injection drug users (IDUs) that is 54 people (56.3%). Almost the same percentage found in length with HIV and most have received treatment with antiretroviral drugs (74%). In all subjects, depressed almost balanced, with 46.9% were depressed and others do not. Anemia was found only in a small proportion of

**Table 1: Univariate analysis of lymphocyte CD4 count against cognitive decline**

| CD4 count | Cognitive decline | | | | p |
|---|---|---|---|---|---|
| | Yes | | No | | |
| | n | % | N | % | |
| ≤200 cells/mm$^3$ | 23 | 47,9 | 25 | 52.1 | 0.02* |
| >200 cells/mm$^3$ | 9 | 18,8 | 39 | 81.3 | |

*stastically significant

patients (21.9%). The proportion of cognitive decline is 32 subjects, or 33.3% in HIV patients.

**The univariate analysis**

Univariate analysis conducted as an initial screening to see the relationship between independent variables with cognitive decline without taking into account a number of other covariates. The number of subjects included in each analysis is 48 patients, that is the group with the count of CD4 lymphocytes d"200 cells/$mm^3$ compared with the count of lymphocytes CD4 >200 cells/$mm^3$. From the analysis of cross-tabulation obtained p=0.02 which is statistically significant. These results indicate that the count of CD4 in HIV patients with cognitive decline differed significantly with no cognitive decline (tabel 1).

**Table 2: Univariate analysis of independent variables with cognitive decline**

| Variables | | Cognitive decline | | | | p |
|---|---|---|---|---|---|---|
| | | Yes | | No | | |
| | | n | % | n | % | |
| Aged | 15-19 | 0 | 0 | 0 | 0 | 0.023* |
| | 20-24 | 3 | 9.4 | 7 | 10.9 | |
| | 25-29 | 9 | 28.1 | 28 | 43.8 | |
| | 30-34 | 7 | 21.9 | 19 | 29.7 | |
| | 35-39 | 3 | 9.4 | 7 | 10.9 | |
| | 40-44 | 6 | 18.8 | 2 | 3.1 | |
| | 45-49 | 4 | 12.5 | 1 | 1.6 | |
| Gender Status | Male | 21 | 65.6 | 45 | 70.3 | 0.404 |
| | Female | 11 | 34.4 | 19 | 29.7 | |
| Education | <Elementary School | 0 | 0 | 0 | 0 | 0.09* |
| | Elementary School | 4 | 12.5 | 1 | 1.6 | |
| | Junior high school | 5 | 15.6 | 6 | 9.4 | |
| | Senior high school | 19 | 59.4 | 28 | 43.8 | |
| | Academic/Diploma | 2 | 6.3 | 12 | 18.8 | |
| | University | 2 | 6.3 | 17 | 26.6 | |
| Mode of transmission | IDU | 15 | 46.9 | 39 | 60.9 | 0.186 |
| | Unsafe Sex | 10 | 31.3 | 17 | 25.0 | |
| | From couples | 2 | 6.3 | 1 | 1.6 | |
| | IDU+sex | 2 | 6.3 | 7 | 10.9 | |
| | Tatto | 3 | 9.4 | 1 | 1.6 | |
| | Others | 0 | 0 | 0 | 0 | |
| Duration of suffering from HIV | <1 year | 19 | 59.4 | 25 | 39.1 | 0.048* |
| | >1 years | 13 | 40.6 | 39 | 60.9 | |
| Marital status | Yes | 25 | 78.1 | 36 | 56.3 | 0.029* |
| | No | 7 | 21.9 | 28 | 43.8 | |
| ARV therapy | Yes | 27 | 84.4 | 47 | 73.4 | 0.173 |
| | No | 5 | 15.6 | 17 | 26.6 | |
| Depression | Yes | 19 | 59.4 | 26 | 40.6 | 0.064 |
| | No | 13 | 40.6 | 38 | 59.4 | |
| Anemia | Yes | 10 | 31.3 | 11 | 17.2 | 0.097 |
| | No | 22 | 68.8 | 53 | 82.8 | |
| Thrombocytopenia | Yes | 2 | 6.3 | 3 | 4.7 | 0.543 |
| | No | 30 | 93.8 | 61 | 95.3 | |

*stastically significant

**Table 3: The count of CD4 lymphocytes in their respective domains of cognitive function**

| Variables | | Count of CD4 | | | | p |
|---|---|---|---|---|---|---|
| | | ≤200 | | >200 | | |
| | | n | % | n | % | |
| Orientation disorder | Yes | 40 | 83.3 | 30 | 62.5 | 0.019* |
| | No | 8 | 16.7 | 18 | 37.5 | |
| Disruption of registration | Yes | 0 | 0 | 0 | 0 | N/A |
| | No | 48 | 100 | 48 | 100 | |
| Impaired attention / calculation | Yes | 28 | 58.3 | 18 | 37.5 | 0.033* |
| | No | 20 | 41.7 | 30 | 62.5 | |
| Impaired of memory recall | Yes | 29 | 60.4 | 19 | 39.6 | 0.033* |
| | No | 19 | 39.6 | 29 | 60.4 | |
| Language disorders | Yes | 11 | 22.9 | 3 | 6.3 | 0.020* |
| | No | 47 | 77.1 | 45 | 93.8 | |
| Visuospatial disturbance | Yes | 31 | 64.6 | 8 | 16.7 | 0.000* |
| | No | 17 | 35.4 | 40 | 83.3 | |
| Impaired of short term memory # | Yes | 36 | 75.0 | 17 | 35.4 | 0.000* |
| | No | 12 | 25.0 | 31 | 64.6 | |
| Impaired processing speed # | Yes | 8 | 16.7 | 2 | 4.2 | 0.045* |
| | No | 40 | 83.3 | 46 | 9.,8 | |

*statistically significant; # From examination of digit span and the Trail Making Test B

**Univariate analysis of independent variables with cognitive decline**

Obtained a significant difference to the age of HIV patients with cognitive decline and without cognitive decline (p=0.02). Other variables were also significant difference is the long-suffering of HIV. There are 59.5% of the subjects with HIV less than 1 year who suffer cognitive decline, while 40.6% of the subjects with HIV more than 1 year also suffer cognitive decline. Significant differences were also obtained in the variable marital status in HIV patients with cognitive decline and without cognitive decline (p=0.029). While variables such as gender, education, mode of transmission, antiretroviral therapy, depression, anemia and thrombocytopenia did not significantly different between HIV patients with cognitive decline and without cognitive decline (Table 2).

Analysis performed on each domain MMSE plus the digit span for short term memory and the Trail Making Test B for processing speed, found that the count of CD4 was significantly different to the disorder all domains of cognitive function in MMSE and also disturbances short term memory and processing speed (Table 3).

## DISCUSSION

There were 32 (33.3%) subjects in the study had cognitive decline. The incidence of cognitive decline in this study is greater than the study by Marcotte et al. (2003) that is 12%,[11] and Njamnshi et al. (2009) is 22,2%.[12] Gendelman et al. (2005) reported on the study, that the incidence of cognitive decline in HIV ranged between 20-30%.[13]

The univariate analysis (Table 1) show the subject with the count of CD4 d"200 cells/mm$^3$ was significantly different to the occurrence of cognitive decline than subjects with the count of CD4 >200 cells/mm$^3$. Same as research by Njamnshi et al. (2009), that the risk of cognitive decline prevalence of more than 2-fold in the group with the count of CD4 d"200 cells/mm$^3$ (33.3%) than the group with the count of CD4 >200 cells/mm$^3$ (16.5%) (p=0.009).[12]

These findings also have similar results with other studies that the risk of cognitive decline was higher in the group with low CD4 cell counts and severe stages of the disease.[14]

Differences in CD4 counts affect of the interference all domains of MMSE include orientation disorder, attention/calculation, memory, language, visuospatial and impaired short term memory and processing speed (Table 3). Other studies also showed the same result, HIV infection is associated with an increased risk of cognitive decline that include domain learning ability/memory, attention, processing speed, language and sensoric and motoric function.[6] Selnes et al. (1995), reported that the decrease are the domain of attention, memory and visuoconstruction.[33]

Cognitive decline in patients with HIV is characterized by changes in three areas; 1) cognition: the ability to understand, process and remember information, 2) behavior: emotional (mood, personality), the ability to perform daily activities, and 3) the motoric coordination: the ability to coordinate muscle or movement.[15] Complete manifestation of cognitive decline is a characteristic of subcortical dementia, which affects the cerebral cortex. In later stages, the increase in metabolism occurs in the thalamus and the basal ganglia, with the decline of cognition and the slowness of the motoric as the predominant characteristic, characterized by changes in behavior at various levels.[16]

Early symptoms may not be obvious and often overlooked or misdiagnosed as depression. In the early stages, memory loss, mental slowness, difficulty in reading and comprehension, and apathy is a common complaint. Typical cognitive declines are; 1) loss of memory, especially the disruption information, 2) impaired ability to manipulate the knowledge gained, 3) changes in personality characterized by apathy, inertia and irritability, and 4) the general slowness of all the thought process.[17] On CT and MRI examination, the most common description is diffuse cortical atrophy. Functional MRI has not been done extensively, but can show abnormal regional brain activity during working memory exercises.[18]

In this study showed that the age of HIV patients with cognitive decline differed significantly with HIV patients without cognitive decline (p=0.023). Similar with Valcour et al. (2004), reported that the risk of cognitive decline increases with age.[19] Furthermore Njamnshi et al. (2009) reported different, that age is not a determinant factor for the prevalence of cognitive decline.[12] This result is also supported by research Kissel et al. (2005), that HIV-positive patients who are older are not at increased risk of cognitive decline.[20]

Education level of subjects in this study were senior high school is 50% of the population. Variable levels of education and employment in this study were not statistically different between HIV patients with cognitive decline and without cognitive decline. These results are consistent with studies by Stern et al. (2001), that of the univariate analysis for educational level did not differ significantly for the occurrence of cognitive decline (p=0.40).[21] The results were not significant in this study is likely due to the tests carried out too easily on a subject that has a high level of education and is unable to show cognitive decline occurs.[13]

Most gender status in this study were male is 68.8% compared with female is 31.2% with a ratio 2.3: 1. In contrast to the study by Njamnshi et al. (2009), that more female than male are 67% or the ratio of female : male was 2.3: 1.[12] This study showed no statistically significant difference between male and female for the occurrence of cognitive decline in both groups (p=0.404). Similar results were also reported by Njamnshi et al. (2009), that the gender status does not predispose to the occurrence of cognitive decline.[12] The results in this study differ from those reported by Chiesi et al. (1996), that a higher risk of cognitive decline occurs in female.[22]

Subjects were infected with HIV through injecting drug users (IDU) is 54 people (56.3%), the sismilar results was also reported by Djauzi & Djoerban (2003), that the prevalence of HIV positive injecting drug users (IDU) in Indonesia between 50-90%.[23] Since 1999 new phenomenon spread of HIV and AIDS, tend to shift the transmission through contact between blood, especially in the IDU. Transmission in IDUs happen quickly because of sharing needles together. Nasronudin (2007)

reported 63% transmission of infections through IDUs.[24]

The duration suffering of HIV among HIV patients with cognitive decline and without cognitive decline was significantly different with p=0.048. Patients who suffer from HIV <1 year had more cognitive decline than HIV-positive >1 year. The diagnosis of HIV infection is an event that is similar to natural disasters due to this infectious disease has a poor prognosis. Individuals who tested positive for HIV will suffer from psychological distress. Normal stress response seen when the diagnosis of HIV infection is feeling confident, feeling stiff, denial accompanied by anger, chaos acute with high anxiety and depression.[24] Patients with depression show greater cognitive decline compared with those without depression.[25]

Along with the course of the disease and the improvement of medical management, support and call to behave in a healthy life is the best choice that will impact reduce illness complaints, felt had recovered and reducing the burden of the disease, positive lifestyle changes both to couples and families.[24]

More than half (63.5%) subjects had been married. Total population is almost the same was reported by Sebit et al. (2003), that 53.9% of the population are married while the rest do not get married or divorced.[26] Marital status also significantly different between HIV patients with cognitive decline and who does not. More than 78% of patients who experience cognitive decline is married. This is probably related to psychosocial stress faced by considering the possibility of the spread of infection to the spouse or child.

Most (59%) among patients do not receive ARV therapy. Most subjects (69%) have not anemia with cognitive decline was found in 78% of subjects. Several studies have reported that the essential ARV therapy in the management of patients with HAD. In this study, patients who received antiretroviral therapy was not significantly different in patients who did not receive antiretroviral therapy for cognitive decline (p=0.173). Not significant results of this study due to the number of subjects who received antiretroviral therapy more that 74 (77%) and who did not receive antiretroviral therapy is 22 (33%) (p=0.04). Similar results were reported by Njamnshi et al. (2009), the results are not statistically significantly different between the two groups (p=0.162).[12]

According to the pathogenic development of cognitive declines, some potential therapeutic strategy to reduce neuronal damage is very important to investigate. ARV therapy with HAART which can pass through blood brain barrier be the first choice, for example stavudin, zidovudine, abacavir, efavirenz, neferapine and indinavir. ARV therapy alone is not sufficient to prevent the activation of macrophages and neurotoxic factors are released, so it needs other adjuvant therapies such as NMDA antagonists, anti-oxidants and neuroprotection.[8] The implication of this finding that the provision of ARVs are not only based on the count of CD4 alone in patients with risk of cognitive decline but also based on the stage of the disease.

In this study, depression does not have a significant difference between HIV patients with cognitive decline and without cognitive decline (p=0.064). Some research suggests that depression does not significantly impair cognition in patients with HIV.[28,29] Different results were reported by Stern et al. (2001), which both use the CES-D as inventory, that the risk of cognitive decline occurs 1.06 times in people with HIV who experience depression than those without depression (p<0.001).[21] This difference is likely due to the early manifestations of cognitive decline in HIV is very vague, so it is often mistaken for depression, alcohol and drug influence or manifestation of opportunistic diseases.[29]

Low hemoglobin level (anemia) in this study did not differ significantly between HIV patients with cognitive decline and without cognitive decline (p=0.097). Different results were reported by Stern et al. (2001) found significant differences in univariate analysis between anemia with cognitive decline, found HIV patients without anemia have an increased risk of cognitive decline by 0.76 times lower than HIV patients with anemia (p=0.006).[21] The use of cut-off point of 10 g / dl by being easy to remember and middle digits between research McArthur et al. (1993) is 10.6 g / dl,[2] and Brokering & Qaqish (2003) is 9,5 g/dl.[30]

Low platelet count was not significantly different between subjects with cognitive decline and without cognitive decline (p=0.54). Different results were reported by Alcorn (2007), that the decrease in platelets greater than 21 x 103 / mL associated with a 2-fold increased risk of dementia. Thrombocytopenia may predict early ADC 6-12 months later. Tracked platelet level in humans after a study that the platelet count dropped sharply before CNS damage develops into moderate to severe damage. This difference is likely due to the differing methods used.[31]

High prevalence of thrombocytopenia in patients with HIV who are homosexuals and injecting drug users. This is likely caused by the high frequency of hepatitis in this population. Thrombocytopenia caused by increased platelet destruction associated with primary immune complexes, trombosist decreased production, increased platelet consumption associated with thrombotic thrombocytopenic purpura (TTP).[32] Thrombocytopenia was generally experienced over 10% of untreated HIV patients, and can lead to frequent bruising, and in more severe cases of bleeding inside. Nearly one-fifth of cases recover spontaneously without treatment.[31]

Limitations of this study are not using all of neuropsychological tests to compare and confirm the results. Besides the possibility of a predictor for the occurrence of cognitive decline such as plasma viral load and cerebrospinal fluid (CSF) is not assessed systematically.

## CONCLUSION

HIV patients who underwent outpatient in Edelweiss Clinic Dr. Sardjito Hospital has a high proportion of cognitive decline. There are differences in CD4 count in HIV patients with cognitive decline and without cognitive decline. Screening should be conducted early cognitive function after a person diagnosed with HIV by a neurologist using neuropsychological tests are complete and carried out periodic monitoring of cognitive function as monitoring the immune status of patients.

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