International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 4, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Relationship between Cluster of Differentiation 4 (CD4) Levels and the Occurrence of Depression in People Living With HIV/AIDS at Ngoerah Hospital Denpasar

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Received: 19.09.2024 Revised: 22.10.2024 Accepted: 10.11.2024

ABSTRACT
Background: Depression is the most common psychiatric complaint associated with HIV/AIDS patients. The depression rate in HIV/AIDS patients is twice as high as in the general population. The issue of depression in people with HIV/AIDS requires serious attention as it can have a broad impact on their health and lives. The lower Cluster Differentiation 4 (CD4) counts in People Living with HIV/AIDS (PLWHA) can be an indicator of depression. This study aims to determine the relationship between CD4 levels and the occurrence of depression in PLWHA.
Method: Analytical observational study with a case-control design. Sampling was done using simple random sampling at the VCT Polyclinic of Ngoerah Hospital Denpasar and involved structured interviews using the Hamilton Depression Rating Scale (HDRS) questionnaire. CD4 levels were obtained from medical records to establish a relationship with depression. The study included 72 subjects, consisting of 36 in the depression group and 36 in the control group. Data analysis included variable descriptions, bivariate analysis, and multivariate analysis using logistic regression.
Results: The results of this study indicate a relationship between CD4 levels <200 and the occurrence of depression ($p < 0.001$) with an Adjusted Odds Ratio (AOR) of 14.968 and a Confidence Interval (CI) of 3.646 – 61.446.
Conclusion: There is a relationship between CD4 levels <200 and the occurrence of depression in patients with HIV/AIDS.

Keywords: HIV/AIDS, Depression, CD4, Hamilton Depression Rating Scale (HDRS)

INTRODUCTION

Human Immunodeficiency Virus & Acquired Immune Deficiency Syndrome (HIV-AIDS) is one of the global health problems, with the number of patients increasing every year. Additionally, the HIV-AIDS epidemic is a global crisis and a significant challenge to development and social progress, as well as one of the leading infectious diseases causing death (KementerianKesehatanRI, 2018).
Data from the United Nations Programme on AIDS (UNAIDS) in 2021 states that there were 37.7 million people worldwide living with HIV in 2020. Of that number, 1.5 million were new cases, and 680,000 deaths were related to AIDS in 2020 (UNAIDS, 2021). Although the trend has fluctuated, the number of HIV/AIDS cases in Indonesia has continued to increase over the years. In the eleven years from 2009 to 2019, the number of HIV cases in Indonesia reached its peak in 2019, with 50,282 cases (KementerianKesehatanRI, 2020).
In a report by the Directorate General of Disease Prevention and Control, Ministry of Health RI, dated May 29, 2020, regarding the Progress of HIV/AIDS in the First Quarter of 2020, the cumulative number of HIV/AIDS cases from 1987 to March 2020 in the Bali Province was 30,340, consisting of 22,000 HIV and 8,340 AIDS cases. This figure places Bali as the 6th highest province in terms of cumulative HIV/AIDS cases nationwide (Harahap, 2020).

HIV primarily attacks the human body by infecting CD4 lymphocytes (Cluster of Differentiation 4) or T-helper cells, resulting in a gradual decrease in the number and function of these lymphocytes over time. T-helper cells play a central role in regulating the body's immune system. As the immune system weakens, the body becomes increasingly susceptible to infections (Djoerban & Djauzi, 2014).

The progression of HIV disease is linked to the decline in the immune system, as indicated by the number of CD4 cells. HIV progression is monitored through CD4 cell counts and viral load, which is the amount of HIV RNA (Ribonucleic Acid) in the blood. The role of CD4 cells in coordinating various immunological functions means that a decrease in their number and performance leads to progressively dominant immune response disorders. In other words, a progressive decline in CD4 reflects immune deficiency (Kinanti et al., 2021).

HIV/AIDS has a significant impact on the lives of people living with HIV/AIDS (PLWHA). This impact can be experienced biologically, socially, economically, and psychologically. HIV/AIDS not only reduces physical quality but also affects the mental health of sufferers. The progressive nature of HIV/AIDS can infect the central nervous system, disrupting the balance of neurotransmitters (dopamine, serotonin, norepinephrine, etc.). During the course of the disease, PLWHA may experience psychiatric disorders such as depression, schizophrenia, bipolar disorder, substance abuse, and other psychiatric diagnoses, which are further exacerbated by medication side effects as well as stigma and discrimination from society (Wicaksono et al., 2018).

A study in the United States reported the most common psychiatric disorders among PLWHA are depression (36%), generalized anxiety disorder (GAD) (15.8%), and panic disorder (10.5%) (Nosik et al., 2021). PLWHA undergoing treatment are at risk of experiencing depression due to lifelong treatment, compounded by unsupportive social and family conditions. Depression is the most common psychiatric complaint associated with HIV/AIDS. The rate of depression in people with HIV/AIDS is twice as high as in the general population. The emotional and physical pain felt during depressive phases is associated with decreased adherence to antiretroviral treatment and worsened HIV/AIDS progression (Yuliani, 2020).

Research conducted by Thu Minh Bui et al., 2021 in Vietnam measured CD4 levels obtained from patient medical records, and depressive symptoms were screened using the Patient Health Questionnaire (PHQ-9). The results showed that moderate to severe depressive symptoms were associated with lower CD4 counts, indicating worse HIV outcomes due to depression as a comorbidity. This correlation was particularly evident in PHQ-9 items for psychomotor agitation/retardation ($p < 0.05$) and suicidal ideation ($p < 0.05$) (Bui et al., 2021). Benton et al., 2019 stated that there is a relationship between CD4 count and improved mental health and well-being. Lower CD4 counts in PLWHA could indicate untreated depression. Chronic depression can negatively impact the disease process, reduce CD4 counts, and increase viral load (Benton et al., 2019). Research by Reis et al., 2017 found that individuals with ≤ 200 CD4 cells per mm3 were 2.1 times (95% CI [1.1, 3.9]) more likely to experience depression (Reis et al., 2017).

A study in Indonesia found a significant relationship between depression, stress, and CD4 levels among PLWHA using the BDI-II (Beck Depression Inventory-II) and CD4 scores. The correlation strength between BDI-II scores and CD4 scores was 0.548, indicating a positive correlation with moderate strength (Effendy et al., 2019). Different findings regarding the relationship between CD4 levels and depression were observed in some studies. Research by Amoko et al. found the highest prevalence of depression among respondents with low CD4 counts (≤349 cells/μL), at 37.0%, and the lowest prevalence among respondents with high CD4 counts (≥500 cells/μL), at 28.3%. However, this relationship was not statistically significant ($p = 0.032$) (Amoko et al., 2020). Research by Kinyanda et al., 2018 also did not find a significant relationship between CD4 levels and depression. Kinyanda et al. found that patients diagnosed with MDD (Major Depressive Disorder) experienced an increase in CD4 cells from baseline data, at 6 months, and at 12 months. The average CD4 increase from baseline to 6 months was 48 cells/μL, while the increase from 6 months to 12 months was 40 cells/μL (Kinyanda et al., 2018).

The relationship between CD4 levels and the manifestation of depression in HIV/AIDS patients is an interesting point. Depression among PLWHA requires serious attention because it can have widespread impacts on their health and lives. Upon conducting a review, the author found a gap where there are differing findings on the relationship between CD4 levels and depression among PLWHA. Furthermore, no research on the relationship between CD4 levels and depression has been conducted in Bali, which makes this an intriguing area for investigation.

METHODS

Study Design

This study utilized an observational analytic design with a case-control approach to investigate the relationship between CD4 levels and depression among people living with HIV/AIDS (PLWHA). The design was chosen to enable comparison between two groups—cases (PLWHA with depression) and controls (PLWHA without depression)—to identify potential associations between CD4 levels and depression status. Depression symptoms were assessed using the Hamilton Depression Rating Scale (HDRS), a widely recognized tool for measuring depression severity, while CD4 levels were extracted from participants' most recent laboratory test results documented in their medical records.

The study was conducted at the Voluntary Counseling and Testing (VCT) Polyclinic of Ngoerah Hospital Denpasar, a tertiary care hospital in Bali, Indonesia. Data collection took place over a six-month period from April to September 2023. The target population for this study consisted of all PLWHA receiving care at the hospital. However, the accessible population included only those attending follow-up appointments at the VCT Polyclinic during the study period and meeting the inclusion and exclusion criteria.

Sampling

Participants were selected using random sampling to ensure representativeness and minimize selection bias. Sampling continued until the desired sample size of 36 participants was reached. The sample size was calculated using a standard formula for case-control studies, with parameters including a 95% confidence interval, 95% statistical power, and estimated proportions of CD4 < 200 among cases and controls of 0.80 and 0.40, respectively.

To be eligible for the study, participants had to meet several inclusion criteria. They were required to be aged between >18 and ≤60 years, diagnosed with HIV/AIDS by a specialist in internal medicine, and have been on antiretroviral therapy (ART) for more than six months. Cases were defined as PLWHA who exhibited psychopathological depression, as assessed by HDRS, while controls were PLWHA without psychopathological depression. All participants had to be receiving care at the VCT Polyclinic during the study period and consent to participate. Exclusion criteria included a history of psychiatric disorders, such as organic mental disorders, mood disorders, schizophrenia, or other ICD-10-coded mental health conditions (F00-F99), as well as altered consciousness (GCS < 15) or refusal to provide informed consent.

Measurements

Data collection involved structured interviews using the HDRS to assess depression symptoms, which were scored based on a 17-item scale. A total score of ≥7 on the HDRS indicated the presence of depression. Demographic information, clinical data, and CD4 levels were extracted from medical records to capture additional variables for analysis. Independent variables included CD4 levels, categorized as <200 cells/μL and ≥200 cells/μL, while the primary dependent variable was depression status. Control variables included age, gender, education level, marital status, employment status, time since HIV/AIDS diagnosis, and comorbid conditions, which were accounted for during analysis to control for confounding effects.

Data Analysis

Statistical analyses were performed using SPSS version 26. Descriptive statistics were used to summarize the characteristics of the study population and variables across case and control groups. Numerical data were presented as means and standard deviations, while categorical data were summarized as frequencies and percentages. A chi-square test was conducted to compare proportions of CD4 levels between cases and controls, followed by logistic regression analysis to assess the relationship between CD4 levels and depression while controlling for confounders. Adjusted odds ratios (AOR) with 95% confidence intervals were reported to quantify the strength of association. Statistical significance was determined at a p-value threshold of <0.05.

This systematic approach ensured robust data collection and analysis, allowing for meaningful insights into the relationship between CD4 levels and depression among PLWHA in the study population.

RESULTS

Demographic Characteristics of PLWHA

The demographic characteristics of people living with HIV/AIDS (PLWHA) are presented in Table 1. Categorical variables are displayed as frequencies and proportions, while numerical variables are presented as means and standard deviations. Based on Table 1, the mean age of PLWHA in the depression group was 38.11 ± 8.021 years, and in the control group, it was 38.44 ± 9.464 years. Statistical analysis of normality testing yielded a p-value of 0.872 (p > 0.05), indicating that the data were normally distributed.

The majority of PLWHA were male, with 51 individuals (70.8%) compared to 21 females (29.2%). Regarding education level, most participants in both groups were senior high school graduates, with 31 (86.1%) in the depression group and 27 (75%) in the control group. Marital status differed between groups, with the majority in the depression group being unmarried (21 individuals, 58.3%) and the majority in the control group being married (20 individuals, 55.6%).

Employment status showed that most participants in both groups were employed, with 28 individuals (77.8%) in the depression group and 30 individuals (83.3%) in the control group. The duration of diagnosis was predominantly within the range of 1–5 years for both groups, with 17 individuals (47.2%) in the depression group and 20 individuals (55.6%) in the control group. Regarding comorbidities, most participants in both groups had no comorbid conditions, with 24 individuals (66.7%) in the depression group and 30 individuals (75%) in the control group.

Table 1. Characteristics of Subjects Based on Case and Control Groups

Variable	Case Group n = 36	Control Group n = 36	p value
Age(year).mean ± SD	38.1±8.0	38.4±9.5	0.872
Sex			
Male	24 (66.7)	27 (75.0)	0.437
Female	12 (33.3)	9(25.0)	
Education			
Elementary School	0(0)	4(11.1)	0.370
Junior High School	1(2.8)	1(2.8)	
Senior High School	31 (86.1)	27 (75.0)	
Diploma	1(2.8)	1(2.8)	
Bachelor	3(8.3)	3(8.3)	
Employment			
Employed	28 (77.8)	30 (83.3)	0.551
Unemployed	8(22.2)	6(16.7)	
Marital Status			
Married	15 (41.7)	20 (55.6)	0.238
Unmarried	21 (58.3)	16 (44.4)	
Duration of Diagnosis			
<1 year	13 (36.1)	8(22.2)	0.473
1-5 year	17 (47.2)	20 (55.6)	
5-10year	6(16.7)	7(19.4)	
>10 year	0(0)	1(2.8)	
Comorbid Condition			
Yes	12 (33.3)	6(16.7)	0.102
None	24 (66.7)	30 (75)	

Note: CI: Confidence Interval; p: significance level, *Significance p<0.05

Description of Depression Among People Living with HIV/AIDS (PLWHA)

In this study, depression among PLWHA was assessed using the Indonesian version of the Hamilton Depression Rating Scale (HDRS), which has been translated and validated. Based on HDRS scores, depression is categorized into four intensity levels: no depression (score <7), mild depression (score 8–16), moderate depression (score 17–23), and severe depression (score >24). The distribution of depression levels among PLWHA in the case group is detailed in Table 2.

Table 2. Description of Depression Among People Living with HIV/AIDS (PLWHA)

Variable		Depression Level		
		Mild (n. %)	**Moderate (n. %)**	**Severe (n. %)**
CD4 Level	**<200**	2 (5.5)	12 (33.3)	11 (30.6)
	>200	7 (19.4)	4 (11.1)	**0 (0)**

Note: CD4: Cluster of Differentiation 4

Relationship Between Cluster of Differentiation 4 (CD4) Levels and Depression

The relationship between CD4 levels and the occurrence of depression was analyzed using the Chi-Square test. The results (Table 3) showed a significant relationship between CD4 levels and depression ($p < 0.001$), with an odds ratio (OR) of 9.4 and a 95% confidence interval (CI) of 3.171–27.951. This indicates that individuals with lower CD4 levels are significantly more likely to experience depression compared to those with higher CD4 levels.

Table 3. Relationship Between Cluster of Differentiation 4 (CD4) Levels and Depression

Variable	Depression Level	
	Yes (n=36)	**None (n=36)**

CD4 Level	**<200**	2 (5.5)	12 (33.3)
	>200	7 (19.4)	4 (11.1)

Effect of Control Variables on Depression Occurrence

In this study, to determine the effect of control variables, namely gender, highest education level, employment status, marital status, duration of diagnosis, and comorbidities, on the occurrence of depression, a multivariate analysis was conducted using logistic regression. The results are presented in Table 4. Based on the multivariate analysis, it was found that CD4 levels <200 were significantly associated with the occurrence of depression, with an Adjusted Odds Ratio (AOR) of 14.968, statistically significant at $p < 0.001$, and a 95% Confidence Interval (CI) of 3.646–61.446.

Table 4. Effect of Control Variables on Depression Occurrence

Variable	AOR	95% CI	p value
Kadar CD4 (<200)	14.968	3.646-61.446	<0.001
Jenis kelamin	0.284	0.065-1.235	0.093
Pendidikan terakhir	0.791	0.378-1.657	0.534
Status pekerjaan	0.713	0.135-3.775	0.691
Status pernikahan	0.401	0.115-1.397	0.151
Lama didiagnosis	0.903	0.563-1.448	0.672
Komorbid	0.704	0.165-2.995	0.634

Note: CI: Confidence Interval; p: significance level, *Significance p<0.05

DISCUSSION

This study was conducted at the VCT Polyclinic of Ngoerah Hospital Denpasar from May to June 2023, involving 72 PLWHA subjects, consisting of 36 individuals in the depression group (cases) and 36 in the non-depression group (controls).Among the participants, 51 were male (70.8%), and 21 were female (29.2%). This aligns with global HIV data showing that men contributed to a higher number of new HIV cases compared to women in 2019 (UNAIDS, 2021). Similarly, Manalu, Harahap, & Sinurat (2019) reported that men are more dominant in HIV/AIDS cases. The higher number of male cases is attributed to several factors, including the increase in HIV cases among men who have sex with men, commercial sex predominantly involving men, and other causes such as drug use and sharing needles. In contrast, women are usually exposed to HIV through heterosexual transmission (sexual contact or transmission from a husband) (Pujati & Narayani, 2021).

The average age of PLWHA diagnosed with depression in this study was 38.1 ± 8.0 years. This finding is consistent with research by Emrahimzadeh et al. (2018), which found that the average age of PLWHA was 38 years, with most infections occurring in the third and fourth decades of life. This age range corresponds to the productive age group for both men and women, during which sexual activity is common. Data from the Ministry of Health of Indonesia in 2021 and the quarterly report on HIV/AIDS and sexually transmitted infections (STIs) in early 2022 also confirmed that the highest percentage of HIV infections occurred in the 25–49 age group, indicating that HIV cases are predominantly found among young adults (Ditjen P2P, 2022).

Regarding education, this study found that high school graduates dominated both groups, with 31 individuals (86.1%) in the depression group and 27 individuals (75%) in the control group. This is similar to findings by Gumarianto et al. (2022), who reported that most HIV patients in their study at RSPAD Gatot Soebroto Jakarta were also high school graduates. A study in China by Zhu et al. (2018) showed that a significant proportion of respondents with HIV/AIDS had higher education levels (35.1%), while only 28.4% had lower education levels (below high school).

However, this finding contradicts Marni et al. (2020), who investigated depression levels and quality of life in PLWHA and found that most respondents had lower education levels (junior high school), while only a few had higher education (diploma or university degrees). Lower education levels contribute to the risk of HIV transmission due to limited knowledge, while higher education correlates with increased awareness and prevention efforts. Differences in these findings may be due to cultural differences between Eastern and Western countries, where individuals with higher education levels may engage in riskier behaviors such as same-sex relationships among men (Marni et al., 2020).

In this study, marital status analysis showed that most individuals in the depression group were unmarried (21 individuals, 58.3%), while the majority in the control group were married (20 individuals, 55.6%). Literature suggests that depression is more common among individuals without close interpersonal relationships or those who are divorced. Divorce increases the risk of depression, and individuals living alone are more likely to experience depression compared to those living with family (Pujiati & Setyawati, 2021). Married patients are more likely to have adequate coping resources and adaptive strategies due to support from their partners, which

fosters optimism in dealing with their condition (Monasel et al., 2022). Studies by Theofilou (2021) found higher rates of depression among those who were divorced, widowed, or unmarried due to a lack of social support and lower quality of life.

In terms of employment, most participants were employed, with 28 individuals (77.8%) in the depression group and 30 individuals (83.3%) in the control group. This finding aligns with Gumarianto et al. (2022), who found that 75.5% of HIV/AIDS patients were employed. HIV cases are more common among working individuals, often linked to those with high mobility, such as healthcare workers, sailors, drivers, and migrant laborers. Employment may contribute to risky behaviors, such as purchasing sex, which increases HIV transmission risk (Gumarianto et al., 2022).

Duration of diagnosis analysis showed that most participants had been diagnosed with HIV/AIDS for 1–5 years, with 17 individuals (47.2%) in the depression group and 20 individuals (55.6%) in the control group. Research by Olley et al. (2016) in South Africa and Yee et al. (2019) in Malaysia found that psychiatric disorders such as depression and anxiety often occur within the first few years after an HIV diagnosis.

Comorbidities also play a significant role in depression among PLWHA. Hou et al. (2020) found that HIV patients with comorbidities have a higher risk of depression and anxiety due to physical discomfort, increased medication requirements, and limited physical activity. Gultom (2022) found that common comorbidities among HIV/AIDS patients included hyponatremia, hypokalemia, dyspepsia, and anemia.

Factors influencing depression among PLWHA include genetics, age, gender, lifestyle, physical illness, chronic disease, and education level. Shresta (2014) reported no significant relationship between age, gender, or ethnicity and depression among PLWHA, suggesting these factors are not directly linked to lifestyle or daily behaviors. Factors associated with depression include perceived family support, HIV-related stigma, and socioeconomic status (Pujiati & Narayani, 2021).

Among the 36 individuals in the depression group, moderate depression was most prevalent (16 individuals, 44.4%), followed by severe depression (11 individuals, 30.6%) and mild depression (9 individuals, 25%). Depression is a common mental health issue among PLWHA, characterized by prolonged sadness, hopelessness, and reduced enthusiasm for daily activities. Research by Psaros et al. (2015) found that 40% of PLWHA experience depression, with higher rates observed in Indonesia. Saragih (2008) reported that 74% of PLWHA at Adam Malik Hospital Medan exhibited depressive symptoms.

This study found that 32 individuals (44.4%) had CD4 levels <200, with 25 (69.7%) in the depression group and 7 (19.4%) in the control group. CD4 levels ≥200 were observed in 40 individuals (55.6%), with 11 (30.6%) in the depression group and 29 (80.6%) in the control group. Studies by Owora (2018) and Shi et al. (2020) reported a significant relationship between low CD4 counts and depression severity.

Chi-square analysis revealed a significant association between CD4 levels and depression ($p < 0.0001$), with an OR of 9.4 (95% CI: 3.171–27.951). This indicates that individuals with CD4 levels <200 are 9.4 times more likely to experience depression than those with CD4 levels ≥200.

The strength of this study lies in its case-control design, allowing for causal inference between CD4 levels and depression. However, limitations include reliance on HDRS for depression screening rather than diagnostic interviews, potentially overestimating depression prevalence. Other factors such as ARV side effects, stigma, and disease stage were not explored in this study.

CONCLUSION

This study establishes a robust association between low CD4 counts and depression in PLWHA, highlighting the critical need for integrated healthcare approaches. Addressing mental health alongside physical health is essential to improving outcomes in this vulnerable population. Routine screening for depression and tailored interventions should be prioritized in HIV care programs, particularly in regions with high HIV/AIDS prevalence like Bali. Future studies should investigate long-term interventions to sustain improvements in mental and physical health.

ACKNOWLEDGEMENT

We sincerely thank the management and staff of Ngoerah Hospital, especially the VCT Polyclinic team, for their support and assistance during this research. Our heartfelt gratitude goes to the participants for their trust and cooperation, as well as to our advisors and colleagues for their valuable guidance. Lastly, we thank our families and friends for their unwavering support throughout this journey.

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