

REVIEW ARTICLE

Relationship Between Depression and Decreased Body Immunity (CD4 Lymphocyte Cells) in HIV Patients: A Literature Review

Dwi Septian Wijaya^{1*} and Wicuk Kurniawati²

1. Department of Public Health Science, the Graduate School, University of Muhammadiyah Prof. Dr. HAMKA, Jakarta, Indonesia

2. Griya Husada School of Health Sciences, Sumbawa, West Nusa Tenggara, Indonesia

*Correspondence to Dwi Septian Wijaya, BSc (dwiseptianw@gmail.com)

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Abstract

Background: Depression is a mental condition experienced by patients due to distress. Patients with HIV are likely to experience depression. The level of depression in patients with HIV is about 60% and in women has doubled. This literature review aims to examine research articles that describe the relationship between depression and decreased CD4 cell immunity in HIV patients. **Methods:** We collected articles from EBSCOhost, NCBI, BioMed Central, Google Scholar, PLOS, and PubMed using the keywords depression, immunology, CD4, and HIV. Additional inclusion criteria were articles published between the years 1993 and 2016. **Results:** We found seven articles related to the keywords. There is a significant relationship which indicates that depression can influence the decline of body immunity (CD4 cells) in HIV patients. **Conclusion:** Literature review showed that the effects of depression can reduce levels of CD4 cells in HIV patients, which may lead to an increased negative impact on the patient. This may cause the patient to have a condition that may worsen their overall situation. In this case, it is expected that health workers and families who can and do provide positive support can help patients avoid depressive disorders.

Keywords: depression, immunology, CD4, HIV

Introduction

Depression is a common mental condition that results in mood disorders or feelings, loss of interest or pleasure, feelings of guilt or low self-esteem, impaired sleep activity, impaired appetite, decreased energy, and decreased concentration. This problem can become chronic or recurrent and lead to a more severe disruption in the ability of

individuals to take care of daily responsibilities¹. The immune system plays a role in depression and may be associated with inflammatory biomarkers such as CD4 cell loss in HIV patients with major depression.

Human immunodeficiency virus (HIV) is one of the diseases that threatens human life. Currently, no country is free

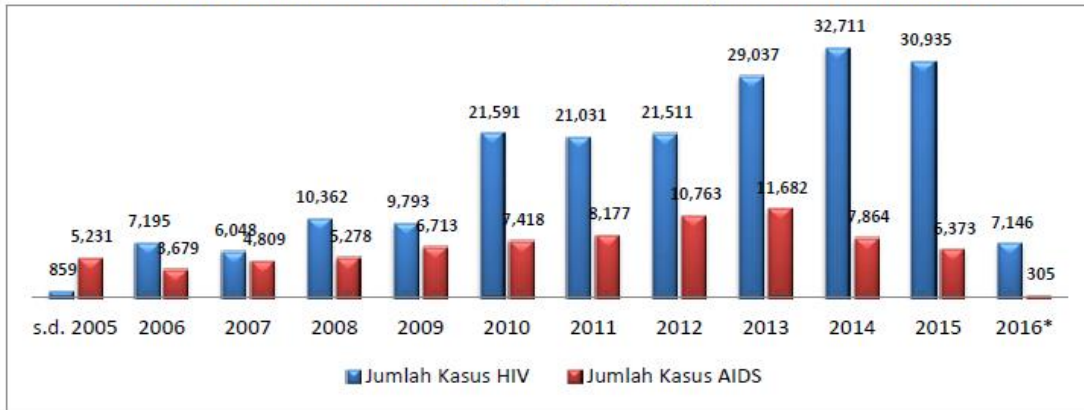
from HIV (Abbas, 2005). More than 42 million people are living with HIV infection and acquired immune deficiency syndrome (AIDS); of those, 70% are in Africa and 20% are in Asia, and nearly 3 million people die every year. This disease is very dangerous because it affects young adults with a total of about half of the 5 million new cases each year in the age range of 15–24 years².

HIV is a virus that attacks the human body's immune system, causing AIDS. HIV is a retrovirus that uses RNA. HIV attacks a type of white blood cell called a T lymphocyte, which serves to ward off infections. These specific T lymphocytes are white blood cells that have CD4 as a marker on their surface. HIV infection will damage the T lymphocytes, especially CD4+ cells, which can cause immunodeficiency. Over time, HIV will become AIDS when the CD4+ T lymphocyte levels drop below 200 cells/ μ L. The reduced CD4 value in the human body shows that reduced white blood cells or lymphocytes were supposed to play a role in overcoming infections that enter the

human body. In people with a good immune system, CD4 levels range from 1400 to 1500 cells/ μ L, whereas in people with an immune system impaired by HIV, CD4 levels have decreased, even to zero.

The HIV epidemic in Indonesia is already a global crisis and one of the most serious threats to development and social progress. This epidemic is expected to increase rapidly. The sharp increase is mostly in adult cases, especially drug users, sex workers, and their customers. Based on the 2016 Ministry of Health report, the progress of HIV in Indonesia in the fourth quarter from October to December 2016 included as many as 13,287 people. The highest percentage of HIV infection was reported in the age group of 25–49 years (68%) followed by the age group of 20–24 years (18.1%) and then the age group of 50 years (6.6%). The ratio of HIV between men and women is 2:1. The percentage of HIV risk factors is the highest in the heterosexual category (53%), followed by the MSM (Men Sex Men) category (35%), then others (11%), and, finally, sterile hypodermic needle use among IDUs (1%)³.

Grafik 1. Jumlah HIV dan AIDS yang Dilaporkan per Tahun sd Maret 2016



*Jumlah AIDS yang dilaporkan mengalami perubahan karena adanya validasi data bersama Dinkes Provinsi pada November 2015

HIV is a virus that attacks and destroys the body's immune system. When the immune system is damaged or weak, the body is susceptible to various diseases that exist around us, such as tuberculosis, diarrhea, skin diseases, etc. HIV transmission can occur through the sharing of bodily fluids, including sex with someone who has HIV/AIDS, blood or wound contact and blood transfusions, sharing needles, and from an infected mother to her unborn child. This literature aims to determine the effect of depression on the decline of CD4 cells in HIV patients.

Method

The approach we used in this literature review was to gather and analyze a wide range of research articles related to the effect of depression on the deterioration of CD4 cells in HIV patients. Articles were obtained from a variety of electronic

journals, including EBSCOhost, NCBI, BioMed Central, Google Scholar, PLOS, and PubMed, using the keywords depression, immunology, CD4, and HIV. The literature review inclusion criteria were articles published between the years 1993 and 2016, which can be accessed in full text.

Results

From this literature review, we found seven research articles that analyzed the effect of depression on the decline of CD4 cells in HIV patients. The details of the articles can be seen below.

Table 1. Study's Synthesis

No.	Research	Title	Objectives	Methods	Results
1	Sasraku Amanor Boadu, Maria Mananita S Hipolito, et al (2016)	Poor CD4 count is a predictor of untreated depression in HIV positive African Americans	To determine whether efforts to improve adherence to antiretroviral therapy (ART) minimize the negative impact of depression on the results of HIV (human immunodeficiency virus)	Cross-sectional to a cohort group of 158 people with HIV	The prevalence of MDD was 39.5% and 66% of individuals with MDD were taking antidepressants. The relationship between MDD and poor CD4+ lymphocyte count remained significant only in people who were not treated. CD4 cell counts could be a marker for clinical depression that is untreated.
2	Dina Zen Castillo, Edward Mezones-Holguin, et al (2008)	The impact of anxiety and depression associated with the CD4 cell counts of patients with HIV / AIDS in northern Peru	To determine whether anxiety and depression associated with CD4 cell counts in HIV	Cohort study	From linear regression, a significant relationship was found between CD4 counts and anxiety levels ($r^2 = 0.05597$, $F = 6.996$, $p = 0.0093$) and depression ($r^2 = 0.1177$, $F = 15.75$, $p = 0.0001$); with levels of anxiety and depression higher, lower CD4 counts were observed.
3	Frank M. Kaharuza, Rebecca Bunnell, et al, (2006)	Depression and CD4 cell counts in patients with HIV infection in Uganda	Identification of depression with CD4 counts of HIV patients	Univariate and multiple regression analysis	Patients with CD4 cell count totals of <50 cells/ μ L tend to experience depression (odds ratio 2.34, 95% confidence level, $P = 0.001$). Depression is common in HIV-

No.	Research	Title	Objectives	Methods	Results
					infected people in rural Uganda and is associated with low CD4 counts.
4	Pinheiro, Souza, et al, (2016)	Depression and diagnosis of neurocognitive impairment in HIV-positive patients	To see the prevalence of NCI in HIV-positive patients in a city in southern Brazil	Cross-sectional	The existence of a relationship between NCI and gender, age, education level, depression, for CD4 cell count. The number of CD4 cells decline in NCI with depression (PR = 1.96, 95% CI = 1.12 to 3.42).
5	Victor Obiajulu Olisah, Oluwatosin Adekeye, (2014)	Depression and CD4 cell count among patients with HIV at the University of Nigeria Teaching Hospital	To determine the prevalence of depression in patients with HIV/AIDS and its association with CD4 cell counts	Multiple regression analysis	There is indication of a relationship between depression and a patient's CD4 count; a patient with a CD4 count of <150 cells/ μ L is more likely to be depressed.
6	Jeffrey H. Burack, Donald C. Barrett, D. Ron Stall, (1993)	Symptoms of depression and the decline in CD4 lymphocytes between men infected with HIV	To determine if level of depression predicts the decline in the number of CD4 lymphocytes in HIV patients	Cohort study	In the basic outline, depression overall associated with decreased CD4 counts $-0.0285 \times 10(9)/L$ per year (95% confidence level, -0.0496 to -0.0073). Overall depression and affective depressive was associated with a decline in the number of CD4 lymphocytes.

No.	Research	Title	Objectives	Methods	Results
7	Moosa, Jeenah, Vorster, (2005)	Depression and CD4 cell counts in HIV in South Africa	To determine the occurrence of depression among HIV-positive patients using the Beck's Depression Inventory (BDI) and to determine the relationship between depressive symptoms and CD4	Comparisons were made by univariate analysis of variance (ANOVA) followed by a chi-square test. The Wilcoxon Rank test and signed-rank test were used for non-parametric data. Levene test used to test the equality of variance.	More than half (56%) of the study sample had BDI amounting to More than half (56%) of the study sample that had BDI amounting to ≥ 10 showed significant depressive symptoms. There is no significant difference in CD4 counts between groups of depressed and non-depressed ($p > 0.05$), and no correlation between CD4 cell count and BDI scores in the overall study sample ($r = 0.27, p > 0.05$).

From the seven articles in the table above, there are six articles that show the greatest relationship between depression and CD4 cell levels in HIV patients. Burack et al. (1993) suggested an association between depression and a decrease in the CD4 cell count of $-0.0285 \times 10^9/L$ per year (level of trust 95%, -0.0496 to -0.0073). Research by Olisah, Adekeye, and Sheikh (2014) states that patients with a CD4 count of <150 cells/ μL are more likely to be depressed. Research by Pinheiro et al. (2016) indicated a relationship between neurocognitive impairment (NCI) and gender, age, education level, and depression for CD4 cell count. Also, the number of CD4 cells declines in NCI with depression (PR = 1.96, 95% CI = 1.12–3.42). Kaharuza et al. (2006) reported that patients with a CD4 count total of <50 cells/ μL tend to experience depression (odds ratio 2.34, 95% confidence level, P = 0.001). Depression is common in people with HIV in rural Uganda and is associated with low CD4 counts. A study by Zeña-Castillo et al. (2008) states that a significant relationship was found between CD4 levels and anxiety levels ($r^2 = 0.05597$, F = 6.996, p = 0.0093) and between CD4 levels and depression ($r^2 = 0.1177$, F = 15.75, p = 0.0001); additionally, the higher the levels of anxiety and depression, the lower the

CD4 count. Research by Amanor-Boadu et al. (2016) stated that major depressive disorder (MDD) prevalence is 39.5% and that 66% of individuals with MDD take antidepressants. The relationship between MDD and poor CD4+ lymphocyte counts remained significant only in people who were not treated. CD4 cell counts in the MDD group could be a sign of clinical depression that is untreated in HIV patients. Similarly, the study by Moosa, Jeenah, and Voster (2005) stated that more than half (56%) of the study sample had a Beck Depression Inventory (BDI) amounting to ≥ 10 , which indicated significant symptoms of depression. The authors concluded that there was no significant difference in CD4 counts between depressed and non-depressed (p > 0.05) groups and there was no correlation between CD4 cell count and BDI scores overall in the study sample (r = 0.27, p > 0.05). Although the results of these studies did not show a significant difference, depression still affected a decrease in CD4 levels in HIV patients.

Discussion

High HIV prevalence tends to increase from year to year. In 2005, there were 5 million new cases and the number has continued to increase, amounting to

39.5 million people living with HIV. There are 4.3 million new infections with 2.8 million of those new infections occurring in Sub-Saharan Africa ⁴. According to the Director General of Communicable Disease Control and Environmental Health, Indonesian Ministry of Health, the number of people with HIV infection and AIDS from 1987 to 2008 is reported to be 5.23 per 100,000. In 2010, the cumulative number of AIDS cases was reported to be as many as 24,131 with a prevalence of 10.46% ⁵. People with HIV have a reciprocal relationship with psychiatric disorders, such as depression. Most studies on the HIV-positive population have shown a higher level of depression among women than men. Research conducted by Ickovics et al. (2001) on a sample of 765 HIV-positive women reported that 42% of study participants had chronic depressive symptoms and 35% had intermittent depressive symptoms ⁶.

Biological Systems

Based on extensive evidence that depression is prevalent in HIV patients, there may be a relationship with neurobiological changes caused by the presence of the virus in the central nervous system (CNS) ⁷. Several groups of researchers found that the virus could penetrate the central nervous system after

systemic infection of peripheral blood mononuclear cells, astrocytes, oligodendrocytes, and neuronal progenitor cells ⁸. These mechanisms are interrelated due to direct and indirect effects of psychological stress HIV patients experience, which can cause the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, subsequently activating the peripheral immune system and the central nervous system ⁹.

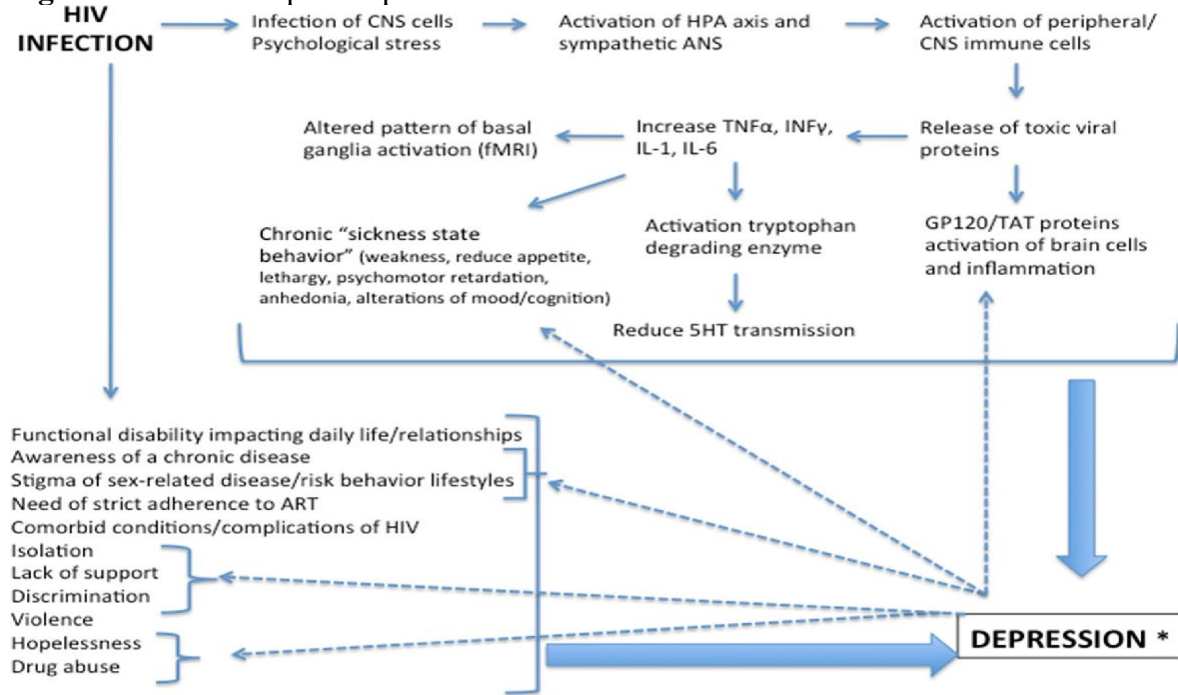
Psychological Systems

The prevalence of mental disorders in HIV patients is reported to be about 5% and 23% ⁴. Symptoms of depression are common psychiatric disorders in HIV patients, and the prevalence of depression was 53.9% in HIV-positive patients at the Hospital of Uganda in a recent study ¹⁰. The cause of low compliance with antiretroviral treatment in HIV patients is depression ¹¹. This is based on the results of the multivariate analysis, which indicated that women with HIV and AIDS coupled with symptoms of chronic depression are at twice the risk of death than women without depression ⁶. Low CD4 count and viral growth rate are also associated with increased mortality, clinical depression, dysthymia, suicide, and anxiety ¹⁰. If CD4 levels are associated with inflammatory

changes in the central nervous system, this could be a marker for HIV-associated lowered immune system, which can lead to

lymphocyte dysfunction, followed by brain damage.

Figure 2. Relationship of Depression and HIV ¹²



Conclusion

The study of this literature shows that depression greatly affects the immune system, which can lead to a decrease in the CD4 cell count of HIV patients. This can have a negative impact on people living with HIV, potentially leading to more severe symptoms. Depression is a very significant danger to people living with HIV. Based on these data, patients need their families, communities, and health care workers to provide positive support, knowledge, and spiritual development. This support can help people living with HIV to avoid the symptoms of depression.

Conflict of Interest

The authors declared that there is no competing interests exist.

References

1. Hawari. Management of Stress, Anxiety and Depression., Jakarta (2011).
2. Abbas AK, Lichtman AH PS. Celluler and Molecular Immunology. 6th ed. Of Philadelphia, WB Saunders; 2007
3. Fact Sheet: Progress Situation Report HIV/AIDS and PIMS to December 2016. www.spiritia.or.id.
4. Abbas, AK Diseases of immunity. in: V. Kumar, A. Abbas, Fausto N. (Eds.)

- Robbins and Cotran: pathologic basis of disease. 7th edition. Elsevier, Philadelphia; 2005: 245-258
5. Dirjen PPM&PL, 2010, Statistics HIV / AIDS cases in Indonesia, DG PPM & PL MOH, (online), (<http://www.aidsindonesia.or.id/repo/LT1Menkes2010.pdf>, acces October 18, 2017.
 6. Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ, Moore J. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: a longitudinal analysis from the HIV Epidemiology Research Study. *JAMA* 2001; 285: 1466-1474 [PMID: 11,255,423 DOI: 10.1001 / jama.285.11.1466]
 7. Owe-Larsson B, L Sall, Salamon E, Allgulander C. HIVinfection and psychiatric illness. *Afr J Psychiatry (Johannesbg)*. 2009; 12 (2): 115-28. The review examines the way in a comprehensive, the prevalence and clinical features of the most common HIV-related neuropsychiatric disorders.
 8. Gendelman HE, LS, L Epstein, Swindells S. *The Neurology of AIDS*. Chapman & Hall; New York: 1998
 9. Leonard BE. The concept of depression as a dysfunction of the immune system. *Curr Immunol Rev*. 2010; 6: 205-212
 10. MastTC, Kigozi G, Wabwire-Mangen F, et al. Measuring quality of life among HIV-infected women using a culturally adapted questionnaire in Rakai district, Uganda. *AIDS Care*. 2004; 16 (1): 81-94
 11. Vranceanu AM, Safren SA, Lu M, et al. The relationship of post-traumatic stress disorder and depression to antiretroviral medication adherence in persons with HIV. *AIDS Patient Care STDs*. 2008; 22: 313-321.
 12. Maria Giulia Nanni, Rosangela Caruso, Alex J. Mitchell, Elena Meggiolaro, Luigi Grassi, *Depression in HIV-Infected Patients: a Review*. Springer Science Media New York.2014