Biomedical Research and Therapy 2023, 10(4):5624-5629

Open Access Full Text Article

Original Research

Application of a Finite Mixture Model to Assess the Role of CD4+ T Cell Count as a Predictor of Memory Loss in HIV+ Patients

Mahtab Norbakhsh[1], Yousef Veisani[2], Hojjat Sayyadi[2], Fathola Mohamadian[3], Maryam Kheiry[2], Ali Delpisheh[4,*]

Use your smartphone to scan this QR code and download this article

ABSTRACT

Introduction: Memory impairment is one of the most important complications in patients with HIV infection. The syndrome is caused by reductions in brain volume and the count of circulating CD4+ lymphocytes. This study was conducted to evaluate the relationship between CD4+ lymphocyte count and memory function in HIV+ patients. **Methods**: This descriptive-analytical study was conducted on 150 HIV+ patients referred to the Behavioral Disorders Counseling Center of Kermanshah City. Memory function in patients was measured using the Wechsler memory scale. The patients' CD4+ cell counts and demographic information were extracted from their medical files. The data were recorded in STATA version 16 software and analyzed using regression and finite mixture models. **Results**: The means ± standard deviations of memory function in three classes of patients were 63.99 ± 7.02, 75.01 ± 14.72, and 85.14 ± 6.43. The results showed that a decrease in CD4+ cell count increased the risk of memory loss in patients ($P < 0.001$). In addition, higher age ($P < 0.001$), female gender ($P < 0.001$), and a lower education level ($P < 0.001$) were significantly associated with an increased risk of memory loss in HIV+ patients. **Conclusion**: The results of the present study confirmed the findings of previous studies noting memory impairment in HIV+ patients as a result of immune system suppression, including the depletion of CD4+ cells. Therefore, it is necessary to monitor cognitive function in these patients and to implement measures to strengthen their memory performance.

Key words: HIV, CD4 lymphocytes, Memory, AIDS, Finite mixture models

[1]*Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam, IR Iran*

[2]*Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, IR Iran*

[3]*Department of Psychology, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran*

[4]*Department of Epidemiology, Faculty of Health, Safety Promotion and Injury Prevention Research Centre Shahid Beheshti University of Medical Sciences Tehran, IR Iran*

Correspondence

Ali Delpisheh, Department of Epidemiology, Faculty of Health, Safety Promotion and Injury Prevention Research Centre Shahid Beheshti University of Medical Sciences Tehran, IR Iran

Email: alidelpisheh@yahoo.com

History

- Received: Mar 11, 2023
- Accepted: Apr 19, 2023
- Published: Apr 30, 2023

DOI : 10.15419/bmrat.v10i4.803

Check for updates

INTRODUCTION

Medical knowledge concerning HIV is rapidly evolving, leading to a deeper understanding of the disease, including its immunology and clinical manifestations[1]. Memory impairment, a secondary effect due to a reduction in brain volume and a decreased CD4+ cell count, is one of the most severe complications in HIV+ patients[2]. The prevalence of this disorder in these patients varies from 30% to 60% and negatively affects their quality of life. The disruption of daily functioning, the development of clinical disorders, and non-compliance with treatment are among the complications associated with cognitive disorders in HIV+ patients[3]. The prevalence of non-compliance with treatment is six times higher in patients with memory impairment than in unaffected patients, leading to misuse of medications, treatment failure, drug resistance, increased viral load, increased risk of disease transmission to healthy people, and a higher mortality rate[4].

The cells of the immune system, including CD4+ T lymphocytes, have a protective role in the brain, and the destruction of CD4+ helper T cells by the HIV virus compromises immunity against pathogenic agents. Immune system dysfunction and the depletion of CD4+ T cells predispose HIV+ patients to neurocognitive disorders and memory loss[5]. The number of CD4+ T cells and the viral load (HIV RNA) are among the laboratory markers that are routinely used to manage HIV/AIDS patients and to predict disease progression and/or treatment outcomes[6].

A study by Sanford *et al.* in 2018 showed that there was a relationship between the number of CD4+ cells and the development of cognitive impairment, and this link was more prominent in patients who had CD4+ T cell counts between 200 and 350 and below 200[7]. Moreover, Fitri *et al.* in 2018 concluded that the number of CD4+ T cells, as a clinical indicator, could be used to predict the development of cognitive disorders, including memory impairment in HIV+ patients[8]. According to the above studies, a reduction in CD4+ T cells can be a predictor of neurocognitive defects and memory impairment in HIV+ patients[9,10]. The early initiation of antiretroviral treatment can reduce the incidence and extent of cognitive impairment by elevating the number of CD4+ T cells[11].

Cite this article : Norbakhsh M, Veisani Y, Sayyadi H, Mohamadian F, Kheiry M, Delpisheh A. **Application of a Finite Mixture Model to Assess the Role of CD4+ T Cell Count as a Predictor of Memory Loss in HIV+ Patients**. *Biomed. Res. Ther.,* 2023; 10(4):5624-5629.

Finite mixture models are widely used in scientific investigation[12]. For example, Hong *et al.* (2021) formalized the concept of individualized mechanical ventilation (MV) strategy by combining finite mixture modeling (FMM) and a dynamic treatment regime (DTR)[13].

As the complete treatment of infected patients is the most effective method of preventing the propagation of HIV in the wider population, care provided to patients should be among the priorities of AIDS control and prevention programs. Therefore, the aim of this study was to evaluate the relationship between the number of CD4+ T cells and memory impairment in HIV+ patients.

METHODS

This was a descriptive-analytical study aiming to determine the relationship between CD4+ T cell count and memory function in HIV+ patients. After obtaining the necessary permissions and ethical approval, the subjects were selected by simple random sampling (using codes available in patients' profiles) among HIV+ patients referred to the Behavioral Disorders Counseling Center of Kermanshah City. The appropriate sample size was estimated as n = 150 according to a study by Diranchi *et al.*[14]. The required data, including the CD4+ T cell counts and demographic information, were extracted from the patients' files.

Inclusion criteria for participating in this study were age over 18 years, giving consent to participate, and having good physical and mental health. Learning disabilities, neurological diseases, psychological disorders, suffering from opportunistic infections, and a history of head trauma were regarded as exclusion criteria. A total of 150 patients were selected for enrollment in the study, and none were excluded from the study due to our exclusion criteria.

In this study, the Wechsler memory scale was used to assess memory function[15]. The test was administered and completed by the psychology expert of the center. This tool provides a visual scale for evaluating memory and identifies conditions such as dissociative identity disorder and memory deficits. The scale assesses learning ability, immediate retrieval, concentration and attention, orientation, and long-term memory retrieval. The subscales of the test include personal awareness, orientation, mental control, logical memory, and spatial memory. The total score for memory function is obtained by summing the scores for each of these subscales.

Statistical analysis

The data concerning memory function were divided into three classes using the regression method of finite mixture models (FMMs), and the results of the regression model were then interpreted for all three classes. STATA software (version 16) was used for data analysis, and the error rate for statistical significance was considered as $P < 0.05$.

RESULTS

The present study evaluated the memory functions of 150 patients with HIV infection. The descriptive analysis of the data using a density plot showed that the distribution of memory function scores in these patients possessed three separate modes. Therefore, three regression models using FMM were utilized to assess the risk of memory impairment in these patients (**Figure 1**).

The means $\pm$ standard deviations of the memory function scores of HIV+ patients in classes I, II, and III were 63.99 ± 7.02, 75.01 ± 14.72, and 85.14 ± 6.43, respectively, with the lowest score in class I compared to the other two classes. The ratios of patients with memory impairment in the three classes were 7%, 33%, and 58%, respectively (**Table 1**).

Regarding the risk factors for memory impairment in HIV+ patients, the predictor variables for the regression model were CD4+ T cell count, gender, age, and education level. The results showed that in patients with poorer memory (i.e., those in class I), scores decreased with increasing age ($P < 0.001$). Also, memory loss was more prominent in women than in men ($P < 0.001$), and a higher level of education had a positive effect on memory function ($P < 0.001$). The results also showed that a reduction in CD4+ T cell count increased the risk of memory loss in these patients ($P < 0.001$). In patients in classes II and III, those who had higher memory function scores than their peers in class I showed no significant relationship between CD4+ T cell count and memory loss (**Table 2**).

DISCUSSION

This study was conducted in order to investigate the relationship between the number of CD4+ T cells and memory function in HIV+ patients. The results showed that the patients could be divided into three classes in terms of memory status, where the mean score for memory function was significantly lower in class I patients compared to those in classes II and III. According to the results of the FMM regression model, CD4+ T cells had a protective role against

Table 1: Means and standard deviations of memory function scores in HIV+ patients in three different classes

Class	N	Mean	SD	Percent	Cum.
I	11	63.99	7.01	7	7
II	50	75.01	14.72	33	40
III	89	85.14	6.43	58	100
Total	150	80.25	13.77	100	100

Table 2: The risk probabilities of input variables entered in the model for three classes of HIV+ patients based on memory function

Class: I Response: Wechsler Memory Scale (WMS). Model: regression				
	Coefficient Std. err.	z	P>|z|	[95% conf. interval]
WMS				
CD4	.01 0.00	18.5	<0.001	.01 .01
Gender (Female/Male)	-9.38 0.49	-19.06	<0.001	-10.34 -8.41
Age	.193 0.03	6.04	<0.001	.13 .25
Education	4.02 0.29	13.58	<0.001	3.44 4.60
intercept	55.83 1.58	35.23	<0.001	52.72 58.93
Class: II Response: WMS. Model: regression				
	Coefficient Std. err.	z	P>|z|	[95% conf. interval]
WMS				
CD4	0 .00 0.00	0.6	0.950	-.00 .01
Gender (Female/Male)	9.68 2.38	4.21	<0.001	5.95 14.31
Age	-0.33 0.14	-2.22	0.026	-.62 - .03
Education	8.92 1.18	7.69	<0.001	6.56 11.00
intercept	54.58 7.52	7.25	<0.001	39.83 69.33
Class: III Response: WMS. Model: regression				
WMS				
CD4	0.00 0.00	1.4	0.138	-.00 .01
Gender (Female/Male)	4.83 3.40	1.4	0.156	-1.84 11.51
Age	.342 0.20	1.65	0.099	-.066 0.750
Education	-3.26 2.14	-1.52	0.127	-7.46 0.93
intercept	68.45 2.14	5.58	<0.001	44.40 92.50

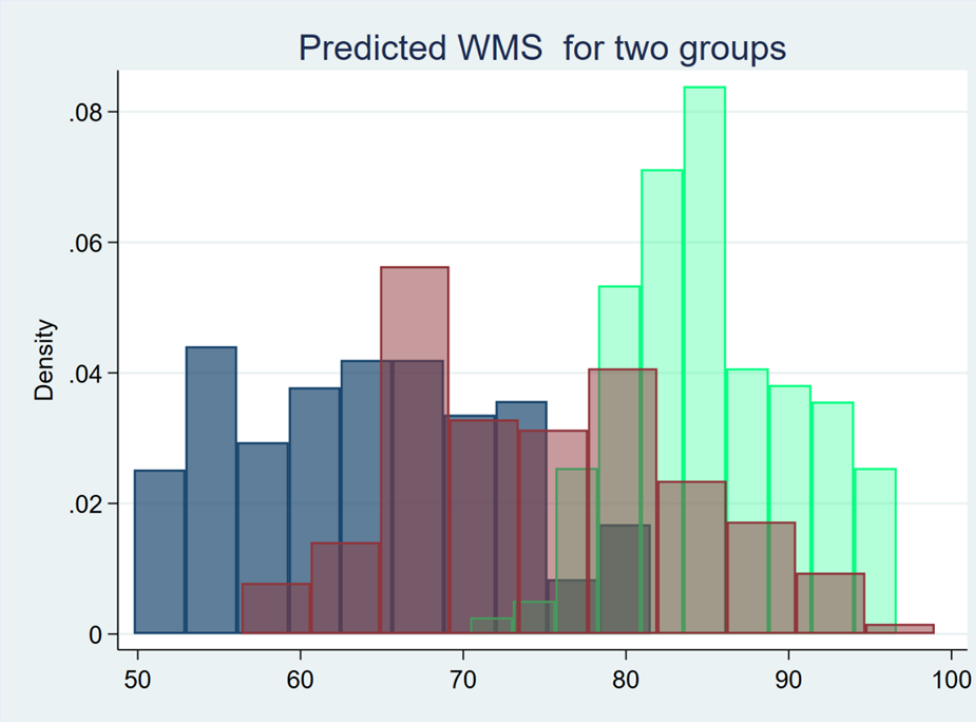

Figure 1: **Density plot for the distribution of memory function scores of HIV patients in two categories.**

memory loss in HIV+ patients, as indicated by a significantly lower mean number of CD4+ T cells in class I patients than in their counterparts in classes II and III. Previous studies investigating the relationship between memory function and the number of CD4+ T cells have also confirmed this observation, noting that a drop in CD4+ T cell count below 200 could aggravate memory impairment in HIV+ patients[8,16–19].

In this study, the average CD4+ cell count was 326, slightly below the mean count of 350 reported to be protective against memory loss in an investigation by Nicoletta *et al.* on 150 patients with HIV[20]. Progressive decline in CD4+ cell counts is associated with human immunodeficiency virus (HIV) disease progression[21]. Recent WHO guidelines advise that a CD4+ threshold of $\leq$ 200 cells/μL should be used to define patients who have advanced HIV disease[22].

According to the results of the present study, memory function in HIV+ patients decreased with increasing age. Schouten *et al.* (2014) showed that HIV-infected individuals were more susceptible to inflammatory diseases that could directly affect multiple organs and indirectly affect cellular metabolic pathways, the circulatory system, and the neuronal system[23]. Studies using neuroimaging have demonstrated continuing cerebral atrophy in HIV+ patients with disease progression and failure to control the viral load[24]. The theory that HIV infection accelerates aging is based on a series of results obtained from studies of infected older adults, and the effect is thought to be associated with persistent stimulation of the immune system, chronic low-grade inflammation, and T-cell dysfunction, symptoms that are assumed to be age-related events[25]. Our findings are consistent with the observation that HIV infection and aging both activate the immune cells residing in the brain, triggering neuroinflammation and neurodegeneration and leading to the loss of cognitive function. Previous studies have also noted an association between increasing age and a decline in verbal memory in HIV+ patients, where the disease stage was reported to be one of the most important predictors of the intensity of verbal memory impairment[26]. In another study on individuals less than 25 years old, a reduced CD4+ T cell count was associated with a lower level of verbal learning. In addition, increasing age was associated with speech delay and poor cognitive memory[27].

In the present study, the level of memory deterioration was more prominent in women compared to men, and a higher educational level had a positive impact on memory retention. Lumbanraja *et al.* (2018) showed that there was a relationship between red blood cell indices and CD4+ T cell counts in

HIV-infected women of childbearing age [28]. Another study demonstrated that neurological symptoms indicating cognitive disability were more common in HIV+ women than in HIV+ men and that measures of viral load were higher for women than for men [29]. Despite limited available evidence to date, there are arguments suggesting differences in immune system responses between men and women, and this may explain the phenomena of a greater decrease in the number of CD4+ T cells in HIV+ females and a more pronounced decrease in their cognitive functions.

CONCLUSIONS

The results of the present study support the findings of previous studies suggesting a link between CD4+ T cell depletion and memory loss in HIV+ patients. The HIV infection suppresses aspects of the immune system, including CD4+ T helper cells, and leads to memory impairment. Thus, it is necessary for healthcare providers and practitioners to pay attention to memory deterioration and its association with CD4+ T cell count. Patients should be monitored for memory status in parallel with regular checking of their CD4+ T cell counts, and they should receive appropriate supportive and therapeutic measures if necessary. Our findings suggest that future studies should investigate the signaling pathways responsible for the differences in viral load and cognitive disorders between HIV+ men and HIV+ women.

ABBREVIATIONS

None.

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

All authors equally contributed to this work, read and approved the final manuscript.

FUNDING

This research was financially supported by the Research and Technology Deputy of Ilam University of Medical Sciences.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by the research ethics committee of Ilam University of Medical Sciences under the code IR.MEDILAM.REC.1398.116.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Melhuish A, Lewthwaite P. Natural history of HIV and AIDS. Medicine (Abingdon). 2018;46(6):356–61. Available from: 10.1016/j.mpmed.2018.03.010.
2. Ripamonti E, Clerici M. The association of memory disorders and chronic HIV disease in the antiretroviral therapy era: a systematic literature review. HIV Medicine. 2020;21(1):9–20. PMID: 31603624. Available from: 10.1111/hiv.12793.
3. Cohen RA, Harezlak J, Schifitto G, Hana G, Clark U, Gongvatana A. Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. Journal of Neurovirology. 2010;16(1):25–32. PMID: 20113183. Available from: 10.3109/13550280903552420.
4. Vassallo M, Fabre R, Durant J, Lebrun-Frenay C, Joly H, Ticchioni M. A decreasing CD4/CD8 ratio over time and lower CSF-penetrating antiretroviral regimens are associated with a higher risk of neurocognitive deterioration, independently of viral replication. Journal of Neurovirology. 2017;23(2):216–25. PMID: 27815816. Available from: 10.1007/s13365-016-0490-z.
5. Miranda CS, Roque S, Santos NC, Nunes JCLP, Costa PS, Palha JA, et al. Effector memory CD4+ T cells are associated with cognitive performance in a senior population. Neurology-Neuroimmunology Neuroinflammation. 2015;2(1):1–8. Available from: 10.1212/NXI.0000000000000054.
6. Hoffmann CJ, Charalambous S, Thio CL, Martin DJ, Pemba L, Fielding KL. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. AIDS (London, England). 2007;21(10):1301–8. PMID: 17545706. Available from: 10.1097/QAD.0b013e32814e6b08.
7. Sanford R, Fellows LK, Ances BM, Collins DL. Association of brain structure changes and cognitive function with combination antiretroviral therapy in HIV-positive individuals. JAMA Neurology. 2018;75(1):72–9. PMID: 29131878. Available from: 10.1001/jamaneurol.2017.3036.
8. Fitri FI, Rambe AS, Fitri A. Correlation between lymphocyte CD4 count, treatment duration, opportunistic infection and cognitive function in human immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS) patients. Open Access Macedonian Journal of Medical Sciences. 2018;6(4):643–7. PMID: 29731931. Available from: 10.3889/oamjms.2018.152.
9. Grauer OM, Reichelt D, Grüneberg U, Lohmann H, Schneider-Hohendorf T, Schulte-Mecklenbeck A. Neurocognitive decline in HIV patients is associated with ongoing T-cell activation in the cerebrospinal fluid. Annals of Clinical and Translational Neurology. 2015;2(9):906–19. PMID: 26401512. Available from: 10.1002/acn3.227.
10. Subra C, Trautmann L. Role of T lymphocytes in HIV neuropathogenesis. Current HIV/AIDS Reports. 2019;16(3):236–43. PMID: 31062168. Available from: 10.1007/s11904-019-00445-6.
11. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS (London, England). 2011;25(14):1747–51. PMID: 21750419. Available from: 10.1097/QAD.0b013e32834a40cd.

12. Chen J. On finite mixture models. Statistical Theory and Related Fields. 2017;1(1):15–27. PMID: 29082363. Available from: 10.1080/24754269.2017.1321883.
13. Hong Y, Chen L, Pan Q, Ge H, Xing L, Zhang Z. Individualized Mechanical power-based ventilation strategy for acute respiratory failure formalized by finite mixture modeling and dynamic treatment regimen. EClinicalMedicine. 2021;36:100898. PMID: 34041461. Available from: 10.1016/j.eclinm.2021.100898.
14. Ronchi DD, Faranca I, Berardi D, Scudellari P, Borderi M, Manfredi R. Risk factors for cognitive impairment in HIV-1-infected persons with different risk behaviors. Archives of Neurology. 2002;59(5):812–8. PMID: 12020265. Available from: 10.1001/archneur.59.5.812.
15. Drozdick LW, Raiford SE, Wahlstrom D, Weiss LG. The Wechsler Adult Intelligence Scale—Fourth Edition and the Wechsler Memory Scale—Fourth Edition. 2018.; 2018.
16. Avci G, Sheppard DP, Tierney SM, Kordovski VM, Sullivan KL, Woods SP. A systematic review of prospective memory in HIV disease: from the laboratory to daily life. The Clinical Neuropsychologist. 2018;32(5):858–90. PMID: 28950745. Available from: 10.1080/13854046.2017.1373860.
17. Balaini N, Sharma A, Sharma S, Sharma A. HIV associated neurocognitive dysfunction and its association with CD4 count in HIV positive patients-a hospital based study. International Journal of Research in Medical Sciences. 2017;5(10):4259. Available from: 10.18203/2320-6012.ijrms20174479.
18. Chen X, Qiu X, Zhu C, Liu P, Huang XJ, editors. Long short-term memory neural networks for chinese word segmentation.; 2015. Available from: 10.18653/v1/D15-1141.
19. Doyle KL, Weber E, Morgan EE, Loft S, Cushman C, Villalobos J, et al. Habitual prospective memory in HIV disease. Neuropsychology. 2015;29(6):909–18. PMID: 25730731. Available from: 10.1037/neu0000180.
20. Ciccarelli N, Grima P, Fabbiani M, Baldonero E, Borghetti A, Milanini B. Baseline CD4(+) T-cell count and cardiovascular risk factors predict the evolution of cognitive performance during 2-year follow-up in HIV-infected patients. Antiviral Therapy. 2015;20(4):433–40. PMID: 25504667. Available from: 10.3851/IMP2925.
21. Kazemi A, Djafarian K, Speakman JR, Sabour P, Soltani S, Shab-Bidar S. Effect of probiotic supplementation on CD4 cell count in HIV-infected patients: a systematic review and meta-analysis. Journal of Dietary Supplements. 2018;15(5):776–88. PMID: 29185825. Available from: 10.1080/19390211.2017.1380103.
22. Organization WH. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. 2017; 2017.
23. Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clinical Infectious Diseases. 2014;59(12):1787–97. PMID: 25182245. Available from: 10.1093/cid/ciu701.
24. Pfefferbaum A, Rogosa DA, Rosenbloom MJ, Chu W, Sassoon SA, Kemper CA. Accelerated aging of selective brain structures in human immunodeficiency virus infection: a controlled, longitudinal magnetic resonance imaging study. Neurobiology of Aging. 2014;35(7):1755–68. PMID: 24508219. Available from: 10.1016/j.neurobiolaging.2014.01.008.
25. Pirrone V, Libon DJ, Sell C, Lerner CA, Nonnemacher MR, Wigdahl B. Impact of age on markers of HIV-1 disease. Future Virology. 2013;8(1):81–101. PMID: 23596462. Available from: 10.2217/fvl.12.127.
26. Seider TR, Luo X, Gongvatana A, Devlin KN, de la Monte SM, Chasman JD. Verbal memory declines more rapidly with age in HIV infected versus uninfected adults. Journal of Clinical and Experimental Neuropsychology. 2014;36(4):356–67. PMID: 24645772. Available from: 10.1080/13803395.2014.892061.
27. Nichols SL, Chernoff MC, Malee K, Sirois PA, Williams PL, Figueroa V, et al. Learning and memory in children and adolescents with perinatal HIV infection and perinatal HIV exposure. The Pediatric Infectious Disease Journal. 2016;35(6):649–54. PMID: 26967812. Available from: 10.1097/INF.0000000000001131.
28. Lumbanraja SN, Siregar D, editors. Association between red blood cell indices and CD4 count in HIV-positive reproductive women. IOP Conference Series: Earth and Environmental Science. IOP Publishing; 2018.
29. Royal W, Cherner M, Burdo TH, Umlauf A, Letendre SL, Jumare J. Associations between cognition, gender and monocyte activation among HIV infected individuals in Nigeria. PLoS One. 2016;11(2):e0147182. PMID: 26829391. Available from: 10.1371/journal.pone.0147182.