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Clinical correlation of CD4 count and dry eye disease (DED) severity among Human Immunodeficiency Virus (HIV) patients: A case study in Voluntary Counseling and Testing Clinic RSUP Prof Ngoerah, Bali

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ABSTRACT

Introduction: Dry eye disease (DED) is a condition affecting the surface of the eye and the stability of tears, influenced by various factors. It has been documented as one of the most common ocular issues in the front segment among individuals with HIV, typically appearing in the later stages of the disease. The study sought to examine the clinical relationship between CD4 count and the severity of the condition.

Method: This study was conducted as a cross-sectional analysis within a hospital setting, involving 75 HIV-positive patients (140 eyes) aged between 18 and 50 years. These patients were referred to the ophthalmology clinic in the Voluntary Counseling and Testing (VCT) center due to complaints related to ocular surface issues, and they were enrolled in the study. All patients underwent a thorough ophthalmological assessment, including the completion of a dry eye questionnaire, specifically the Ocular Surface Disease Index (OSDI), and measurement of tear film break-up time (TBUT).

Results: The research revealed a notable moderate positive correlation between CD4 count and TBUT (r=0.509; p=0.005), and a negative correlation with OSDI score (r=-0.252, p=0.035). Significant differences were observed in CD4 count between mild and moderate dry eyes (p=0.005) as well as between mild and severe dry eyes (p=0.005). No significant difference was found between moderate and severe dry eyes (p=0.435). The severity of dry eye in HIV patients appears to vary across different clinical stages of the disease, coinfection statuses, and treatment histories, although these differences did not reach statistical significance in the results.

Conclusion: A correlation exists between CD4 count and the severity of dry eye disease among HIV patients. HIV patients with lower CD4 counts are at a higher risk of developing severe dry eye disease.

Keywords: CD4, dry eye disease, tear break up time, ocular surface disease index.
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INTRODUCTION

Dry eye disease (DED), also known as dry eye syndrome, keratoconjunctivitis sicca or keratitis sicca, is a multi-factorial ocular surface and tear film instability disease, resulting in varying degree of ocular discomfort symptoms ranging from mild to severe.[1,2] Dry eye disease is one of the most common ocular conditions encountered in daily clinical practice, with worldwide prevalence between 5-50% and 27% in Indonesia specifically.[1] Several risk factors, with high level of evidence, are associated with increasing incidence of DED, including: age, sex, hormone therapy, collagen vascular disease, medication, vitamin deficiency, and previous history of corneal refractive surgery.[2,3]

Dry eye disease is characterized by a loss of homeostasis in the lacrimal functional unit and increased osmolarity of the tear film.[4] Failure of homeostatic mechanism contribute to decreased tear production and altered quality of tear constituents, resulting in a chain of subsequent inflammatory response and neurosensory abnormality of the ocular surface.[4,5] Stress to the ocular surface caused by exogenous and endogenous stress, infection, and genetic factors is postulated as the initial pathogenetic triggering mechanism.[6,7]

Human immunodeficiency virus (HIV) is a global pandemic causing morbidity and mortality to millions of people.[8] Recent data in Indonesia reported that an estimate of 640.000 people is living with HIV. Ocular manifestation in HIV-positive patient is a common finding and it is said that up to 80% patients will exhibit at least one ocular manifestation at some point during the course of the disease that correlate with CD4 count or viral load.[9,10]

Past studies focused primarily on posterior segment manifestation, however

at present, the introduction of Highly Active Antiretroviral Therapy (HAART) has dramatically changed the dynamics of HIV/AIDS clinical presentation.[11] Anterior segment is affected in about 25% of ocular manifestations associated with HIV. The cause of dry eye in HIV population is a complex mechanism involving viral-induced inflammation and destruction of lacrimal and salivary gland, as well as direct HIV infection to the conjunctiva.[11-13]

Reduced quality of life is reported in many DED patients. With increasing health burden of HIV, there is also increasing need to identify, treat, and reduce ocular morbidity that is associated with its ocular manifestation. Number of studies concerning anterior segment and ocular surface disorder in HIV-patients is now rapidly growing. As per literature, there are still no studies to date analyzing the correlation of CD4 count with severity of DED in HIV patients in Indonesia. The present study aimed to correlate level of CD4 count with severity of DED in HIV patients in Bali, Indonesia.

METHODS

Study Design and Participants

The study was a hospital-based cross-sectional investigation conducted over a duration of 33 months, spanning from June 2020 to March 2023, within the ophthalmology department of a tertiary care teaching hospital located in Bali, Indonesia. All individuals between the ages of 18 and 60 who were HIV-positive and registered at the Voluntary Counseling and Testing Clinic were included in the study. They were examined by ophthalmology residents for complaints related to ocular disease. Patients with confounding factors and comorbidities such as diabetes, corneal scars, lid abnormalities, Stevens-Johnson syndrome (SJS), and other connective tissue disorders were excluded from the study. Additionally, patients who were already receiving treatment for dry eye syndrome, taking oral contraceptive pills, pregnant females, and those using medications such as antidepressants, antihistamines, and anxiolytics, which could independently cause dry eye, were also excluded. Furthermore, seriously ill patients and those who refused to cooperate for ophthalmological examination were excluded from the study. Out of the initial 168 HIV patients examined, a total of 75 patients met the inclusion and exclusion criteria and were ultimately included in the study. All included patients were receiving Highly Active Antiretroviral Therapy (HAART).

Data Collections

Data collection was conducted using a pre-designed, pre-tested, semi-structured interview schedule, as well as from medical records. Information regarding socio-demographic characteristics such as age, gender, occupation, duration of antiretroviral therapy (ART), duration of the disease, and other relevant variables were gathered from these sources. Following the completion of the standardized proforma, each patient underwent a comprehensive ophthalmological evaluation, which included the administration of a dry eye questionnaire - the Ocular Surface Disease Index (OSDI), as well as measurement of tear film break-up time (TBUT).

Dry Eye Questionnaire – Ocular Surface Disease Index (OSDI)

The OSDI questionnaire was administered to all patients as part of the assessment process. For patients who were not proficient in English, the questions on the OSDI questionnaire were explained to them in their local language to ensure understanding. The final OSDI score was computed by multiplying the sum of all individual scores by 25 and then dividing the total by the number of questions answered. The scores range from 0 to 100, with 0-12 indicating a normal condition, 13-22 indicating mild dry eye disease (DED), 23-32 indicating moderate DED, and scores greater than 33 indicating severe DED.

Tear Film Break Up Time (TBUT)

Tear film break-up time was conducted by moistening a fluorescein strip with sterile, non-preserved saline solution and gently applying it to the inferior tarsal conjunctiva. Following multiple blinks, the tear film was evaluated using a cobalt blue filter. Tear break-up time is defined as the duration between the last blink and the initial appearance of the first randomly distributed dark discontinuity in the fluorescein-stained tear film. A tear break-up time of less than 20 seconds was deemed abnormal, with 10-20 seconds indicating mild dry eye, 5-9 seconds indicating moderate dry eye, and less than 5 seconds indicating severe dry eye.

Statistical Analysis

The data were analyzed and statistically evaluated using SPSS software, version 26 (IBM Corporation in Chicago, Illinois, USA). Quantitative data were presented as mean and standard deviation, while qualitative data were expressed as percentages. Statistical differences between proportions were assessed using either the Chi-square test or Fisher's exact test. The Spearman correlation coefficient was employed to examine the correlation between two quantitative variables. A p-value of less than 0.05 was regarded as statistically significant.

RESULTS

The study was conducted with 75 HIV patients with dry eyes. During the study, there are a total of 45 men (60%) and 30 women (40%) in which majority of patients belonged to the age group of 30-39 years with average of 36.66 years of age. Patient mostly lived around Denpasar area and 58 patients (77.33%) were actively working during recruitment of the study and had graduated either high school or university (69.33%). The sociodemographic data of the study is shown below in table 1.

Patients was mostly in stage III of HIV disease (46.67%) with each stage groups did not differ much except for stage I was only found in 7 patients (9.33%). All patients were already on ARV treatment (ART) with average length of treatment was 26.73 ± 3.12 months. CD4 count was ranging between each group and majority of patients belonged to 200-499 cells group, averaged 244.24 ± 204.86. Fifty out of 75 patients in total showed signs and symptoms corresponding to moderate dry eye (71.4%) with average TBUT was 7 ± 2.27 seconds and OSDI score 27.30 ± 5.35.

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Table 1. Socio-demographic and clinical characteristics of subjects

Variable	n (%) / mean ± SD
Gender	
Male	45 (60%)
Female	30 (40%)
Age	36.66 ± 9.21
20-29 years	14 (18.67%)
30-39 years	45 (60%)
>40 years	16 (21.33%)
Residential	
Denpasar	54 (72%)
Outside Denpasar	21 (28%)
Work background	
Working	58 (77.33%)
Not working	17 (22.67%)
Level of education	
Low (Not attending high school)	23 (30.67%)
High (Graduated high school and university)	52 (69.33%)
Dry eyes severity	
Mild	9 (8.6%)
Moderate	50 (71.4%)
Severe	16 (20%)
Tear Break Up Time (TBUT)	7 ± 2.27
Ocular Surface Disease Index (OSDI)	27.30 ± 5.35
CD4 count	244.24 ± 204.86
< 200	10 (13.33%)
200 – 499	53 (70.67%)
> 500	12 (16%)
Length of ARV treatment	26.73 ± 3.12
<1 year	12 (16%)
1-5 years	60 (80%)
>5 years	3 (4%)
Clinical stage of HIV	
Stage I	7 (9.33%)
Stage II	10 (13.33%)
Stage III	35 (46.67%)
Stage IV	23 (30.67%)
Co-infection	
Yes	47 (62.67%)
No	28 (37.33%)

30 women (40%) in which majority of patients belonged to the age group of 30-39 years with average of 36.66 years of age. Patient mostly lived around Denpasar area and 58 patients (77.33%) were actively working during recruitment of the study and had graduated either high school or university (69.33%).

The data above were analyzed using Spearman correlation because the normality test for data shown that it were not normally distributed with Kolmogorov-Smirnov test p-value = 0.003. Table 2 describes severity of dry eye disease related to different variables recorded in the study. Older age (³ 40 years) tends to experience increasing incidence of dry eye than the younger age but the result was not significant (p=0.483). Other sociodemographic variables such as gender, residential, working background and level of education was found to be not statistically correlated to severity of dry eye in HIV patients in the study. Regarding to treatment, longer duration of ARV treatment tends to be associated with increasing severity of dry eye, but the result was not statistically significant (p=0.228). Lastly, patients who develop severe dry eye disease tend to have lower CD4 count < 200 compared to higher CD4 group with significant statistical difference (p=0.005).

Bivariate analysis of CD4 with TBUT and CD4 with OSDI were both proven significant statistically with p-value 0.005 and 0.035 respectively. The coefficient of the correlation was positive for CD4 and TBUT with r = 0.509, while the correlation between CD4 and OSDI was negatively related with r = -0.252. The association between CD4 and dry eyes severity was analyzed using ANOVA and was shown statistically significant with p-value = 0.005.

This ANOVA result was then further analyzed with post hoc test using Bonferroni approach. There is a significant difference of CD4 count between mild dry eyes and moderate dry eyes with p-value = 0.005. This difference in CD4 count also significantly different between mild dry eyes and severe dry eyes (p-value = 0.005). However, there was no significant difference between moderate and severe dry eyes in terms of CD4 count (p-value = 0.475).

DISCUSSION

The results of this study indicate that there is a significant relationship between lower CD4 counts and increasing severity of dry eye disease. A low CD4 count also correlates with a lower TBUT and higher OSDI score. This study used TBUT and OSDI as dry eye disease parameters because based on the Tear Film & Ocular Surface Society Dry Eye Workshop (TFOS DEWS II), dry eye must be diagnosed based on a combination of subjective symptoms and objective examination. Objective symptoms of dry eye can be evaluated by TBUT, Schirmer's test without anesthesia, Rose Bengal stain, osmolarity test, and assessment of meibomian dysfunction. Subjective examination can be evaluated with the OSDI questionnaire.[4]

Dry eye disease is one of the most common ocular manifestations in HIV patients. The reported prevalence of dry eye disease in HIV patients reaches 11-50%[2], even one study reported a prevalence of up to 84.2%.[11] Dry eye disease can cause ocular discomfort and contribute to poor quality of life, emphasize the importance for investigating its risk factor, including CD4.

Table 2. Distribution of subjects and severity of dry eye according to sociodemographic and clinical characteristics

Variables	Dry Eye Severity			p-value
	Mild (n=9) n (%)	Moderate (n=50) m (%)	Severe (n=16) n (%)	
Gender				
Male	4 (8.89)	31 (68.89)	10 (22.22)	
Female	5 (16.67)	19 (63.33)	6 (20.00)	0.380
Age				
20 – 29 Years	0 (0.00)	10 (71.42)	4 (28.58)	
30 – 39 Years	6 (13.33)	31 (68.89)	8 (17.78)	0.483
>40 years	3 (18.75)	9 (56.25)	4 (25.00)	
Residential				
Denpasar	6 (11.11)	39 (72.22)	9 (16.67)	
Outside Denpasar	3 (14.28)	11 (52.38)	7 (33.33)	0.112
Work background				
Working	6 (10.34)	39 (67.24)	13 (22.41)	
Not working	3 (17.64)	11 (64.70)	3 (17.64)	0.231
Level of education				
Low	1 (4.34)	18 (78.26)	4 (17.39)	
High	8 (15.38)	32 (61.53)	12 (23.07)	0.102
Length of ARV treatment				
< 1 year	0 (0.00)	9 (75.00)	3 (25.00)	
1 - 5 years	9 (15.00)	39 (65.00)	12 (20.00)	0.085
> 5 Years	0 (0.00)	2 (66.67)	1 (33.33)	
Clinical stage of HIV				
Stage I	2 (28.57)	5 (71.43)	0 (0.00)	
Stage II	2 (20.00)	6 (60.00)	2 (20.00)	
Stage III	4 (11.42)	20 (57.14)	11 (31.42)	0.513
Stage IV	1 (4.34)	19 (82.60)	3 (13.04)	
Coinfection				
Yes	6 (12.76)	29 (61.70)	12 (25.54)	
No	3 (10.71)	21 (91.30)	4 (17.39)	0.228
CD4				
< 200	0 (0.00)	3 (30.00)	7 (70.00)	
200-499	4 (7.54)	41 (77.36)	8 (15.09)	0.005
>500	5 (41.67)	6 (50.00)	1 (8.33)	

Table 3. Coefficient correlation of CD4 with TBUT and OSDI

Variables	CD4	
	r	p-value
Tear Break-Up Time	0.509	0.005
Ocular Surface Disease Index	-0.252	0.035

The results of this study were supported by several previous studies. Gowda et al stated that HIV patients with high CD4 counts had a lower prevalence of dry eye disease. The results of the Schirmer's test were positive in 58.8% of eyes in patients with a CD4 count <100 cells/mm3, indicating that there is a lack of aqueous layer in conditions of low CD4 counts. The study also showed more positive TBUT results for DED in the group with CD4 <100 cells/mm3 than in the group with CD4 counts of 100-500 cells/mm3 and >500 cells/mm3. In addition, the Rose Bengal stain was all negative in HIV patients with a CD4 count >500 cells/mm3.[14]

Mathebula et al compared the results of Schirmer's and TBUT in 130 HIV/Aids patients on ART with 48 controls. These results showed that the Schirmer and TBUT results were lower in HIV patients than the controls. There was a significant correlation between the CD4 count and Schirmer's results (r=0.7) and between the CD4 count and TBUT (r=0.48). Dry eye was found more often in patients with CD4 count <200 cells/mm^3.[11] A similar study by Sharma et al showed a significant correlation between CD4 count with Schirmer test without anesthesia and TBUT in 90 eyes. However, this study did not show a relationship between the CD4 count and the OSDI score. Patients with low CD4 counts showed a trend of severe dry eye, although this relationship was not significant.[15]

Nguyen et al found that meibomian gland dropout was more common in HIV patients than controls, even though the patients did not experience significant dry eye symptoms. This emphasizes the structural damage of the meibomian glands which is the origin of dry eye disease can occur even before symptoms of dry eye disease are felt. Meibomian gland dropout also correlated negatively with CD4 count (r=-0.69).[16]

The mechanism of dry eye disease in HIV patients is still unclear, but it is hypothesized to be due to the infiltration

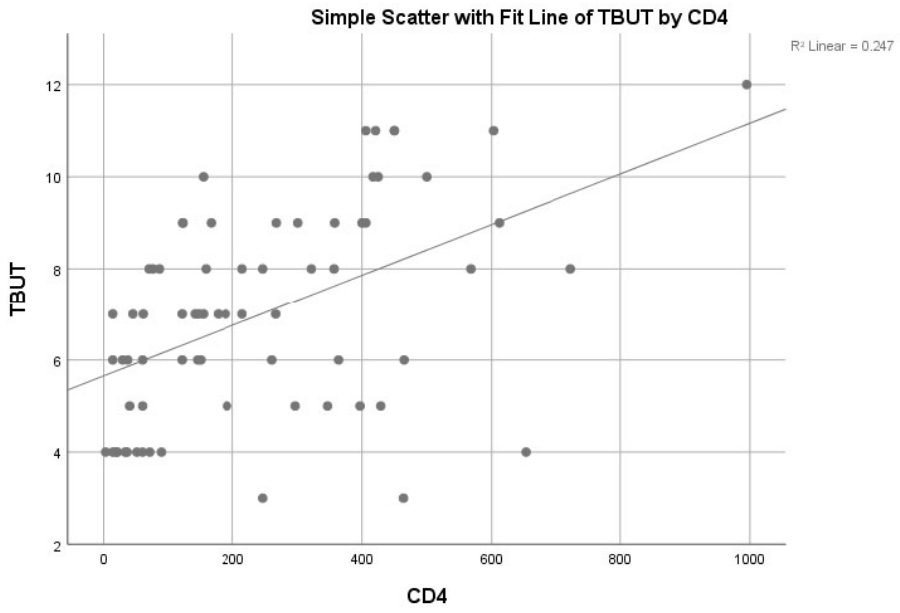

Figure 1. Scatter and plot graph showing CD4 and TBUT correlation.

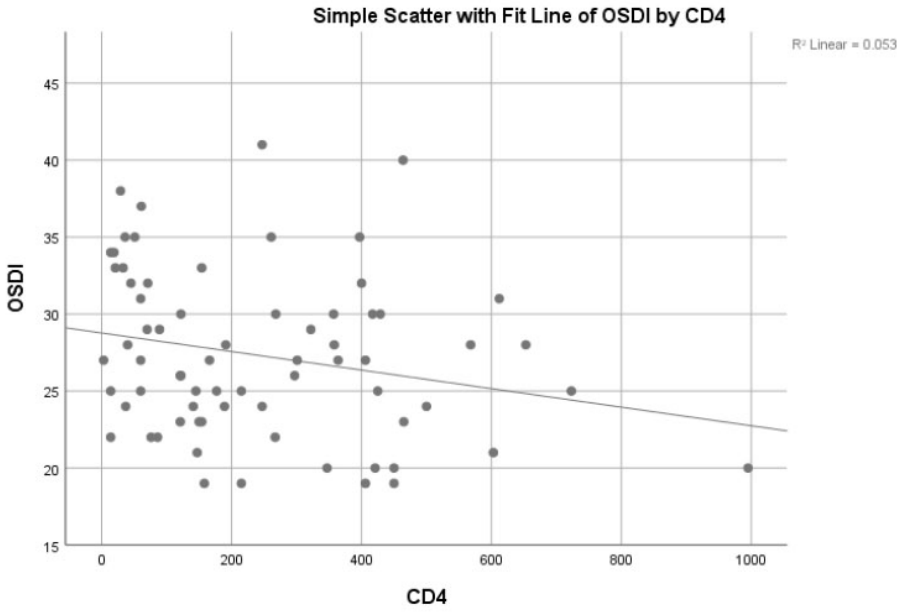

Figure 2. Scatter and plot graph showing CD4 and OSDI correlation.

Table 4. ANOVA Analysis of CD4 and Dry Eyes Severity

Dry Eyes Severity	CD4			
	n	Mean ± SD	95% CI	p-value
Mild	9	554.17 ± 227.20	315.73 – 792.60	**0.005**
Moderate	50	232.28 ± 168.44	184.41 – 280.15	
Severe	16	154.14 ± 205.73	35.36 – 272.93	

of the HIV virus into the lacrimal function unit (LFU), which includes the conjunctiva, lacrimal glands, meibomian glands, and the cornea.[11] This is evidenced by the discovery of HIV RNA in tears of patients with low CD4 counts or those not taking ART, but none in patients with high CD4 counts. The discovery of HIV RNA in tears indicates HIV replication in the lacrimal glands.[7] This was also confirmed by Nguyen et al who stated that there was damage to the meibomian glands in HIV patients which was correlated with the CD4 count. This finding implies that meibomian gland dysfunction may be a reflection of immune-driven meibomian gland damage that occurs early in HIV infection. Increased immune cell recruitment, which may be pertinent to a variety of immune-mediated illnesses, is one potential route for immune-driven injury to the meibomian gland.[16]

Under normal circumstances, there are extremely tight cell junctions that limit blood flow from the retina (blood retinal barrier). The HIV virus produces Tat protein which causes an increase in BRB permeability, so that the HIV virus can enter the eye and replicate within the eye. The HIV virus then enters the LFU mediated by lymphocytes, macrophages, dendritic cells, and CD4 T cells. This is the reason why HIV can only infiltrate the LFU when the CD4 count is low. Such infiltration will result in disruption of the lacrimal function unit (LFU), including destruction of the lacrimal acini, ductal system, and conjunctiva.[17] Disorders of the LFU will lead to tear deficiency and increased evaporation, causing dry eye. Another mechanism of dry eye in HIV patients according to Gichuhi and Arunga is the long-term use of ART and HIV-mediated vitamin A deficiency, although on the other hand ART also causes an increase in CD4 and the body's immune system.[9]

The strength of this study is the ability to highlight the correlation of CD4 and the severity of dry eye disease in a study with representative sample size and exclude the possible confounding factors. We performed detailed anamnesis and ophthalmological examination to rule out the confounding factors. However, this study still has some limitations. There were some patients who refused to have their eyes examined, that could lead to selection bias. The reasons for the patient to refuse eye exam were mostly because they feel little to no disturbing eye complaints, were in a hurry, or had their eyes examined previously whether in ophthalmologist or in optometrist. In fact, routine eye examination is important to detect the ocular manifestations of HIV. Even though during the previous examination the results of the patient's eye

examination were normal, it did not rule out the possibility of abnormalities being found on subsequent examinations. The sample in this study was also less varied because it only took samples of patients who came to the VCT clinic. Patients who can come to the polyclinic usually have better clinical conditions and CD4 than patients in the emergency room or wards. This study also has not evaluated the duration of ART consumption, which could be a confounding factor.

CONCLUSION

There is a correlation between CD4 Count and dry eye disease among HIV patients. The lower the CD4, the higher the risk for HIV patients to get severe dry eye disease. This shows the importance of CD4 control and monitoring to prevent more serious ocular morbidity and manifestation related to HIV.

CONFLICT OF INTEREST

All authors report no conflict of interest exist with regards to this study.

ETHICAL STATEMENT

This study has obtained ethical clearance with No: 2361/UN14.2.2.VII.14/LT/2022.

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AUTHORS' CONTRIBUTION

All authors contributed equally in preparation of the study, writing, and drafting this manuscript.

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