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Ocular manifestation of HIV-positive patients in VCT clinic of tertiary hospital in bali, indonesia



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ABSTRACT

Introduction: Human Immunodeficiency Virus (HIV) and Acquired Immuno Deficiency Syndrome (AIDS) have become health problems that causing complications in the eye. This study was structured to determine the characteristics, description of ocular manifestations and their relationship with CD4 levels and HIV RNA.

Method: This is a descriptive study, conducted June to November 2020. The samples taken were selected by snowball sampling of patients with HIV infection who attended the VCT clinic Sanglah General Hospital Bali, Indonesia. Data analysis was performed using characteristic analysis and the relationship between variables was analyzed using the chi-square method.

Result: A total of 71 HIV patients including 57.7% male and 42.3% female. Majority patients age group is those who were more than 40 years old (54.9%) and from Denpasar (52.11%). About 52.1% of patients had been diagnosed with HIV for 1-5 years, with 91.5% were having received ART therapy. Of a total of 28 out of 71 patients (39.4%) had HIV-related ocular manifestations.

Conclusion: Ocular manifestations occurred more frequently at detectable viral load levels and CD4 counts of 250-500 cells/ μ L. There was no significant association between ocular manifestations and CD4 and HIV RNA levels with almost the same prevalence in men and women. Voluntary eye examinations by asymptomatic HIV patients are still difficult.

Keywords: *Human Immunodeficiency Virus*, ocular manifestations, characteristic, Bali.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) and Acquired Immuno Deficiency Syndrome (AIDS) have become health problems since the first case in 1980. This infection causes a gradual decrease in CD4 + T lymphocytes leading to opportunistic infections and neoplasia, then 70% of patients infected with HIV develop complications later on the eye.¹

World Health Organization (WHO) estimates that since the early 1980s, more than 50 million people worldwide have been infected with HIV, and the global prevalence rate is estimated at 0.8%. It is possible that 15,000 to 20,000 new infections occur each day. More than 1 million children are infected with HIV. Nationally, the estimated HIV prevalence

in the population aged 15 - 49 years in the epidemic area is concentrated at 0.4%, while in the provinces of Papua and West Papua it is 2.4% in the population of the same age group. The seven provinces with the largest number of PLWHA are Papua, West Papua, DKI Jakarta, West Java, Central Java, East Java and Bali.²

Eye abnormalities are reported in 6-48% of HIV patients in Ghana, 8-48% in India, 24 - 46% in China, 25% in Ethiopia, 29% in Korea, 34% in Thailand, 43% in Nepal, 45% in United States and 54% in Indonesia. HIV patients experience blindness ranging from 6.9-23% of all HIV patients. The most common eye conditions in adults are HIV retinopathy/microvasculopathy, dry eye, optic neuropathy, and atrophy. Cytomegalovirus (CMV) retinitis is seen in nearly 30% to 40%

of patients with HIV, uveitis, and Herpes Zoster Ophthalmicus (HZO); whereas in children the most common are peripheral retinal vessel perivasculitis, lacrimal gland dysfunction, CMV retinitis, and HZO.³ Unlike other eye diseases, eye infections in these immunosuppressed patients have signs of minimal inflammation.

Anterior segment involvement in HIV includes sika keratoconjunctivitis, keratitis, and iridocyclitis. Meanwhile, the involvement of the posterior segment in HIV is quite common and can cause vision loss, namely retinal microangiopathy, CMV retinitis, VZV retinitis, toxoplasma retinocoroiditis, bacterial and fungal retinitis. HIV infection is also capable of causing orbital abnormalities such as orbital lymphoma and orbital cellulitis. On this basis, a research on ocular

manifestations was carried out in HIV patients who were treated at the Voluntary Counseling and Testing (VCT) Polyclinic of the Sanglah General Hospital Denpasar. However, this study is constrained by the COVID-19 pandemic so that the number of patients examined is limited.

METHOD

This study was conducted in a prospective descriptive manner to determine the characteristics and ocular manifestations of HIV patients. This research was conducted from June 2020 to November 2020 at the VCT polyclinic at Sanglah Hospital Denpasar. The population in this study were all patients who were HIV patients who visited the VCT polyclinic of Sanglah Hospital Denpasar who were collected during the study period. Sampling was done using non-randomized technique with snowball technique with interview technique and request for informed consent eye examination using simple equipment such as a flashlight, Snellen chart, mydriatic eye drops, indirect, Ishihara and funduscopy. Exclusion criteria were HIV patients who refused to undergo eye examinations. The research scheme is shown in Figure 1. This study has received an ethical clearance certificate from the Research Ethics Committee of the Faculty of Medicine, Udayana University No. 2191 / UNUD.14.2.VII.14/ LT / 2020. The data were collected by the researcher and entered into a special data collection sheet, then entered into a special data collection sheet, and descriptive data analysis using SPSS, v.26 (SPSS Inc, Chicago, Illinois, USA). The relationship between CD4 and HIV RNA levels with ocular manifestations was analyzed using the chi-square method and the research data were presented in writing and tables. then entered in a special data collection sheet, and descriptive data analysis using SPSS, v.26 (SPSS Inc, Chicago, Illinois, USA). The relationship between CD4 and HIV RNA levels with ocular manifestations was analyzed using the chi-square method and the research data were presented in writing and tables. then entered in a special data collection sheet, and descriptive data analysis using SPSS, v.26 (SPSS Inc, Chicago, Illinois, USA). The relationships between CD4 and HIV

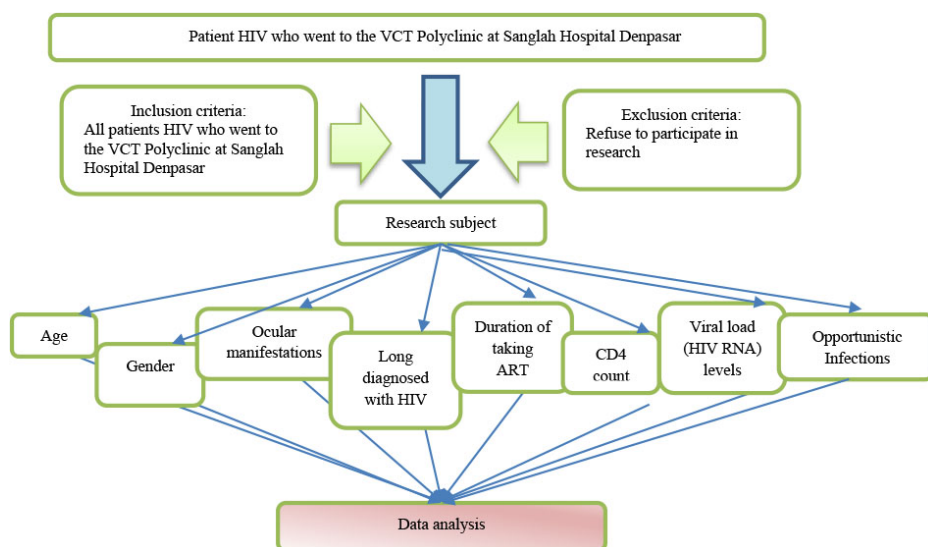


Figure 1. Research Scheme.

RNA levels with ocular manifestations was analyzed using the chi-square method and the research data were presented in tabular form.

RESULT

The research subjects were 71 patients *Human Immunodeficiency Virus* (HIV) who went to the VCT Polyclinic at Sanglah Hospital Denpasar and did a complete eye examination. Table 1 shows the distribution of HIV patients who went to the VCT Polyclinic of Sanglah Hospital based on gender, 41 patients (57.7%) were male and 30 female (42.3%). 37 patients (52.11%) live in Denpasar, and 16 patients (22.53%) live in Badung. The educational level of patients who went to the VCT Polyclinic at Sanglah Hospital was quite diverse, with 38 (53.52%) high school / vocational high school graduates and 12 (16.9%) junior high school graduates. The patient's history showed that 50 patients (70.42%) were self-employed with 7 patients (9.58%) being housewives. 39 patients (54.9%) were in the age group over 40 years and 22 patients (31%) were in the 30-39 years age group. 37 patients (52.1%) patients had been diagnosed with HIV for 1-5 years and 21 patients (29.6%) had been diagnosed for less than 1 year. 65 patients (91.5%) were on ART and 6 patients (8.5%) had not received ART treatment. 22 patients (31.0%) with CD4 cells less than 100 cells / μ L and the remaining 49 patients (69%) with CD4 cells more than

100 cells / μ L. 58 patients (81.69%) had the best-corrected vision better than 6/18, the remaining 13 patients (18.31%) had the best-corrected vision less than 6/18. Of a total of 71 patients, 28 patients (39.4%) had HIV-related ocular manifestations, while the remaining 43 (60.6%) had no HIV-related ocular manifestations.

Ocular manifestations that appear in patients based on their sex, in Table 2 it is found that the female sex (25.35%) appeared more ocular manifestations of HIV than men (18.3%), with p 0.029. Ocular manifestations were more prevalent at more than 40 years (32.39%) and the age range 30-39 years (9.85%). The p value obtained by HIV ocular manifestations by age is 0.022 and is depicted in Table 3. Table 4 describes the group for the period of 1-5 years with the most 15 people (21.12%), while more than 5 years there are 8 people (11.26%) with a p value is 0.35. The duration of ART consumption for a range of less than 1 year - 5 years, the most occurrence of ocular manifestations was 15.49%, while in a period of more than five years it was 8.45% with p value of 0.261.

CD4 and HIV RNA tests were performed in all patients with HIV. This CD4 count is usually done in a span of 6 months to assess the success of treatment. In addition, CD4 levels are said to be associated with ocular manifestations of HIV. Table 6 shows the ocular manifestations of HIV according

Table 1. Characteristics of Human Immunodeficiency Virus (HIV) Patients attending the VCT Polyclinic at Sanglah Hospital.

Characteristics of Research Subjects	n (%)
Gender	
Male	41 (57.7)
Female	30 (42.3)
Age	
<20 years	1 (1.4)
20-29 years	9 (12.7)
30 - 39 years	22 (31.0)
> 40 years	39 (54.9)
Domicile	
Denpasar	37 (52.11)
Badung	16 (22.53)
Gianyar	9 (12.67)
Karangasem	3 (4.22)
Buleleng	1 (1.4)
Tabanan	2 (2.8)
Klungkung	3 (4.22)
Last education	
Elementary School	11 (15.49)
Junior High	12 (16.90)
Senior High	38 (53.52)
D3	4 (5.63)
S1	6 (8.45)
Profession	
Labor	1 (1.4)
Janitor	1 (1.4)
Teacher	2 (2.8)
Salon workers	1 (1.4)
Housewife	7 (9.58)
Construction laborers	1 (1.4)
Student	1 (1.4)
Craftsmen	1 (1.4)
Tailor	2 (2.8)
Sales	1 (1.4)
Security officer	1 (1.4)
Therapist	1 (1.4)
Waitress	1 (1.4)
entrepreneur	50 (70.42)
Long time diagnosed with HIV	
<1 year	21 (29.6)
15 years	37 (52.1)
> 5 years	13 (18.3)
Duration of taking ART	
Not yet consumed	6 (8.5)
<1 year	15 (21.1)
15 years	36 (50.7)
> 5 years	14 (19.7)
CD4	
<100 cell / μ L	22 (31.0)
100 - 249 cell / μ L	16 (22.5)
250 - 500 cell / μ L	25 (35.2)
> 500 cell / μ L	8 (11.3)
<i>Best Corrected Visual Acuity</i>	

to CD4, where the ocular manifestations of HIV were most present at levels 250 - 500 cells / μ L as much as 12.67%. Then at least at levels > 500 (4.22%), followed by 100 - 249 cells / μ L (7.04%) and <100 cells / μ L (15.49%) with a p value of 0.656. [Table 7](#) shows the presence of ocular manifestations that appeared at 16.9% detected HIV RNA levels, while 22.53% at undetectable HIV RNA levels with p value of 0.453 to indicate the HIV RNA levels against ocular manifestations.

The most ocular manifestations of HIV appear in stage IV HIV infection (WHO) on HAART as much as 29.57%. with p value of 0.484 shown in [table 8](#). [Table 9](#) shows the presence of ocular manifestations that appeared on 1st line therapy as much as 29.57%, whereas in 2nd line it was 9.85% with p value of 0.38 to indicate the type of drug against ocular manifestations.

The ocular manifestations of HIV found in 25 HIV patients, were 15 cases (60%) found in the anterior segment. 14 patients were diagnosed with dry eye and 1 patient with blepharoconjunctivitis due to Steven Johnson Syndrome (SJS); 7 cases (28%) involved the posterior segment with a diagnosis of vitritis, HIV retinitis and CMV retinitis and 3 cases (12%) regarding neuro-retina with a diagnosis of Neuroretinitis ec syphilis, secondary atrophic papillae and binocular diplopia (N.III, IV lesions) ec syphilis are shown in [Table 10](#). [Table 11](#) shows the levels of HIV RNA amount that can cause ocular manifestations, where in the table shows 56% of ocular manifestations are found at the level of HIV RNA detected, while 32% the level of the amount of HIV RNA is not detected.

[Table 12](#) shows the CD4 level with dry eye syndrome, which shows that the level of 250-500 CD4 count for 8.45% causing dry eye syndrome with p value of 0.947 which was not significant. [Table 13](#) shows that the type of ART has no relationship with dry eye syndrome, where in the table it shows that the highest level of first-line ART was 16.90%, which is associated with dry eye syndrome with p value of 1.00 which is not significant. But this is also thought to have relation with the patient's medication adherence.

Characteristics of Research Subjects		n (%)
> 6/18		58 (81.69)
6/18 - 6/60		4 (5.63)
6/60 - 3/60		4 (5.63)
<3/60		5 (7.04)
Ocular Manifestations		
Yes		28 (39.4)
Not		43 (60.6)
HIV RNA		
Not checked yet		11 (15.50)
Detected		34 (47.88)
Not detected		26 (36.62)
Opportunistic Infection History		
Nothing		30 (42.25)
Old diarrhea		8 (11.26)
Lungs		14 (19.71)
Skin		12 (16.90)
Neurological		7 (9.85)

Table 2. HIV Ocular Manifestations by Gender.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
Gender	Men	13 (18.3)	28 (39.43)	0.029
	Woman	18 (25.35)	16 (16.90)	

Table 3. HIV Ocular Manifestations by age.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
Age (years)	<20	0	1 (1.4)	0.022
	20 - 29	1 (1,4)	8(11,26)	
	30 - 39	7 (9,85)	15 (21,12)	
	> 40	23 (32,39)	16 (22,53)	

Table 4. HIV ocular manifestations based on duration of HIV diagnosis.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
Duration of HIV diagnosis (years)	<1	8 (11,26)	13 (18,30)	0.35
	1 - 5	15 (21,12)	22 (30,98)	
	> 5	8 (11,26)	5 (7,04)	

Table 5. HIV Ocular Manifestations by duration of ART consumption.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
Duration of ART consumption (years)	Not yet	2 (2,81)	4 (5,63)	0.261
	<1	9 (12,67)	6 (8,45)	
	1 - 5	11 (15,49)	25 (35,21)	
	> 5	6 (8,45)	8 (11,26)	

DISCUSSION

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) have become health problems since the first case in 1980. This disease greatly affects human life in terms of economy, social, education and health. A person with HIV / AIDS infection has a high probability having complications in their body. One of the complications that caused by this disease can occur in the eye. Manifestations in the eye can also be a sign that someone is suffering from HIV. Blindness can also be a problem that disrupts the life of someone with HIV.

This study was conducted to determine the distribution of HIV ocular manifestations in patients with HIV infection carried out at Sanglah Hospital's VCT clinic in June - November 2020. In this study, 71 study subjects met the inclusion and exclusion criteria, where the majority of patients were male. Males amounted to 41 patients (57.7%) while women totaled 30 patients (42.3%). Based on age, it was found that the most experienced ocular manifestations were 20 people (28.16%) which more than 40 years old, and the age range of 30-39 years as much 6 people (8.45%). This study is in line with research in Ethiopia by Hothi et al, where age > 35 years is a risk factor for the emergence of ocular manifestations, this can arise due to the effect of age on patient immunity and research conducted by Odoom et al, in Ghana where age ranges were obtained. Most of the HIV patients who had ocular manifestations were in the range 31-45 years.^{1,8}

A study by Amsalu et al reported that patients receiving HAART therapy for less than 5 years were 2.5 times more likely to develop ocular manifestations than their counterparts. This is because long-term use of HAART reduces plasma HIV RNA to low levels permanently, decreases viral load, and increases CD4 cell count, and improves the patient's immune status which can reduce the incidence of opportunistic infections.¹⁰ These findings are consistent with this study in which the group that had ocular manifestations and received HAART therapy for less than 5 years was 3.8 times greater than the group that received HAART therapy for more than 5 years.

Table 6. HIV Ocular Manifestations based on CD4 count.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
CD4 (cell / μL)	<100	11 (15,49)	11 (15,49)	0.656
	100 - 249	5 (7,04)	11 (15,49)	
	250 - 500	9 (12,67)	16 (22,53)	
	> 500	3 (4,22)	5 (7,04)	

Table 7. HIV Ocular Manifestations based on HIV RNA.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
HIV RNA	Detected	12 (16,9)	14 (19,71)	0.453
	Not detected	16 (22,53)	29 (40,84)	

Table 8. HIV Ocular Manifestations by WHO HIV stage.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
WHO stage	Pre-HAART stage I HIV	1 (1,4)	0	0.484
	WHO stage I HIV infection on HAART	4 (5,63)	6 (8,45)	
	WHO stage II HIV infection on HAART	1 (1,4)	3 (4,22)	
	WHO stage III HIV infection on HAART	1 (1,4)	0	
	WHO stage IV HIV infection on HAART	21 (29,57)	34 (47,88)	

Table 9. HIV Ocular Manifestations by type of drug.

Risk Factors		Ocular Manifestations		p
		Yes n (%)	Not n (%)	
Type of Medicine	Line 1	21 (29,57)	36 (50,7)	0.38
	Line 2	7 (9,85)	7 (9,85)	

Table 10. Distribution of HIV Ocular Manifestations by CD4 Count.

Ocular Manifestations	CD4 cell / μL				Total n (%)
	<100 n (%)	100 – 249 n (%)	250 – 500 n (%)	> 500 n (%)	
Dry eye	4 (16)	3 (12)	5 (20)	2 (8)	14 (56)
Blefarconjunctivitis (Steven Johnson Syndrome)	0	0	0	1 (4)	1 (4)
Vitritis	1 (4)	0	1 (4)	0	2 (8)
Neuroretinitis ec syphilis	0	0	1 (4)	0	1 (4)
Binocular diplopia (N.III, IV lesions) ec syphilis	0	0	1 (4)	0	1 (4)
Secondary Papil Atrophy ec HIV related	0	0	1 (4)	0	1 (4)
Retinitis HIV	3 (12)	0	0	0	3 (12)
Retinis CMV	1 (4)	1 (4)	0	0	2 (8)
Total	9 (36)	4 (16)	9 (36)	3 (12)	25 (100)

As much 20 patients (28.16%) of the 26 patients with ocular manifestations in this study occurred in patients taking 1st-line ART. This is in line with a study by Odoom et al which showed 83% of ocular manifestations occurred in the first-line ART regimen with $p < 0.001$. This shows that there is a positive effect from the use of second line therapy compared to line 1 on ocular manifestations. However, in this study the p value was 0.758, where further investigation with a more even and larger number of samples is needed to confirm this assumption.

The most common ocular manifestations in this study were in the anterior segment, namely dry eye, which found 14 people (53.85%) out of 26 people who had ocular manifestations. This study also found dry eye manifestations appearing at CD4 count levels of 250-500 cells / μL. This is almost in line with several studies including those conducted by Mathebula et al, where from the study found that 80% of HIV and AIDS patients tested had dry eye, where this incident also correlated with CD4 counts below 200 cells / μL which could cause a decrease in tear production. In addition, Methabula et al also stated that the cause of the incidence of dry eye in HIV-infected people is a disturbance in the lacrimal function unit (LFU). Disorders of this LFU often occur in people infected with HIV, causing a deficiency of tears or increased evaporation.¹⁷ This study is more in line with the study conducted by Gowda et al, in which the study found a 50% decrease

Table 11. Distribution of HIV Ocular Manifestations by HIV RNA.

Ocular Manifestations	HIV RNA		Total n (%)
	Detected n (%)	Not detected n (%)	
<i>Dry eye</i>	7 (28)	7 (28)	14 (56)
Blepharoconjunctivitis (Steven Johnson Syndrome)	0	1 (4)	1 (4)
Vitritis	2 (8)	0	2 (8)
Neuroretinitis ec syphilis	1 (4)	0	1 (4)
Binocular diplopia (N.III, IV lesions) ec syphilis	1 (4)	0	1 (4)
Secondary Papil Atrophy ec HIV related	0	1 (4)	1 (4)
Retinitis HIV	2 (8)	1 (4)	1 (4)
Retinis CMV	1 (4)	1 (4)	2 (8)
Total	14 (56)	8 (32)	25 (100)

in tear production in patients with HIV infection, however, in this study there was no association between CD4 cell count and increased incidence of dry eye.¹¹

Diagnosis of stage IV HIV infection (WHO) on HAART obtained is the most cause of ocular manifestations, namely 20 patients (28.16%). This finding is in line with a study conducted by Sharew et al where there were ocular manifestations in stage III and IV infections and a study by Odoom et al which showed that ocular manifestations occurred in advanced HIV infection. This situation can be a determinant of the fairly high prevalence of ocular complications.^{1,12} A slightly different statement was made in the study by Hothi et al, which showed that the most ocular manifestations were stage II-III (WHO) on HAART at 76% whereas only 11% at stage IV (WHO) on HAART.⁸

The duration of person was diagnosed also different in each group. The study by Amsalu et al showed that ocular manifestations were more common in patients with HIV infection who had been diagnosed for less than 12 months, namely 86.6% compared to those without ocular manifestations. Compared with the duration of diagnosis of more than 12 months, the group diagnosed with <12 months tended to have a higher prevalence.¹⁰ This finding is in contrast to the findings in this study which found only 8.45% patients diagnosed for less than 1 year had ocular manifestations than the group diagnosed for more than 1 year. This difference is likely due to lack of diversity and the small sample size in this study.

A CD4 count less than 100 cells / μ L is known to increase the risk of incidence of ocular manifestations. This study found

Table 12. Relation between Dry eye syndrome and CD4 count.

Treatment line	Dry Eye Syndrome		Total n (%)	p
	Yes (%)	Not (%)		
ART Line I	12 (16.90)	45 (63.38)	57 (80.28)	1,000
ART Line II	3 (4.22)	11 (15.49)	14 (19.72)	
Total	15	56	71	

Table 13. Relationship between Dry Eye syndrome and the use of ART.

CD4 count	Dry eye Syndrome		Total n (%)	p
	Yes (%)	Not (%)		
<100	4 (5.71)	18 (25.35)	22 (30.98)	0.947
100-249	3 (4.22)	13 (18.30)	16 (22.53)	
250-500	6 (8.45)	19 (26.76)	25 (35.21)	
> 500	2 (2.81)	6 (8.45)	8 (11.26)	
Total	15 (21.12)	56 (78.88)	71 (100)	

that patients with CD4 cells less than 100 cells / μ L and had ocular manifestations were 11.26%, whereas the ones with most ocular manifestations in this study were patients with CD4 cells of 250-500. cell / μ L, amounting to 14.08%. Another study by Labh et al in Nepal in 2016 where patients with CD4 cells more than 200 cells / μ L experienced more ocular manifestations of HIV (57.5%) and also a study in Chiang in 2018 where patients with CD4 cells more than 200 cells / μ L who experienced ocular manifestations of HIV more (22.4%) than CD4 cells less than 200 cells / μ L. This is more because patients with HIV infection only do eye examinations if it has interfered with their daily activities.^{6,13}

Studies related to total viral load (HIV RNA) levels in the presence of ocular manifestations were found in several

studies. One of them is a study conducted by Abu et al, where it was found that the ocular manifestations suffered by people infected with the HIV virus were related to low levels of immunity and the large number of viruses present in the body.¹⁴ Di Yi et al, where from this study it was said that the HIV virus was still present in aqueous humor, tears and vitreous humor even though ART treatment had been carried out and the results of the HIV RNA test were not detected. This is almost in line with this research where it is found 9 patients (12.67%) whose HIV virus is still detected and has ocular manifestations.

The results of this study still have several limitations. The limitations experienced by the researchers are that there are still many patients who refuse to do eye examinations because they still feel they have no eye complaints, and there

are still many patients who do not want to have their viral load checked and CD4 count due to economic factors.

CONCLUSION

Ocular manifestations occurred more frequently at detectable viral load levels and CD4 counts of 250-500 cells / μ L. There was an insignificant association between ocular manifestations and CD4 and HIV RNA levels with almost the same prevalence in men and women. Voluntary eye examinations by asymptomatic HIV patients are still difficult.

CONFLICT OF INTEREST

The author states that he has no conflict of interest.

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