IJRETINA
International Journal of Retina

CLINICAL MANIFESTATIONS AND CD4 COUNT CHARACTERISTICS OF PATIENTS WITH CYTOMEGALOVIRUS (CMV) RETINITIS

Yunneke Renna Xaverina[1], Ovi Sofia[1]

[1]*Department of Ophthalmology, Universitas Brawijaya, Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia*

Abstract

Introduction: To describe the clinical manifestations and CD4 count characteristics of patients with cytomegalovirus (CMV) retinitis.

Methods: This is a retrospective study of patients diagnosed with CMV retinitis at the Ophthalmology Outpatient Clinic at Dr. Saiful Anwar General Hospital, Malang, between January 2016 to December 2019. The patients' characteristics and clinical data including gender, age, visual acuity, slit lamp biomicroscopy, indirect ophthalmoscope, and laboratory findings were collected from medical records.

Result: Twenty-one eyes from thirteen patients with CMV retinitis were enrolled. The mean age was 30.9 ± 7.12 years, with 54% of them male. Bilateral lesions were observed in 62% of the patients, and the mean visual acuity during the initial visit was 1.50 ±1.07 log MAR. All patients presented with the classic form of CMV retinitis. Mean CD4 count when commencing treatment was 62.23 ±11.82 cells/µL with 77% below 50 cells/µL. Patients with CD4 count < 50 cells/µL mostly presented with posterior uveitis, bilateral lesion, and visual acuity ≤1.00 logMAR. Ten patients were given oral valganciclovir and antiretroviral therapy. Retinal detachment condition was noted at seven eyes. Candidiasis was the most presenting opportunistic infection.

Conclusion: Cytomegalovirus retinitis was found in patients infected with AIDS with low CD4 counts. In this study, patients with CD4 counts of below 50 cells/µL tend to have more severe clinical presentations.

Correspondence to:
Yunneke Renna Xaverina,
Dr. Saiful Anwar General Hospital,
Malang, Indonesia,
yunnekerenna@gmail.com

INTRODUCTION

Cytomegalovirus (CMV) retinitis is frequently found in immunocompromised patients, but it can also be present in immunocompetent individuals.[1] This opportunistic infection usually takes place in patients with a low CD4 count at around 50 cells/µL.[2] Marked with hemorrhage and necrosis located according to the retinal vessel arcades. This condition can threaten vision due to its location at the posterior pole.

Cotton-wool spots may act as the early manifestation of CMV retinitis, with the lesion growing larger and accumulating as time goes by. More than half of all patients with CMV retinitis show no symptoms and abnormalities may be identified once funduscopic screening is undertaken. Common findings include a decline in visual acuity, floaters, or scotoma.[2-4] Antiretroviral therapy in patients with HIV has been reported to reduce the incidence of CMV retinitis in developed countries up to 80–90%. However, in developing countries, patients are diagnosed at a late stage with a low CD4 count, which indicates that CMV retinitis remains a major problem.[3] This also takes place in Southeast Asia, including Indonesia, whereCMV retinitis is still prevalent in patients with AIDS and is the leading cause of blindness.[5]

Researchers in Singapore in 2012 pointed out that > 90% of patients with CMV retinitis are male and are, at the time, undergoing ARV. The median CD4 count of patients upon being diagnosed with CMV retinitis is 38 cells/µL where they saw declines in their CD4 count compared with when they were first diagnosed with HIV.[6] A study in Vietnam in 2013 reported the prevalence of CMV retinitis to be 7% with a mean age of 32 years, 77% of whom were male, a median CD4 count at the time of examination to be 47 cells/µL, and 62% undergoing antiretroviral therapy.[7] Another study conducted in Bandung, Indonesia, in 2018 showed a mean age of 38.3 years with a higher prevalence in males, all of them received antiretroviral therapy (ART) and treatment provided to the patient is intravitreal ganciclovir.[8] One study carried out in Myanmar in 2019 revealed the prevalence of patients with AIDS and a CD4 count <100 cells/µL diagnosed with CMV retinitis was 10.7%.[9]

The recommended therapy for CMV retinitis is oral valganciclovir due to its ability to treat systemic CMV infections, easier administration route, and minimal side effects. In addition to the oral route, therapy for CMV retinitis can also be given intravenously or intravitreally. The therapies of choice via intravenous route consist of ganciclovir, foscarnet, or cidofovir; meanwhile, the intravitreal route may use ganciclovir implant or injection.[10] Administering valganciclovir therapy can begin with an induction dose of 900 mg twice daily for 2–3 weeks, followed by 900 mg once a day as a maintenance dose.[4] The prognosis of CMV retinitis is determined by the location of lesions, retinal detachment, and the general condition of the patient.[11] A possible complication that may arise aside from retinal detachment is the appearance of immune recovery uveitis (IRU) in patients receiving therapy.[10]

To date, research discussing the characteristics of clinical manifestations and CD4 count in patients with CMV retinitis in Indonesia has been meager. Thus, our study attempts to collect data on patients with CMV retinitis through their medical records in order to identify clinical manifestations and CD4 count also follow up characteristics in patients with CMV retinitis in Dr. Saiful Anwar General Hospital, Malang.

METHODS
Design

This is a retrospective study conducted at the Eye Polyclinic of the Infection and Immunology Division at Dr. Saiful Anwar General Hospital (RSSA), Malang. Research samples were collected using the consecutive sampling method, involving data of new patients diagnosed with CMV retinitis obtained from the outpatient medical record data at the Eye Polyclinic within the span of 4 years from 1 January 2016 to 31 December 2019.

Diagnostic criteria

Diagnosis is established when clinical examination indicates lesions that are characteristic of CMV retinitis on the retina, which may be classic, granular, perivascular form.

Demographic data

Demographic data include the age and sex of the patients.

Clinical data

The symptoms are defined as the complaints reported by the patients upon admission, which may comprise declining visual acuity (blurriness), photopsia (flashes), floaters (squiggly lines across one's vision) or a combination of those. The patient's clinical data comprise examination results on visual acuity, anterior segment, and posterior segment. Visual acuity refers to the result of testing a patient's sharpness of vision upon admission, which was then converted into logMAR. Slit-lamp biomicroscopy examination was undertaken on the anterior segment of the eye to identify any indications of inflammation in the anterior chamber and the vitreous (based on the Standardization of Uveitis Nomenclature criteria)[12] or any other abnormalities. The posterior segment was examined using an indirect funduscopy to identify any signs of necrotizing retinitis, which may include hemorrhage and necrosis according to the vascular arcades or other retinal abnormalities.

The adjunct test involves the patient's CD4 count upon commencing therapy and every month for the next 6 months. The systemic status includes other opportunistic infections present in the patient, such as candidiasis, tuberculosis, genital ulcer, herpes zoster, or toxoplasmosis identified during the examination at the Internal Medicine Polyclinic. Treatment is the type of medication therapy provided, which can be ARV only or ARV with oral valganciclovir. Complications may present as retinal detachment, immune reactive uveitis (IRU), or optic neuropathy on the affected eye, and an evaluation is to be done on the other eye (fellow eye). Follow-ups span 6 months after therapy, taking note of whether or not the patients come each month for their follow-up. Research data are presented in the form of descriptive data, while the research subjects' characteristics are displayed in tables and diagrams.

Inclusion and exclusion criteria

The inclusion criteria comprise all patients diagnosed with CMV retinitis on classic, granular, or perivascular form; on the other hand, the exclusion criteria consist of incomplete or missing medical record data.

Research Ethics

This study has been approved by the Committee of Medical Research Ethics of Dr. Saiful Anwar General Hospital, Malang with number 400/261/K.3/302/2020.

RESULTS

Based on the 4-year long medical record, this study found that the number of patients diagnosed with CMV retinitis is 21 eyes from 13 patients.

Table 1. **The Patients' Demographic Data and Clinical Results.**

Variable	Frequency
Age (mean ±SD)	30.9 ± 7.12 years
Age Group	
20–29 years	5/13 (39%)
30–39 years	6/13 (46%)
> 40 years	2/13 (15%)
Sex	
Male	7/13 (54%)
Female	6/13 (46%)
Complaint Initial Visit	
Blurred Vision	13/13 (100%)
Glare	1/13 (8%)
Laterality	
Unilateral	5/13 (38%)
Bilateral	8/13 (62%)
Visual Acuity (mean ±SD)	1.50 ±1.07 logMAR
Visual Acuity Group	
≤1.00 logMAR	7/21 (33%)
>1.00 logMAR	14/21 (67%)
Uveitis Type	
Posterior	17/21 (81%)
Panuveitis	4/21 (19%)

Table 1 illustrates the demographic data and clinical examination results of the patients. The mean age of the 13 patients is 30.9 ± 7.12 years, and most of them were 30-39 years old, which were 6 patients. There are more male patients than female patients. While all of them complained of blurred vision upon

admission to the polyclinic, more patients had bilateral lesions than unilateral lesions. The mean visual acuity of the patients in this study is 1.50 ± 1.07 logMAR with most of them having a visual acuity of >1.00 logMAR or below 20/200. Of the examination results using indirect funduscopy, all patients show the classic form.

Figure 1. A Fundus Photo of a Patient with CMV Retinitis. A 30-year-old patient with a CD4 count of 34 cells/μL in which we found a classic-form feature.

All patients diagnosed with CMV retinitis demonstrated immunocompromised condition with AIDS. The mean CD4 count upon arriving at the outpatient clinic is 62.23 ± 11.82 cells/μL, where 10 patients (77%) have a CD4 count <50 cells/μL. According to the CD4 count test, only 3 patients have >50 cells/μL (58, 130, and 418 cells/μL).

Table 2. **CD4 Count of Patients with CMV Retinitis.**

Variable	Frequency		
	<50 cells/μL	≥50-100 cells/μL	>100 cells/μL
Initial Visit	10/13 (77%)	1/13 (8%)	2/13 (15%)
Lesion Laterality			
Unilateral	4/13 (30%)	-	1/13 (8%)
Bilateral	6/13 (46%)	1/13 (8%)	1/13 (8%)

According to lesion laterality, in the 10 patients with a CD4 count of 50 cells/μL, there is more bilateral lesion than unilateral lesion (46%).
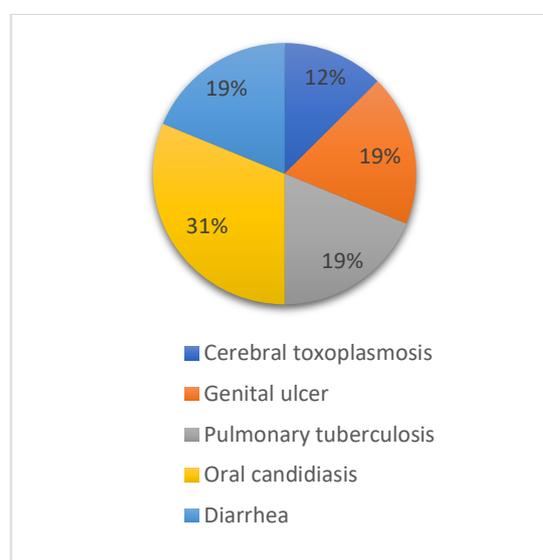
Table 3. **CD4 Count of Eyes with CMV Retinitis.**

| Variable	Frequency		
	<50 cells/μL	≥50-100 cells/μL	>100 cells/μL
Uveitis Type			
Posterior Uveitis	13/21 (62%)	2/21 (9,5%)	2/21 (9,5%)
Panuveitis	3/21 (14%)	-	1/21 (5%)
Visual Acuity			
≤1.00 logMAR	4/21 (19%)	1/21 (4,5%)	2/21 (9,5%)
>1.00 logMAR	12/21 (57%)	1/21 (4,5%)	1/21 (4,5%)

In patients with a CD4 count < 50 cells/μL, there are more eyes with posterior uveitis than those with panuveitis, which is 62%. The results of the visual acuity test on the 16 patients with a CD4 count < 50 cells/μL indicate that most of them have a visual acuity > 1.00 logMAR (57%).

Opportunistic infections may emerge in patients with CMV retinitis while also posing risks of concurrent infections. Oral candidiasis is the most prevalent opportunistic infection in this study, which involves 5 patients (38%), followed by 3 patients having genital ulcer, pulmonary tuberculosis, or diarrhea, and 2 patients with cerebral toxoplasmosis. Retinal detachment as a complication of CMV retinitis was observed in 7 eyes (33%) of the 13 patients in this study.

Figure 2**. Opportunistic Infections in Patients with CMV Retinitis.**
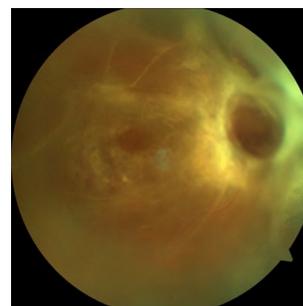
Figure 3. **A Fundus Photo of Retinal Detachment.** The fundus photo of retinal detachment in a 40-year-old male patient with CMV retinitis with bilateral lesion and a CD4 count of 34 cells/μL.

Of the 31 patients diagnosed with CMV retinitis, 10 patients receive ARV therapy + valganciclovir. Of the 10 patients, 4 patients lost to follow-up. Consequently, only 6 patients have complete follow-up data throughout the 6 months.
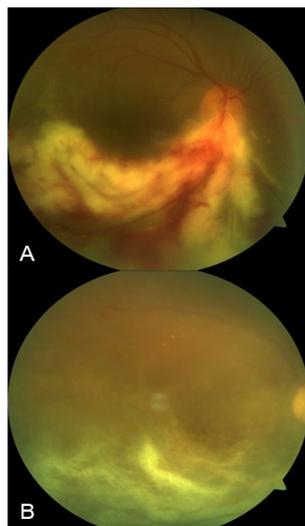
Figure 4. **A Follow-Up Fundus Photo of a Patient.** The follow-up fundus photo of a 30-year-old male patient (A) before initiating therapy, with a CD4 count of 34 cells/μL, and (B) after receiving ARV therapy + valganciclovir for 3 months, with a CD4 count of 85 cells/μL.
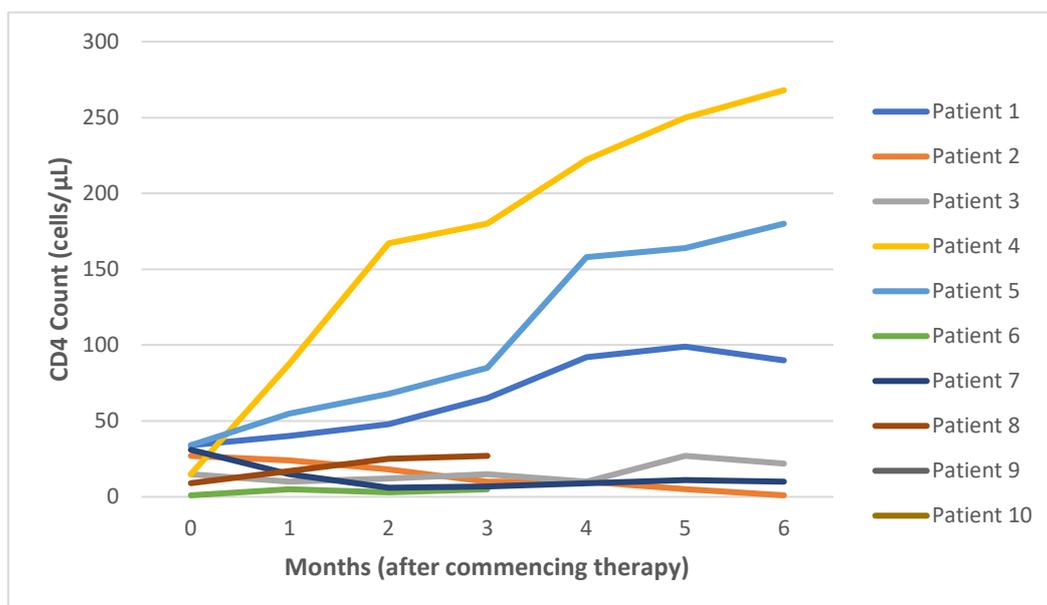

Figure 5. **Follow-Up Data of the CD4 Count of Patients with CMV Retinitis Undergoing ARV therapy + Valganciclovir.**

Of the 6 patients having complete follow-up data for 6 months, there are 2 patients receiving complete valganciclovir therapy until CD4 count >100 cells/μL for 3 consecutive months. Throughout the follow-up period, all patients do not experience any change in visual acuity and there was no involvement of the fellow eye.

DISCUSSION

According to the study results, the mean patient age is 30.9 ± 7.12 years, and there are more people who were 30–39 years old and more male patients (54%) than female patients. Similar findings were also reported in a study by Singh et al.[3] in India,

Leenasirimakul et al.[5] in Thailand, Colby et al.[7] in Vietnam, and Sovani et al.[8] in Indonesia, where the mean age of patients with CMV retinitis ranged from 30 to 40 years, and > 50% of them were male. All of the patients diagnosed with CMV retinitis in this study are patients with AIDS. H This is supported by data from the Center of Data and Information, Indonesian Ministry of Health (InfoDATIN) stating that, in 2019, the number of people with AIDS in Indonesia was 7,036, and East Java Province places third with 958 people. Most of the cases involve people in their productive age, which is 25–49 years, with men having a higher prevalence (68.6%) than women.[13]

In this study, all patients came with a complaint of blurred vision, with bilateral lesion slightly more common (62%) than the unilateral lesion. The mean visual acuity is 1.50 ±1.07 logMAR. Patients with CMV retinitis often complained of blurred vision, floaters, or scotoma. Research conducted by Singh et al.[3], Sovani et al.[8], and Adeiza et al.[14] also pointed out that blurred vision is the commonest complaint reported by patients. This is in accordance with the findings related to decreased visual acuity and bilateral lesion in these studies. In developing countries, patients will likely be seeking help to hospitals or ophthalmologists only when their condition has gotten worse or when manifestations appear on both eyes. In other words, they will come to healthcare facilities when their condition has grown serious and therapy can be very challenging. Several reasons that may explain these issues are the possibility that there are still a large number of people lacking the necessary education, people with an inadequate economic condition, and people finding difficulties in accessing health care. Screening can be performed on patients with a CD4 count < 100 cells/µL. Because CMV retinitis may not display symptoms, it's still highly recommended that patients undergo screening early to receive the necessary therapy immediately and to prevent blindness.[3, 9, 14] Factors that may affect the visual acuity of patients with CMV retinitis include macular involvements, retinal detachment, or the condition of the optic nerve.[15] A study by Iu et al.[16] argued that significant macular involvement is a factor in poor prognosis of visual acuity with visual acuity test < 20/200. The majority of retinitis lesions will turn into areas of retinal atrophy. Macular involvement will entail permanent visual impairment with poor visual acuity.

All eyes in patients with CMV retinitis demonstrate the classic-form feature, in which 67% are posterior uveitis. This finding is similar to that of a study by Sovani et al.[8] in which the classic form is the dominant clinical finding. The classic or fulminant form is a clinical feature of CMV retinitis with its characteristic pizza pie or cottage cheese with ketchup appearance.[17] However, the lesions of CMV retinitis may also manifest in a granular or perivascular form. They can also present with or without inflammation of the aqueous or vitreous humor. Retinitis lesions can be unifocal or multifocal based on the perivascular distribution. Usually, there are signs of mild to moderate inflammation of either the aqueous or vitreous humor.[15] In this study, all patients with CMV retinitis also have AIDS with a mean CD4 count upon admission at 62.23 ± 11.82 cells/µL. There are 11 patients (85%) with a CD4 count < 100 cells/µL. Similar findings are reported by Ho et al.[15] and Singh et al.[3] in their study, where the mean CD4 count of patients when they first arrived was 50–100 cells/µL. A CD4 count <100 cells/µL poses greater risks of cytomegalovirus infection, which oftentimes manifests in the eye as retinitis.[18] Some patient in our study have CD4 >50 cells/µL at initial visit, in our limitation we don't know the initial CD4 count when the patient have symptom because the patient already have scar lesion.

An examination result of CD4 count < 50 cells/µL poses a risk of CMV retinitis infection in patients with AIDS. The Longitudinal Study of Ocular Complication of AIDS (LSOCA) describes that a CD4 count < 50 cells/µL is the sole crucial risk factor in the development of CMV retinitis.[19, 20] Of the 13 patients with CMV retinitis in this study, 10 of whom have a CD4 count of < 50 cells/µL. Therefore, these 10 patients receive ARV and valganciclovir therapy. In Indonesia, the use of valganciclovir therapy during the era of Indonesian Healthcare and Social Security Agency is limited to those with a CD4 count <50 cells/µL.

A precondition of providing therapy for patients with CMV retinitis is that there has to be a clinical finding of lesion typical of CMV retinitis upon indirect funduscopy examination.[10, 21] The current recommended therapy calls for the administration of valganciclovir at a dose of 900 mg two times a day throughout the induction phase (2–3 weeks), followed by 900 mg once daily for the maintenance phase. Valganciclovir administered via oral route has the same efficacy and bioavailability with intravenous ganciclovir. Systemic delivery of therapy may become an option to treat extraocular CMV diseases, prevent contralateral eye involvement, and mitigate mortality. Should the patient's CD4 count reach > 100 cells/µL by 3–6 months with inactive lesion, then the therapy can be stopped.[10, 20, 22]

In this study, oral candidiasis is the commonest (38%) opportunistic infection, followed by pulmonary tuberculosis, genital ulcer, diarrhea, and cerebral toxoplasmosis. Multicenter research undertaken in Korea from 2006 to 2013 also concluded that candidiasis, particularly oral candidiasis, is the most frequently encountered opportunistic infection in patients with AIDS, the second being tuberculosis. The opportunistic infections likely to be found in conditions where the CD4 count is < 500 cells/μL are tuberculosis, bacterial pneumonia, herpes zoster, oral candidiasis, salmonellosis, Kaposi's sarcoma, and non-Hodgkin lymphoma.[18, 23] There are 7 eyes (33%) showing retinal detachment as a complication in this study. A study by Singh *et al.*[3] also described that the prevalence of retinal detachment was 21.8%. Retinal detachment is one of the reasons causing declining visual acuity in patients with CMV retinitis. Rhegmatogenous, which is a type of retinal detachment, emerges from the retinal break in a necrotic retina. Risk factors of retinal detachment consist of retinitis over a wide area, bilateral lesion, and active retinitis near the vitreous base.[8, 19]

This is a retrospective study that collects data from the patients' medical records, which has a number of limitations, such as limited number of samples, incomplete medical records, patients who are lost to follow-up and the Indonesian Healthcare and Social Security Agency policy regarding the duration of therapy and limit of CD4 count who are eligible to receive oral valganciclovir.

CONCLUSION

Cytomegalovirus (CMV) retinitis was found in patients infected with AIDS with low CD4 counts. Patients with a CD4 count < 50 cells/μL exhibit more severe clinical symptoms, including posterior uveitis, bilateral lesion, and visual acuity >1.00 logMAR. This study recommends further research using the prospective study design, ideally with a larger sample and a longer research duration so that evaluations can be made regarding therapy efficacy and fellow eye involvement in patients with CMV retinitis.

REFERENCES

Miyazaki D, Shimizu D, Shimizu Y, Inoue Y, Inoue T, Higaki S, et al. Diagnostic efficacy of real-time PCR for ocular cytomegalovirus infections. 2018;256(12):2413-20.

2. Chiotan C, Radu L, Serban R, Cornăcel C, Cioboata M, Anghel AJJom, et al. Cytomegalovirus retinitis in HIV/AIDS patients. 2014;7(2):237.

3. Singh SR, Dogra M, Kaur S, Bajgai P, Tigari B, Handa S, et al. Spectrum of newly diagnosed cytomegalovirus retinitis in a developing country in the HAART era. 2018.

4. Rosati D, Widjaja SA, Sasono W, Firmansjah M, Yustiarini I, Prakosa AD, et al. Challenges in Cytomegalovirus (CMV) Retinitis Management. 2019;2(2).

5. Leenasirimakul P, Liu Y, Jirawison C, Khienprasit N, Kamphaengkham S, Ausayakhun S, et al. Risk factors for CMV retinitis among individuals with HIV and low CD4 count in northern Thailand: importance of access to healthcare. 2016;100(8):1017-21.

6. Teoh SC, Wang PX, Wong EPJIo, science v. The epidemiology and incidence of cytomegalovirus retinitis in the HIV population in Singapore over 6 years. 2012;53(12):7546-52.

7. Colby DJ, Vo DQ, Teoh SC, Tam NT, Liem NT, Lu D, et al. Prevalence and predictors of cytomegalovirus retinitis in HIV-infected patients with low CD4 lymphocyte counts in Vietnam. 2014;25(7):516-22.

8. Sovani I. Clinical Characteristics and Management of Cytomegalovirus Retinitis with HIV in Cicendo Eye Hospital National Eye Centre, Bandung. 2018;1:2.

9. Ei WLSS, Pyar Soe K, Hilbig A, Murray J, Heiden D, editors. Routine immediate eye examination at the point of care for diagnosis of AIDS-related cytomegalovirus retinitis among patients with a CD4 count< 100 in Myanmar. Open forum infectious diseases; 2019: Oxford University Press US.

10. Dunn JMD. CMV retinitis, Johns Hopkins HIV Guide. 2011.

11. Kim DY, Jo J, Joe SG, Kim J-G, Yoon YH, Lee JYJR. Comparison of visual prognosis and clinical features of cytomegalovirus retinitis in HIV and non-HIV patients. 2017;37(2):376-81.

12. ophthalmology SoUNWGJAjo. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. 2005;140(3):509-16.

13. Kemenkes RJKKR, Jakarta. infoDATIN, Pusat Data dan Informasi Kementerian Kesehatan RI, HIV AIDS 2020. 2020.

14. Adeiza M, Habib AJNjocp. A cross-sectional study of cytomegalovirus retinitis in HIV-1 infected adults in Nigeria. 2019;22(3):293.

15. Ho M, Invernizzi A, Zagora S, Tsui J, Oldani M, Lui G, et al. Presenting features, treatment and clinical outcomes of cytomegalovirus retinitis: Non-HIV patients vs HIV patients. 2019.

16. Iu LP, Fan MC, Lau JK, Chan TS, Kwong Y-L, Wong IYJAJoO. Long-term follow-up of cytomegalovirus retinitis in non-HIV immunocompromised patients: clinical features and visual prognosis. 2016;165:145-53.

17. Tabbara KF, El-Asrar AMA, Khairallah M. Ocular infections: Springer; 2014.

18. Singh N, Kumar L, Singh DN, Kumar V. Frequency of opportunistic infection in PL HIV and its role in monitoring of ART 1 failure. 2020. 2020;7(7):8 %J International Journal of Advances in Medicine.

19. Port AD, Alabi RO, Koenig L, Gupta MPJCor. Cytomegalovirus retinitis in the post-cART era. 2018;6(2):133-44.

20. Stewart MWJCO. Optimal management of cytomegalovirus retinitis in patients with AIDS. 2010;4:285.

21. Huang JJ, Gaudio PA. Ocular inflammatory disease and uveitis manual: diagnosis and treatment: Lippincott Williams & Wilkins; 2012.

22. Schachat AP, Wilkinson CP, Hinton DR, Wiedemann P, Freund KB, Sarraf D. Ryan's retina e-book: Elsevier Health Sciences; 2017.

23. Kim YJ, Woo JH, Kim MJ, Park DW, Song J-Y, Kim SW, et al. Opportunistic diseases among HIV-infected patients: a multicenter-nationwide Korean HIV/AIDS cohort study, 2006 to 2013. 2016;31(5):953.