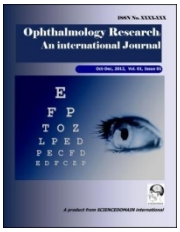

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Ocular Manifestations in HIV/AIDS- Prevalence in South India

Vijayalakshmi Valathuru[1], Chandrakala Kambar[2*], Sankar Kurli[2], Rajasulochana Pisipati[3] and Savitri Desai[3]

[1]Department of Ophthalmology, RIMS, Kadapa, India.
[2]Department of Pharmacology, SMC, Vijayawada, India.
[3]Department of Pharmacology, SMC, Vijayayawada, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author VV designed the study. Author SK wrote the protocol. Author CK wrote the first draft of the manuscript. Author RP managed the literature searches. Author SD performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Human immune deficiency virus (HIV) related ocular manifestations may affect 50-75% of HIV infected people worldwide at some point during the course of their illness.
Aim: To estimate the prevalence of Ocular manifestations in HIV patients attending the Anti Retroviral Therapy (ART) centre.
Place and Duration of the Study: ART centre at Government general hospital and Department of Pharmacology, Siddhartha Medical College, Vijayawada, Andhra Pradesh in south India. The study was conducted for six months from January 2010 to June 2010.
Study Design: This was a cross-sectional and observational study done on 1003 patients with or without ocular manifestations.
Methodology: All the patients were examined for anterior and posterior segment by using slit lamp and indirect ophthalmoscopy. Visual acuity was recorded in all patients.
Results: The prevalence of HIV associated ocular diseases was seen in 24.32 % of HIV patients. The most common findings were seen in anterior segment in 157(15.65%) patients followed by posterior segment in 87(8.67%) patients. 8.57% of conjunctival microvasculopathy, 1.59% of uveitis, 1.19% of herpes zoster and 0.89% of xerosis were the most common findings seen in the anterior segment. 2.47% of HIV retinopathy, 0.99%

**Corresponding author: E-mail: chandook2@gmail.com;*

of chorioretinitis, 0.89% of cytomegaloviral retinitis, 0.69% of choroiditis, and 0.69% of optic atrophy were the most common posterior segment findings. Tuberculosis was the main systemic finding seen in 156 patients.
Conclusion: All these ocular findings are directly related to the severity of the clinical stage of the disease and to the severity of immunosupression.

Keywords: HIV; AIDS; Prevalence; anterior segment; posterior segment.

1. INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is the most devastating disease complex that mankind has ever faced. It is caused by Human immuno deficiency virus (HIV) which belongs to the family Retroviridae and subfamily lentivirinae, shows great genetic diversity and breaks down human immune system leaving victim to vulnerable life threatening opportunistic infections, neurological disorders or unusual malignancies [1]. As per current US Centers for Disease Control and prevention (CDC) classification system for HIV infected adolescents and adults, AIDS patient is defined as 'any HIV infected individual with CD4+ T cell count of <200/ microlitre regardless of the presence of symptoms or opportunistic diseases [2]. According to WHO (World Health Organisation) Clinical staging HIV/AIDS is classified into five groups as Primary HIV infection, Clinical stage I, II, III and IV [3].

The number of people newly infected with HIV globally is continuing to decline, but national epidemics continue to expand in many parts of the world especially in developing countries. AIDS remains one of the world's most serious health challenges, even today in this era of Highly Active Anti Retroviral Therapy (HAART). A new era of hope has emerged in countries and communities across the world that had previously been devastated by AIDS. However, a world in which AIDS has been eliminated can only be achieved through renewed and sustained commitment and solidarity and only if the available evidence and limited resources are used as efficiently and effectively as possible [4]. Introduction of HAART has definitely prolonged the survival of AIDS patients but meticulous clinical examinations and better follow-ups can make the patients' quality of life better than before.

HIV affects all the systems of the body and produces various abnormalities. These manifestations are common in the course of HIV infection and may be the direct result of HIV, secondary infections, neoplasms or side effects of drug therapy, along with individual characteristics such as genetic predisposition, gender and age [5]. Among these, ocular manifestations are also common. HIV related ocular manifestations may affect 50-75% of HIV infected people worldwide at some point during the course of their illness. This generally takes the form of opportunistic infections that can affect any of the ocular tissues from anterior segment to posterior segment.

There are a number of opportunistic infections associated with HIV infection. CMV retinitis is the most common ocular infection in AIDS and other intraocular infections that more frequently occur in patients with AIDS include syphilis, toxoplasmosis, tuberculosis, *Candida* infection and cryptococcosis. These have to be differentiated from CMV infection. Herpesvirus infections other than CMV infection can also cause a viral retinitis in patients with HIV infection. Herpes zoster ophthalmicus may be an early sign of HIV infection. Herpes zoster retinitis accompanied by acute retinal necrosis and herpes simplex retinitis has occasionally been seen in patients with AIDS. These viral retinal infections are often difficult to differentiate clinically from CMV retinitis. However, these studies were completed early in

the history of the AIDS i.e. pre HAART era (Highly Active Anti Retroviral Therapy) and the percentages may have been decreased after the introduction of HAART. Very few studies were reported after HAART era on the prevalence of various types of ocular manifestations and morbidity in HIV patients especially in developing countries like India, where paucity in reporting is observed. This indicates that the epidemiology of ocular manifestations in HIV infection is not well understood. These manifestations may be due to HIV infection or opportunistic infections or due to immune reconstitution after initiation of therapy or due to the ART(antiretroviral therapy) itself.

Though many studies were done in different parts of the world, very less and precise data is reported from south Indian population. In this scenario, a cross-sectional and observational study was conducted on 1003 HIV patients attending ART centre in Siddhartha Medical college/ Government General Hospital, Vijayawada, Andhra Pradesh, South India to know the prevalence of various ocular manifestations in HIV patients in South India.

2. MATERIALS AND METHODS

This was a cross sectional and observational study. The protocol was approved by the institutional ethics committee of Siddhartha Medical College, Vijayawada. Informed written consent was obtained from all the patients enrolled in this study in local language and for the patients less than 14 years the consent was obtained from the parents or guardians. Patents' identity and details were maintained strictly confidential. This study was carried out at highly populated ART Centre, Siddhartha Medical College / Govt. General Hospital, Vijayawada functioning under NACO guidelines. The study was conducted for six months from January 2010 to June 2010.

2.1 Inclusion Criteria

1. Patients diagnosed with HIV/AIDS attending ART centre.
2. Patients of all ages were recruited.

2.2 Exclusion Criteria

Patients with ELISA negative (HIV- negative) were excluded from the study.

2.3 Materials

1. A formulated questionnaire.
2. Torches.
3. Snellen chart- literate and illiterate.
4. Slit lamp.
5. Direct and indirect ophthalmoscope.
6. Loupes +20, +90 Ds.
7. Mydriatics: tropicamide, cyclopentolate.
8. Scheme and sheet for fundus drawing.

2.4 Methodology/Procedure

On average, about 50 patients were seen daily. Only 10 patients were selected for the study following the inclusion and exclusion criteria. The procedure was explained and those who gave consent were recruited in the study and the following examinations were done:

1. Visual acuity test with Snellen chart.
2. Color vision test with Ishihara charts.
3. Anterior segment examination by Slit lamp.
4. Fundus examination with 90 D slit lamp biomicroscopy and with indirect ophthalmoscopy.
5. Medical records of patients were observed to obtain information on systemic diseases, HIV status, CD4 counts and anti retroviral therapy.

2.5 Statistics

The data was recorded on a well structured questionnaire. Care was taken to minimize the risk for missing and erroneous data. Data was then cleaned and entered on a specially designed SPPS data analysis sheet. Data was analysed using Chi- square test and p value of less than 0.05 was considered statistically significant.

2.6 Limitations

1. Laboratory tests like CD4 counts, renal function tests and histology for conjunctival tumours had already been done where appropriate. So, it was difficult to confirm some diagnosis or get the new tests done if needed. Some patients' diagnosis was made based on clinical judgement.
2. Unable to estimate Viral RNA.

3. RESULTS

A total of 1003 patients were examined in the present study who attended a highly populated ART centre located in Vijayawada, Andhra Pradesh, South India which is functioning under NACO (National AIDS Control Organisation, India). Age distribution is shown in Fig. 1. More number of patients with anterior and posterior segment manifestations were in between 26 and 35 years of age group and next highest number of patients with these manifestations were in between 36 and 45 years of age group. Chi-square value is 1.97, df (degrees of freedom) is 6 and *P* =.922.

Male patients were 511 (50.9%) and female patients were 492 (49.1%).In male patients there were 85 anterior segment manifestations and 56 posterior segment manifestations, where as in female patients it was 56 and 31 respectively. Prevalence of HIV related ocular conditions were more in males. Chi-square value is 2.40, df is 1 and *P*=.121, which is not significant.

The total number of patients in clinical stage III was 745, stage IV was 122 and stage V was 1. More patients were in stage III. Chi-square value is 17.2, df is 4 and *P*=.002 and is highly significant. Prevalence of ocular manifestations was also more in Clinical stage III as shown in Fig. 2 and it implies that ocular manifestations were more with progressing clinical stage of HIV disease.

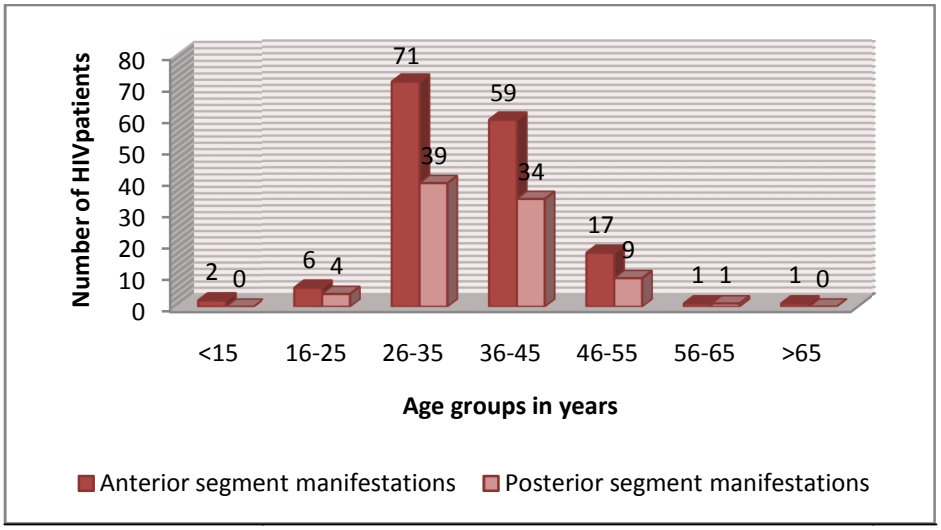

Fig. 1. Prevalence of Ocular manifestations in different age groups

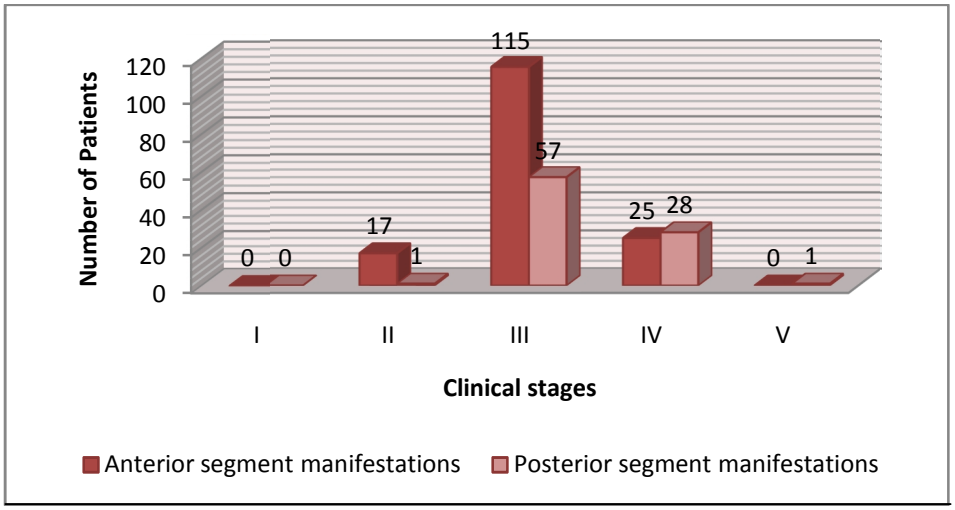

Fig. 2. Prevalence of ocular manifestations in different clinical stages of AIDS

The prevalence of HIV associated ocular diseases was 24.32% (244/1003). The most common findings were observed in the anterior segment in 15.65% of patients and 8.67% in posterior segment.

Various ocular manifestations in posterior segment and anterior segment were observed on ophthalmic examination. All the anterior segment manifestations and posterior segment manifestations are listed in Table 1 and 2 respectively.

Table 1. Various anterior segment manifestations and no. of patients affected

S. No.	Anterior segment manifestations (ASM)	n=157(15.65%)
1.	Complicated cataract	11(1.09%)
2.	Conjunctival congestion	83(8.27%)
3.	Uveitis	16(1.59%)
4.	Episcleritis	4(0.39%)
5.	Herpes Zoster	12(1.19%)
6.	Xerosis	9(0.89%)
7.	Pthisis bulbi	5(0.49%)
8.	Chronic dacrocystitis	1(0.97%)
9.	Corneal opacity	4(0.39%)
10.	Hemiparesis with ophthalmoplegia	1(0.097%)
11.	Chicken pox	1(0.097%)
12.	Facial palsy	5(0.49%)
13.	Molluscum contagiosum	2(0.19%)
14.	Adherent leucoma	1(0.097%)
15.	Corneal ulcer	2(0.19%)

Table 2. Various posterior segment manifestations and no. of patients affected

S. No.	Posterior segment manifestations (PSM)	n=87(8.67%)
1.	Chorioretinitis	10(0.99%)
2.	Vitreal opacities	4(0.39%)
4.	Acute retinal necrosis	5(0.49%)
5.	Optic atrophy	7(0.69%)
6.	HIV Retinopathy	25(2.49%)
7.	Choroiditis	7(0.69%)
8.	Cyto Megalo Viral Retinitis(CMVR)	9(0.89%)
9.	Tractional Retinal detachment	5(0.49%)
10.	Peripheral vasculitis	5(0.49%)
12.	Papillitis	1(0.097%)
14.	Retinitis	1(0.097%)
15.	Vitreous haemorrhages	2(0.19%)
16.	Macular oedema	3(0.29%)
17.	Papilloedema	3(0.29%)

More number of ocular manifestations (ASM= (n) 95 and PSM= (n) 48) were seen in patients with CD4 counts < 100 cells/mm^3. As the CD4 counts decrease the prevalence of ocular manifestations was more as per the data shown in Table 3. Chi-square value is 7.42, df is 4 and *P*=0.115 (not significant).

The HIV infected patients recruited in this study (n=830)were given different anti retro viral therapy regimens as ZLN (zidovudine+lamivudine+nevirapine), SLN (stavudine+ lamivudine+ nevirapine), ZLE (zidovudine+ lamivudine+ efavirenz) and SLE (stavudine+ lamivudine+ efavirenz) as per the NACO (National AIDS Control Organisation, India) guidelines. The rest of the patients (n=173) were not on any regimens as they were newly diagnosed cases and about to start the treatment. In these patients also ocular manifestations (Posterior Segment Manifestations (PSM)=13 and Anterior segment Manifestations (ASM)=27) were noticed. Ocular manifestations were more in patients on ZLN treatment as shown in Table 4. Chi-square value is 4.47, df is 4 and *P*=.346.

Table 3. Number of ocular manifestations in HIV patients with different CD4 counts

CD4 COUNT In cells/mm^3	n	Anterior Segment Manifestations	Posterior Segment Manifestations	Total Ocular Manifestations n (%)
<100	332	59	48	107(10.6)
101 - 150	231	40	17	57((5.68)
151 - 200	191	26	11	37(3.68)
201 – 250	155	18	7	25(2.49)
>250	94	14	4	18(1.79)
Total	**1003**	**157**	**87**	**244(24.3)**

Table 4. Number of ocular manifestations in HIV patients taking different ART (Anti retroviral treatment) regimens

S. No	ART regimen	n	Anterior Segment Manifestations	Posterior Segment Manifestations	Total Ocular Manifestations n (%)
1.	ZLN	446	60	38	98(9.77)
2.	SLN	261	48	18	66(6.58)
3.	SLE	58	18	10	28(2.79)
4.	ZLE	65	14	6	20(1.99)
5.	ART not started	173	17	15	32(3.19)
6.	Total	1003	157	87	244(24.3)

Tuberculosis was the systemic manifestation seen in 156 HIV patients and they were on ATT (Anti tuberculosis treatment) as per RNTCP (Revised national tuberculosis control programme) guidelines. Ocular manifestations data is shown in Table 5. Chi-square value is 14.7, df is 1 and *P*=.001 which is significant.

Table 5. No. of patients with ATT and with ocular manifestations

S. No	Anti Tuberculous Treatment(ATT)	n	Anterior Segment Manifestations	Posterior Segment Manifestations	Total Ocular Manifestations n (%)
1.	Patients taking ATT	156	28	35	63(6.28)
2.	Patients without TB	847	129	52	181(18.04)
3.	Total	1003	157	87	244(24.3)

Visual acuity was tested for all the patients and complete blindness (bilateral) was seen in seven patients affected with CMVR(n=1), HIV retinopathy(n=1), Uveitis(n=1), Optic atrophy(n=1), acute retinal necrosis(n=1), Papilloedema(n=1), and Perivasculitis(n=1).

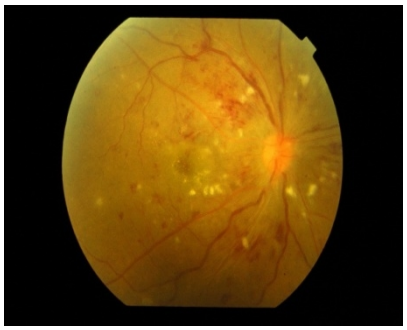

Fig. 3. HIV retinopathy with cotton wool spots and haemorrhages

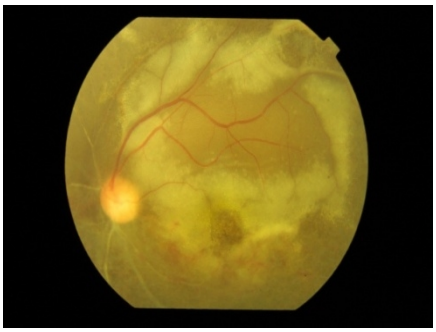

Fig. 4. Acute retinal necrosis involving the posterior pole

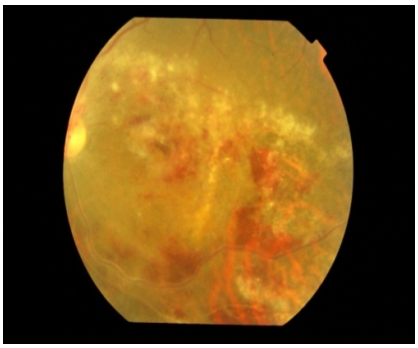

Fig. 5. Fulminating CMV retinitis with brush fire pattern

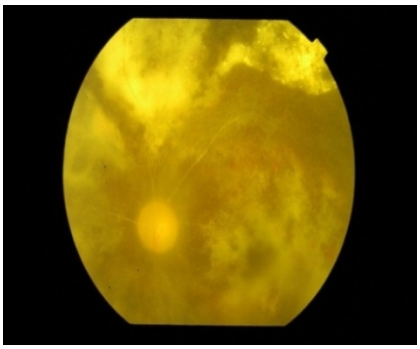

Fig. 6. End stage CMV retinitis with optic atrophy

The above Figs from Fig. 3 to 6 show some selected pictures of fundus examination in HIV patients with description.

4. DISCUSSION

HIV-1 infection, the cause of AIDS, is a worldwide pandemic with enormous adverse health and economic implications, particularly in the developing world. This bloodborne and sexually transmitted disease, which evolved from simian immunodeficiency virus, infects and replicates in helper T cells and macrophages and utilizes CD4 and a chemokine coreceptor for entry. Immune deficiency occurs as a result of virally induced attrition of CD4 T cells, resulting in the development of opportunistic infections and malignancy [6].

Numerous ophthalmic manifestations of HIV infection may involve the anterior or posterior segment of the eye. Since the first report of the ocular manifestations of AIDS by Holland et al. in 1982, [7] subsequent studies have described several AIDS related conditions in the eye and orbit. More than 70% of adult AIDS patients will experience an ocular complication at some point of their illness. [8]

More number of patients were male than female and more were seen in the age group of 26-35years, because of active sexual life and other life styles which lead to more incidence of AIDS and ocular manifestations consecutively.

The presentation is more common in clinical stage III because at this stage usually more number of patients will be symptomatic and become aware to seek medical advice. The number of cases enrolled in this study were more in Clinical stage III(n=745), and so the more ocular manifestations.

A study performed by Lamichhane et al. showed that ocular involvement was seen in 55 (47%) HIV/AIDS patients [9]. In this study the prevalence of ocular manifestations is 24.3%. This is comparable with the studies done by Gharai et al. [10]. Where in their study 45% (45/100) patients had ophthalmic manifestations, the most common being cytomegalovirus (CMV) retinitis (20%) (20/100). But in this study, CMV retinitis was 0.89%(9/1003), this was comparable with the study done by Elizabeth A et al, in which the CMV retinitis was 0.36/100 person years and the incidence was more with less CD4+ counts [11]. Immunosuppression as indicated by decreased CD4+ counts is the main reason for incidence of more number of ocular manifestations. This is because incidence of opportunistic infections increase with decreasing CD4+ counts.

As per Vraber et al. [12], Fifty-seven patients (28.5%) had ocular manifestations, and they showed significantly lower CD4+ T cell count than patients without ocular manifestations. This is comparable with this study, as the incidence of ocular manifestations was 24.3% and more ocular manifestations were noticed with decreasing CD4+ counts. But there was no significant linear trend in the HIV positives with decreasing CD4+ counts as per the study of Dilys Morgan et al. [13].

About 50% (19/40) patients had CD4+ count below 100 cells/micro liter and 70% (28/40) patients had CD4+ count below 200 cells/micro liter as per the study done by Gharai et al. [10] and this is comparable with this study where 40% patients had CD4+ counts<100 cells/micro litre and 38.6% with <200 cells/micro litre.

In general, the $CD4^+$ T-lymphocyte count has been used to predict the onset of certain ocular infections in patients who are HIV positive. A $CD4^+$ T-cell count below 500/mL is associated with Kaposi sarcoma, lymphoma, and tuberculosis. A $CD4^+$ T-cell count below 250/mL is associated with Pneumocystitis and toxoplasmosis. A $CD4^+$ T-cell count less than 100/mL is associated with Retinal or Conjunctival microvasculopathy, Cytomegalovirus (CMV) retinitis and Varicella-zoster virus (VZV) retinitis. [3]

The predictive value of the $CD4^+$ T-cell count for ocular complications in HIV infection has been called into question by reports of HIV related ocular complications in patients with $CD4^+$ cell counts more than 200 cells/mL. The patients reportedly were taking highly active antiretroviral therapy (HAART). While such findings are against the protective effect of an increased $CD4^+$ cell count, the possibility that these manifestations preceded the recovery of $CD4^+$ cell count. As seen in this study, there was significance regarding the prevalence of more ocular manifestations as the clinical staging of HIV progresses, when compared to the data seen with CD4 cell count. Thus, whether a reconstituted T-cell count will serve as a better predictor of specific ocular infection is under active evaluation.

The ocular findings seen in this study related to HIV infection are very less to draw any conclusions. CMV retinitis in this study was seen in 9(0.89%) patients, which is very less when compared with most of the previous studies where the incidence was from 20-40% [11,12,14,15,16].

AIDS patients with Tuberculosis tended to have more retinal microangiopathy, but this was not statistically significant in the study done by Beare et al. [17], in African areas where as in this study, the prevalence of ocular manifestations in patients with Tuberculosis and HIV was highly significant. These differences most likely result from different socioeconomic conditions and basic health care availability and from different patterns of endemic disease, prevalent before the HIV/AIDS epidemic.

Due to the potentially devastating and rapid course of ocular infections, all persons with HIV disease should undergo routine ophthalmologic examinations. Any HIV-infected person who experiences ocular symptoms also should receive prompt and competent ophthalmologic care. Nonetheless, eye infections associated with sexually transmitted diseases (STDs) such as herpes simplex virus, gonorrhoea and chlamydia are more frequent in HIV-infected patients. Therefore, clinicians should screen for HIV in the presence of these infections.

Fortunately, many of these infections are now treatable with therapeutic agents. Early recognition of these infections is important so that appropriate therapy can be instituted. Immune system recovery following initiation of antiretroviral therapy (ART) may modify clinical presentation of ocular infections and can affect response to treatment.

Therefore, HIV-infected patients still require close ocular follow up even if they are on HAART. Occasionally, HAART may cause vision loss via the mechanism of immune recovery uveitis. It may be characterized by vitritis and optic disc and macular edema.

5. SUMMARY AND CONCLUSION

Practising ophthalmologists, those in the developing world, where there is HIV pandemic, are faced with the following challenges. One, they must be able to diagnose and treat vision-threatening conditions. Two, they must be able to identify unusual presentations. Three, ophthalmologists must be able to identify and document manifestations as early as possible in a HIV positive patients in the course of their disease and also during the treatment period.

The ART centres run by NACO, are not provided with adequate ophthalmic examinations. Thus, it is advisory to get all the HIV patients attending these centres to be examined for vision threatening complications, both medical and surgical ocular complications.

The study has to be done in more centres and more number of patients has to be included to confirm these findings.

CONSENT

All authors declare that ‘written informed consent was obtained from the patients in local language for publication of this case report and accompanying images.

ETHICAL APPROVAL

Authors have obtained all necessary ethical approval from Siddhartha Medical College, Vijayawada Institutional Committee.

COMPETING INTERESTS

All authors declare that no competing interests exist.

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