

Evaluation of Ocular Manifestations in HIV/AIDS Patients on HAART in a Tertiary Care Hospital in Southern India : A Cross Sectional Study

Damdamraju Murali Krishna¹, Cheedella Sandhya S², Gajjala Vijay Bhaskar MS³

Abstract

Human immunodeficiency virus (HIV)/Acquired immune deficiency syndrome (AIDS) is one of the most feared infectious diseases of the late 20th century with Indian estimates of 21.17 lakhs patients living with HIV contributing to highest numbers among the world. Ocular disease continues to be a major cause of morbidity, among HIV-infected population. Introduction of Highly active antiretroviral therapy (HAART) in India led to a dramatic reduction in ocular morbidity. There are only few studies in Indian sub-continent that have evaluated the prevalence of HIV related ocular lesions in patients on HAART. The Purpose of present study is to evaluate ocular manifestations in patients on HAART in a tertiary care hospital. *Context: Aims:* To study the ocular manifestations among HIV patients on HAART To study the relationship between ocular findings and the duration of HAART *Settings and Design:* observational study was done in the Anti Retroviral Therapy (ART) centre, Sri Ram Narayan Ruia Government General Hospital (SVRRGGH) attached to Sri Venkateswara Medical college (SVMC), Tirupati between November 2013 to September 2017. The study was approved by the Institutional ethic committee of the Institution. *Methods and Material:* 1026 HIV positive patients who are on HAART fulfilling the inclusion criteria were examined as per protocol and results were analyzed *Statistical analysis used:* SPSS 13 *Results:* 1026 HIV positive patients on HAART were examined during study period out of which 221 (21.53%) patients had ocular manifestations. incidence of ocular manifestations was higher in males compared to females (57.02% vs. 42.98%). The commonest ocular manifestation was HIV retinopathy (14.2%). New manifestations observed were presenile cataract (9.50%). Iatrogenic manifestations observed were Immune recovery uveitis (3.61%), anaemic retinopathy (9.95%). *Conclusions:* Our study evaluated the prevalence of ocular manifestations in HIV-infected patients on HAART. Screening this patient population is of particular importance not only because of the high prevalence of ocular manifestations due to disease but also due to the potential for worsening of ocular conditions due to HAART induced IRIS and anemic retinopathy. This shows the importance of ophthalmic evaluation of all HIV patients on HAART.

Keywords: Human Immunodeficiency Virus (HIV); Highly Active Antiretroviral Therapy (HAART); Cytomegalovirus Retinitis (CMV); Cluster of Differentiation 4 (CD4) Cells, HIV Retinopathy; Immune Reconstitution Inflammatory Syndrome (IRIS)

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Introduction

Human immunodeficiency virus (HIV)/

Acquired immune deficiency syndrome (AIDS) is one of the most feared infectious diseases of the late 20th century [1]. Ocular manifestations of HIV/AIDS are very common and can be the presenting sign of an underlying systemic infection in an otherwise asymptomatic HIV positive patient. Ocular disease continues to be a major cause of morbidity, which may affect 50-75% of HIV-infected people worldwide at some point during the course of their illness [2]. The disease can affect any of the ocular tissues, from eye lids to the retina and ocular adnexa. Low socio economic patients typically start Highly active antiretroviral

Author Affiliation: ¹Associate Professor, ²Professor & Head, ³Senior Resident, Department of Ophthalmology, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh 517507, India.

Corresponding Author: Cheedella Sandhya S, Professor & Head Department of Ophthalmology, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh 517507, India.

E-mail: cheedella.sandhya@gmail.com

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therapy (HART) at low cluster of differentiation 4 (CD4) cells count and may be at high risk of ocular opportunistic infections. In addition the causes of ocular morbidity may include HIV retinopathy, immune recovery uveitis after HAART initiation, drug induced anaemic retinopathy and ischemic maculopathy. Identification and treatment of this is important to prevent further progression of disease and morbidity.

Highly active antiretroviral therapy (HAART) has changed the face of HIV acquired immune deficiency syndrome (AIDS) by leading to dramatic decrease in HIV-related morbidity and mortality in the developed as well as developing world [3,4]. Introduction of generic HAART in India has led to a dramatic reduction in the incidence of opportunistic infections particularly CMV retinitis by around 87%. India has the third highest number of estimated people living with HIV in the world. According to the HIV estimations 2015, the estimated number of people living with HIV/AIDS in India was 21.17 lakhs of which undivided Andhra Pradesh has a share of 3.95 lakhs [5].

Ocular manifestations of HIV in India was first reported in 1995. The estimated prevalence of HIV-related eye disease in India is reported to be between 8-45% [6]. Data are scarce concerning the burden of ocular disease in patients on HAART therapy. Most of the estimates till now are based on symptoms or Ophthalmological referrals. The ART centre located in SVRRGG Hospital, Tirupati, Andhra Pradesh, India has about 14,000 of registered patients and the previous statistics showed that very small percentage of them seeks advice for ophthalmic problems. In view of paucity of data available on HIV related ocular manifestations, the present work aims at evaluating the ophthalmic problems in this area. This also helps in educating and treat the patients having eye problems.

Aims and Objectives

- To study the ocular manifestations among HIV patients on HAART
- To study the relationship between ocular findings and the duration of HAART

Materials and Methods

This cross sectional observational study was done in the ART centre, Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati, India from November 2013 to September

2017. HIV positive patients on HAART attending ART centre were included in this study. The study was approved by the Institutional ethics committee of Sri Venkateswara Ramnarain Ruia Government General Hospital and S V Medical College, Tirupati. 1026 HIV positive patients on HAART were included in the study. Patients who were not on HAART known to have ocular manifestations before being diagnosed as HIV infected and patients not willing to participate in this study were excluded from the study.

After obtaining written and informed consent a detailed history was taken from all the patients. Information on the antiretroviral regimen, WHO clinical staging of HIV infection, the length of time since initiating the HAART was obtained from the patient's records at ART center.

A detailed ophthalmic examination was carried out in all patients irrespective of ocular symptoms. Visual Acuity was recorded with Snellen's chart, Slit lamp examination, and direct ophthalmoscopic examination was done for all patients. Gonioscopy, Indirect ophthalmoscopy was done in required cases.

Patients presenting primarily with ophthalmic findings or complaints were managed by the ophthalmologists based on the clinical diagnosis. The results were analysed statistically. Data were analyzed using SPSS version 13 software and $p < 0.05$ was considered significant.

Results

An observational clinical study with 1026 HIV positive patients on HAART was undertaken to study the incidence of ocular manifestations in relation to HAART. 1026 HIV positive patients on HAART were examined during study period out of which 221 patients had ocular manifestations. A thorough ophthalmic workup was done in all patients included in the study. In the present study, maximum incidence was found in age group of 21-40 years amounting to 46.60%. Out of 221 patients 103 patients were in the income earning and sexually active age group (Table 1).

Table 1: Age distribution of patients with ocular manifestations

Age in years	Number of patients	% (Percentage)
0-20	14	6.33
21-40	103	46.60
41-60	76	34.38
>60	28	12.66

The incidence of ocular manifestations was higher in males compared to females (57.02% vs. 42.98%) the male: female ratio was 1.32:1.166 patients belongs to rural (75.11%) area and 55 patients belong to urban area (24.88%) (Table 2). In the present study, the incidence of ocular manifestations was higher in males compared to females (57.02% vs. 42.98%) the male: female ratio was 1.32:1.166 patients belongs to rural (75.11%) area and 55 patients belong to urban area (24.88%)

Table 2: Gender distribution of patients with ocular manifestations

Gender	Number of patients	% (Percentage)
Male	126	57.02%
Female	95	42.98%
Total	221	100

In the present study more number of patients with ocular manifestations was from rural area.

Table 3: Distribution of patients with ocular manifestations based on duration of HAART

Months since HAART started	Number of patients	% (Percentage)
<12	11	4.97
13-24	52	23.07
25-60	150	67.87
>60	8	3.61

HAART: Highly Active Anti Retroviral Therapy

Nearly 73% of patients were on HAART therapy for more than 2 years (67.87% between 25-60 months range and 4.97% more than 60 months). (Table 3). In the present study 31 patients (14.02%) had HIV retinopathy, which is the most common manifestation (Fig. 1). In opportunistic infections CMV retinitis was the most common manifestation seen in 10 (4.52%) patients (Fig. 2A, B). Other opportunistic infections observed were herpes simplex keratitis (4.07%), herpes zoster Ophthalmicus (1.35%), fungal keratitis (3.1%) and choroiditis (3.16%). In Drug related manifestations Anaemic retinopathy was seen in 22 patients (9.95%) (Fig. 3A, B) and Immune recovery uveitis was seen in 8 patients (3.61%). Conjunctivitis and Blepharitis was seen in 23 patients (10.40%) and 22 patients (9.95%) respectively. Pre senile cataract was seen in 21 patients (9.50%) and 17 patients (7.69%) had Iridocyclitis. Neuroophthalmic manifestations like Optic atrophy (2.26%), Papilloedema (1.80%) was also observed. Retinal detachment was seen in 4 patients (1.80%). Other manifestations were External Hardeolum (2.26%) and Dry eye (8.59%). (Table 4).

Table 4: Types of ocular manifestations

Ocular Manifestations	Number of patients	% (Percentage)
Blepharitis	22	9.95
Conjunctivitis	23	10.40
Dry eye	19	8.59
Herpes simplex keratitis	9	4.07
Herpes zoster Ophthalmicus	3	1.35
Fungal corneal ulcer	7	3.1
IRU	8	3.61
Pre senile cataract	21	9.50
Iridocyclitis	17	7.69
Nerve palsy	4	1.80
Hardeolumexternum	5	2.26
HIV retinopathy	31	14.02
CMV retinitis	10	4.52
Retinal detachment	4	1.80
Anaemic retinopathy	22	9.95
Choroiditis	7	3.16
Optic atrophy	5	2.26
Papilloedema	4	1.80

IRU: Immune related uveitis

CMV retinitis: CytoMegalovirus retinitis

HIV retinopathy: Human Immunodeficiency Virus retinopathy

The distribution of ocular manifestations based on duration of HAART was grouped in to four categories and analysed statistically. In that Immune recovery uveitis ($p \leq 0.001$) and CMV retinitis ($p \leq 0.001$) were statistically significant (Table 5). Patients on HAART for less than 12 months were included in the first category in which CMV retinitis and IRU were seen in 36.36% of patients each.

Retinal detachment was observed in 18.18% patients and choroiditis was observed in 9.09% patients. In second category (Duration of HAART between 13-24 months) Iridocyclitis was the most common manifestation. More number of patients included in third category (Duration of HAART between 25-60 months). Conjunctivitis (13.92%) was the most common manifestation followed by Blepharitis (12.65%), HIV retinopathy (12.65%), Pre senile cataract (10.75%), Dry eye (10.75%) and Anaemic retinopathy (10.12%). In fourth category (Duration of HAART > 60 months) HIV retinopathy was the most common manifestation (37.5%) followed by Anaemic retinopathy (25%) (Table 5).

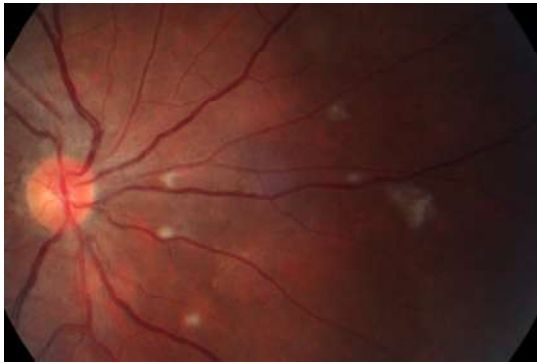


Fig. 1:

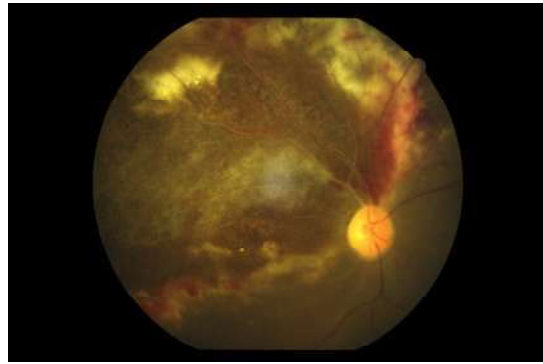


Fig. 2A:

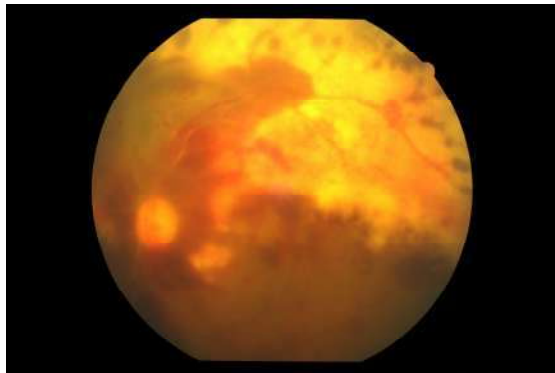


Fig. 2B:

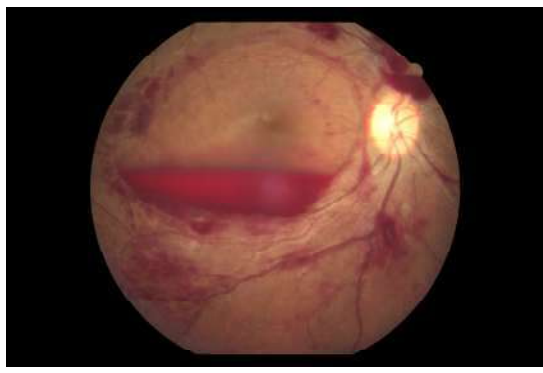


Fig. 3A:

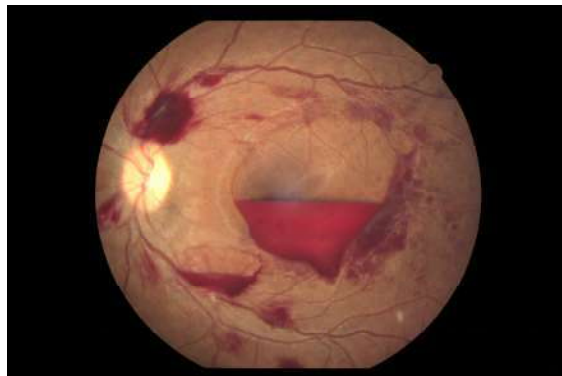


Fig. 3B:

Discussion

Ophthalmic manifestations of HIV and AIDS in a region depend on several factors like availability of healthcare, regional variation in disease patterns, etc. In the present study, out of 1026 patients with HIV on HAART, 221 patients had ocular manifestations. In present study 21.53% patients had ocular manifestations, which is in concordance with the study which was conducted by Bennet Amare *et al.*(7) whereas the study done by Gharai S, venkatesh P *et al.*, Biswas J et al showed a higher incidence of ocular manifestations (8)(6).

The reduced incidence of ocular involvement in present study and study conducted by Bennet Amare *et al.* can be attributed to effective HAART therapy because in both studies study sample was taken from patients who were on HAART therapy. In our study (57.02%) affected patients were males, 95 (42.98%) patients were females with a male to female ratio was 1.32:1(similar to YaredAseefa *et al.* and Lamichanne *et al.* (9)(10). Majority of the patients (46.60%) were in the age group of 21-40 years followed by 34.38% patients in the age group of 41-60 years which shows economic burden on the society. In present study HIV retinopathy was the

Table 5: Association of ocular manifestations according to duration of HAART

Manifestations	Duration of HAART in months				p- value
	<12 (n=11)	13-24 (n=52)	25-60 (n=150)	>60 (n=8)	
Blepharitis	0 (0%)	1 (1.92%)	20 (12.65%)	1 (12.5%)	0.018
Conjunctivitis	0 (0%)	1 (1.92%)	22 (13.92%)	0 (0%)	0.014
Dry eye	0 (0%)	2 (3.84%)	17 (10.75%)	0 (0%)	0.121
Herpes simplex keratitis	0 (0%)	2 (3.84%)	6 (3.79%)	1 (12.5%)	0.961
Herpes zoster Ophthalmicus	0 (0%)	0 (0%)	3 (1.89%)	0 (0%)	0.647
Fungal corneal ulcer	0 (0%)	2 (3.84%)	4 (2.53%)	1 (12.5%)	0.673
IRU	4 (36.36%)	4 (7.69%)	0 (0%)	0 (0%)	<0.001
Pre senile cataract	0 (0%)	4 (7.69%)	17 (10.75%)	0 (0%)	0.45
Iridocyclitis	0 (0%)	9 (17.30%)	8 (5.06%)	0 (0%)	0.04
Nerve palsy	0 (0%)	3 (5.76%)	1 (0.63%)	0 (0%)	0.13
Hardeolumexternum	0 (0%)	3 (5.76%)	2 (1.26%)	0 (0%)	0.28
HIV retinopathy	0 (0%)	8 (15.38%)	20 (12.65%)	3 (37.5%)	0.89
CMV retinitis	4 (36.36%)	4 (7.69%)	2 (1.26%)	0 (0%)	<0.001
Retinal detachment	2 (18.18%)	2 (3.84%)	0 (0%)	0 (0%)	0.008
Anaemic retinopathy	0 (0%)	4 (7.69%)	16 (10.12%)	2 (25%)	0.378
Choroiditis	1 (9.09%)	3 (5.76%)	3 (1.89%)	0 (0%)	0.20
Optic atrophy	0 (0%)	0 (0%)	5 (3.16%)	0 (0%)	0.354
Papilloedema	0 (0%)	0 (0%)	4 (2.53%)	0 (0%)	0.474

most common ocular manifestation. This was seen in 14.02% of patients with ocular manifestations. HIV retinopathy was also one of the most common ocular manifestations in the studies conducted by Gharai S *et al.* (11%) and Pavanakrishnaraja acharya *et al.* (13%) [8,11]. Studies conducted by Yaredaseefa *et al.* and Lamichhane G *et al.* showed higher incidence of HIV retinopathy. This may be due to the fact that all patients are on HAART with a consequent decrease in the viral load. Similarly CMV retinitis also decreased (4.5%) compared to the above said studies. The incidence of HZO in present study was 1.35%. this was lesser compared to studies conducted by Gharai S *et al.*, Yaredaseefa *et al.* and Vidyanarajkumari *et al.* [8,9,12]. Presenile cataract was seen in 9.5% of patients. All 9.5% of patients proved negative for other causes of pre senile cataract. Previous studies have not shown presenile cataract as an ocular manifestation of HIV/AIDS or complication of HAART. A prospective cohort study was conducted by John H. Kempen *et al.* to evaluate the risk of cataract in the setting of AIDS. The incidence of cataract in that study was 0.37%/eye-year [13]. Thorne *et al.* (2006) showed that cataract was one of the common causes of loss of visual acuity, primarily in patients with HAART induced immune recovery [14]. Anaemic retinopathy was observed in 9.95% of the patients. In previous

studies only Sridharan sudharsan *et al.* mentioned Anaemic retinopathy as ocular manifestation and they observed only in 0.73% of the patients [15]. The cause of anemic retinopathy might be due to prolonged Zidovudine therapy.

Anterior uveitis was seen in 7.69% of patients which was close to Yaredaseefa *et al.* study. Immune recovery uveitis was seen in 3.61% of patients. Yaredaseefa *et al.* and Gharai S *et al.* studies showed 5% incidence of Immune recovery uveitis. Sridharan sudharsan *et al.* (6.28%) study observed 17.4% of incidence of Immune recovery uveitis [8,9,15].

Blepharitis was seen in 9.95%, Conjunctivitis was seen in 10.4% and Dry eye was seen in 8.59% of the patients with ocular manifestations. In present study these manifestations had no statistical significance. Kaposi's sarcoma was not seen in the present study which might be due to low prevalence of AIDS-related malignancies in South Asia, and is thought to be due to low prevalence of human herpes virus-8 in this population.

In present study the effect of the duration of disease on ocular manifestations was divided into four categories. Present study showed direct correlation between duration of disease and ocular manifestations. In first category (duration of HIV <12 months) 12.8% of the patients showed ocular

involvement. In second category 16.75%, in third category 26.48% and in fourth category 24.13% had ocular manifestations. More number of patients were in third and fourth categories. The association between ocular manifestations and duration of the disease was statistically significant. (p = 0.0006). The duration of the disease also may be an important predictor of the presence of HIV-related eye diseases. (Table 6)

Table 6: Correlation between ocular manifestations and duration of disease

Months since HIV diagnosis	With manifestations	Without manifestations	P-value
<12 (n=78)	10	68	0.0006
13-24 (n=336)	54	282	
25-60 (n=540)	143	397	
>60 (n=72)	14	58	

A different association was observed between ocular manifestations and duration of HAART therapy. This might be due to effect of HAART on HIV related ocular manifestations and effect of HAART on eye. The incidence of ocular manifestations like Immune recovery uveitis which was due to effect of HAART therapy was observed more in early months of the therapy. Anemic retinopathy which was another manifestation supposedly due to Zidovudine therapy was observed a few months after initiation of HAART therapy. All Immune recovery uveitis patients (8 patients) were on HAART therapy for less than two years only. Of patients with anemic retinopathy almost 82% were on HAART for more than two years. The incidence of CMV retinitis decreased with increased duration of HAART.

The association of duration of HAART and ocular manifestations was statistically insignificant (P:0.375). This may be due to the protective effect of HAART from systemic disease and all the patients in the study group were on HAART (Table 7).

Table 7: Correlation between manifestations and Duration of HAART

Months since ART started	With manifestations	Without manifestations	P-value
<12 (n=53)	11	42	0.375
13-24 (n=274)	52	222	
25-60 (n=648)	150	498	
>60 (n=51)	8	43	

Conclusion

HIV/AIDS is one of the new diseases afflicting mankind, which was virtually unknown 30 years

ago. Today more than 34 million people are living worldwide with HIV/AIDS. In this population about 50-80% patients have ocular manifestations at some point during the course of illness and many a times leading to visual disability and making them socio-economically unproductive and putting them into hardships in an already strained existence

The study evaluated the prevalence of ocular disease in HIV-infected patients on HAART, duration of HAART and duration of disease. Screening in this patient population is particularly important not only because of the high prevalence of ocular manifestations due to disease but also in view of the potential for worsening of ocular conditions due to HAART induced IRIS and other drug induced complications like anaemic retinopathy. We hereby conclude that HIV/AIDS has become a common disease in our population and affects the reproductive age group with male preponderance. HIV retinopathy was the most common ocular manifestation observed in our study With increasing duration of HAART incidence of ocular manifestations decreased. Anemic retinopathy was observed in patients who were on HAART for long duration and immune recovery uveitis was observed in early months of HAART

Recommendations

Further work is indicated to formally evaluate the validity of patient’s symptoms in detecting different types of HIV associated ocular disease. The results of present study suggest that ophthalmic screening examinations might be prioritised for all HIV/AIDS patients on and before HAART. Strategies for screening high-risk populations for HIV-related ocular disease are needed as well as provision for management and treatment of these conditions one detected.

Key Messages: With the advent of increased ART availability, life expectancy for HIV-infected persons is likely to improve. However, the burden of HIV-related ocular disease is likely to remain stable or even increase with possible immune reconstitution ocular complications. Strategies for screening high-risk populations for HIV-related ocular disease are needed.

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Conflict of Interest: NIL

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