

Original Article

Current Spectrum of HIV Associated Ophthalmic Diseases among the Patients Enrolled for Antiretroviral Therapy and its Correlation with CD4-T Cell Count — A Cross Sectional Study

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Background : Various studies have demonstrated 40-45% of HIV patients have Ophthalmic Manifestations. Previous prevalence estimates done within populations selected based on symptoms or ophthalmological referral. This study aims to analyze the prevalence and nature of HIV-related eye involvement in all newly diagnosed HIV patients, before commencing Anti Retro-viral Therapy (ART).

Materials and Methods : This cross-sectional study was done on 271 newly diagnosed HIV-infected patients. Based on a typical ocular lesion with systemic infection the diagnosis of ocular HIV was done. All data were analyzed on SPSS.

Results : Ocular manifestations found in 33.6% of HIV patients. The majority were male (53%) and 14.3% of patients had low vision. The most common involvement was posterior segment (48%). We have found a large number of patients with Ophthalmic Manifestations were asymptomatic (46.2%). Increased chances of HIV ophthalmopathy are observed with increasing severity of HIV infection as evidenced by 74.1% and 91.7% of patients of stage 3 and stage 4 respectively having ocular involvement. The percentage of eye involvement is gradually increasing with decreasing CD4-T Cell Count that is 34.7% of patients of 200 to 500/ μ L CD4 count and 77.1% patients of less than 200/ μ L CD4-T Cell Count have ocular involvement.

Conclusion : Multi-disciplinary approach with proper Ophthalmological evaluation is a must for patients with advanced immune deficiency as manifested by WHO clinical stages 3 or 4 and lower CD4 counts.

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Key words : HIV, Ophthalmic Manifestation, Anti Retro-viral Therapy, CD4-T Cell Count.

Human Immuno-deficiency Virus (HIV) causes multisystem involvement but the ophthalmic disease does affect 70-80% of the patients with HIV infection sometime during the natural history of their infection. Various studies have demonstrated that 40-45% of HIV-infected patients do have some Ophthalmic Manifestations when they are examined by an ophthalmologist^{1,2}. There is a wide spectrum of HIV-associated Ophthalmopathy, which ranges from

Editor's Comment :

- Ophthalmic screening examination must be prioritized for all HIV positive patients before initiation of ART to halt the potentially blinding complications. As ophthalmic manifestations are still not very uncommon even in present scenario where ART is initiated irrespective of CD4-T cell count.

adnexal disorder to posterior segment involvement, including the optic nerve. These ocular manifestations can be sometimes the presenting signs of a systemic infection in an otherwise asymptomatic individual. The severity of ophthalmic involvement of HIV increases as Immuno-competency decrease which is measured by CD4-T Cell Counts³. This study aims to conduct an epidemiological study to evaluate the prevalence and nature of HIV-related eye disease, in all newly diagnosed HIV-infected patients, before commencing Anti Retro-viral Therapy (ART) and its relationship with CD4-T Cell Count.

MATERIALS AND METHODS

This observational cross-sectional study was conducted over 12 months with 271 newly diagnosed HIV-positive patients, who are candidates for ART,

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attending in ART clinics of a Tertiary Care Centre.

Sampling :

All newly diagnosed HIV positive patients, satisfying the inclusion and exclusion criteria were taken for the study. With proper permission from the In-charge of the ART clinic, all patients are requested to be sent to the Department of Ophthalmology for eye examination before starting ART.

Inclusion Criteria :

All newly diagnosed HIV-positive patients satisfying the criteria for initiating ART [All HIV positive patients, irrespective of CD4-T Cell Counts and clinical staging of HIV, are the candidate for ART, according to recent NACO guidelines^{4,5}], attending the ART clinics irrespective of the presence or absences of visual symptoms are included for the study.

Exclusion Criteria :

Patients who already started ART (Old cases), have not satisfied the criteria for initiation of ART, have not given the consent for examination, have other immunosuppressive diseases that can cause a similar types of ocular manifestations ie, uncontrolled diabetes, on Immuno-suppressive drugs etc. were excluded from the study.

Tools and Techniques :

Demographic and medical information was obtained by a combination of direct questioning by the ART clinic counsellor and a review of the medical case notes. Data obtained include present CD4 count, WHO clinical stage and duration since HIV diagnosis. Then a detailed history and comprehensive ophthalmic examination were done. Relevant systemic investigations were done for the diagnosis of ocular diseases.

Statistical Analysis :

Collected data were compiled in SPSS (Statistical Packages for Social Sciences) version 20 and checked for completeness. Descriptive and inferential statistics were used to analyze and present it. Normally distributed data from continuous variables were presented in the form of mean (\pm SD) and the data from discrete variables were presented in the form of frequency and proportion. Independent sample t-test was performed for normally distributed data from continuous variables and Chi square test was done for normally distributed data from discrete variables. A P-value of <0.05 was considered significant.

Ethical Issues :

Ethical clearance was taken from Institutional Ethics Committee and informed consent was taken from all participants before including them in the study

if they diagnosed with any ophthalmic disease, have been treated accordingly or referred to a higher center after consultation with the In-Charge of the ART clinic.

RESULT

In this study, we have examined both eyes of total 271 newly diagnosed HIV-positive patients, who are candidates for ART. Among them, 33.6% have Ophthalmological Manifestations (91 out of 271 patients). Among our study population, male to female ratio was 1.1:1 but 40.3 % of male patients have Ophthalmological Manifestations whereas only 26% of female patients have Ophthalmological Manifestations. Our study shows there are significant chances of developing Ophthalmological Manifestation among male patients (Table 1).

Among our study populations, the majority (133 patients out of 271 ie, 49 %) of the patients are staying at home (they are either housewives or students), 27% of patients are skilled labor and 24% of patients are unskilled labor. But disease frequency is more among skilled labor (43.8%) than unskilled labor (35.4%) and at the home group (27.1%) which is statistically significant (p-value 0.048). Our study showed, the majority of the patients (65.3%) came from rural areas than urban areas (34.7%). But urban populations have more ophthalmic manifestation (41.5%) than rural populations (29.4%) which is also statistically significant (ie, df-1, p-value 0.045).

In this study, the mean age of the study population is 33 years; Standard Deviation is 12 years ranging from 5 years to 68 years. We have found most of the patients belong to the 31-45 age group (52.8%) but the maximum disease frequency was noted (52.2%) in 46-60 years of age followed by 31-45 years of age (36.4%). In the box plot, we have found that median age is higher among those who have Ophthalmic Manifestations in comparison to the patients without the same (p=0.004) (Fig 1). The mean body weight of the patients with or without Ophthalmological Manifestations are 49, which according to the box plot retains the null hypothesis (p-value 0.996) showing there is no significant correlation between the body weight of the patients and the development of Ophthalmological Manifestations (Fig 2).

In this study, we have found 17.4 % of patients

Sex	Ophthalmological Manifestation		Total	p value
	Absent	Present		
Male	86(59.7%)	58(40.3%)	144(100%)(53%)	0.013
Female	94(74.0%)	33(26.0%)	127(100%)(47%)	
Total	180(66.4%)	91(33.6%)	271(100%)(100.0%)	

have binocular involvement, 16.2 % have uniocular involvement and the majority of the study population has no ocular involvement (66.4%). Among total of 91 patients with ocular involvement most commonly involved structure is the posterior segment (48%), followed by the anterior segment (31%) and adnexa (30%) but 9 % of patients have multiple structures involved.

The majority (81.3%) of the patient with HIV-related ocular disease (N=91) have a normal vision at the time of diagnosis but 14.3 % of patient have low vision and only 4 patients out of 91 are blind. Among the patients with normal vision, 16.2% patients have uniocular involvement and 13% have binocular involvement. We have also found, 10 out of 13 (77%) of low vision patients and all 4 blind patients have both eye involvement, so vision significantly depends on eye involvement (p-value 0.000)(Table 2).

In our study we have found, out of 91 patients with ocular involvement 53.8% (49 out of 91) patients have ocular symptoms, among them most frequent symptoms are low vision (46.9%) followed by redness (30.6%), watering (18.6%) and pain (18.4%) and 22.4 % patients have multiple symptoms. But many patients with Ophthalmic Manifestation are Asymptomatic (46.2%).

In our study majority (74.9%) of the patients belongs to stage-1 followed by 10.7% in stage-2, 10% in stage-3 and 4.4 % of patients belong to stage-4. But only 24.1% of stage -1 patients have ocular manifestation whereas 74.1 % and 91.7 % patient of stage 3 and 4 respectively have ocular manifestations. So we have found that the chances of the development of Ophthalmological Manifestation is increasing with

Visual Acuity	Eye Involvement			Total	p value
	None	One eye	Both eye		
Normal	180 (70.8%)	41(16.2%)	33(13%)	254 (100%)(93.7%)	0.000
Low vision	0	3 (23%)	10 (77%)	13 (100%)(4.8%)	
Blind	0	0	4 (100%)	4 (100%)(1.5%)	
Total	180 (66.4%)	44 (16.2%)	47 (17.4%)	271 (100%)(100%)	

increasing severity of HIV infection which is also statistically significant (p-value 0.000)(Fig 3).

In this study, we have found that 12% of the study population have associated co-morbidity like Tuberculosis and Thalassemia. We have also found that the patients with co-morbidity have more chances of developing eye diseases 75% (ie, 24 out of 32 patients) which is statistically significant (p value-0.000).

We have found,45.8 % of patients have a CD4 count within 200-500/ μ L,41.3 % patients have a CD4 count of more than 500/ μ L and only 12.9 % patients have a CD4 count less than 200/ μ L. Among them 18.8 % of patients of more than 500/ μ L CD 4 count have eye involvement, while the percentage of eye involvement is gradually increasing with decreasing CD4 count (ie, 34.7% of patients of 200 to 500/ μ L CD4 count and 77.1% patients of less than 200/ μ L CD4 count have ocular involvement), which also is statistically significant (p-value 0.000)(Fig 4).

We have also found that patients with CD4 count of more than 500/ μ L have 7.1 % adnexal and posterior segment involvement each and 3.6 % anterior segment involvement. Patients with CD4 count 200-500/ μ L have 11.3 % of the posterior segment and anterior segment each and 10.5% have adnexal involvement. But patients with CD4 count less than 200/ μ L have 42.9 % posterior segment,17.1% anterior segment, 8.6% adnexal with posterior segment and 5.7 % anterior with posterior segment involved. So chances of posterior segment involvement is increasing with decreasing CD 4 count which is statistically significant (p-value 0.000)(Table 3).

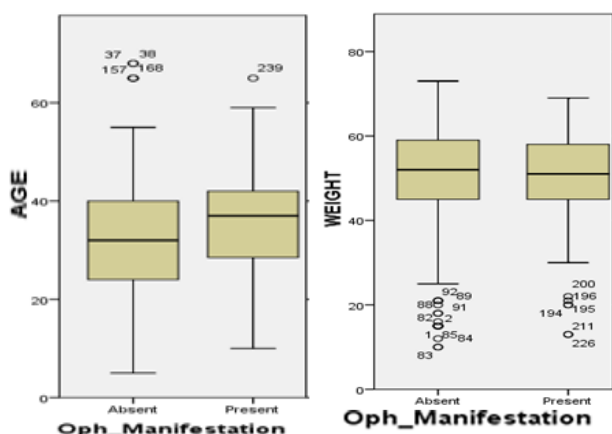


Fig 1 — Box plot showing median age of patients with or without Ophthalmic Manifestations

Fig 2 — Box plot shows distribution of weight of patients with Ophthalmic Manifestations (n=271)

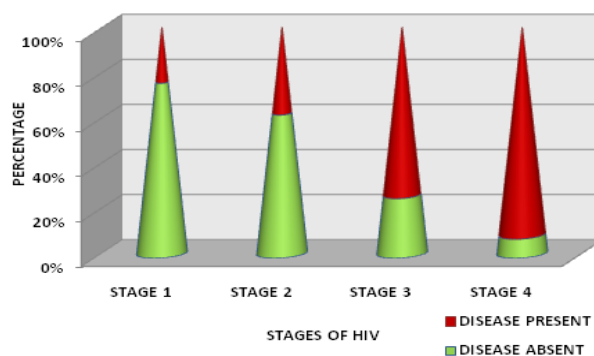


Fig 3 — Composite bar diagram showing distribution of Ophthalmic Manifestations with stages of HIV

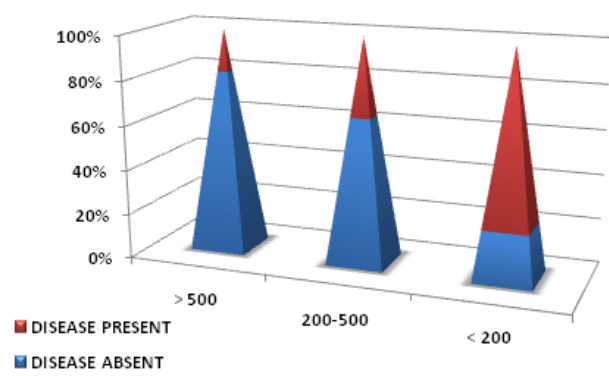


Fig 4 — Composite bar diagram shows Frequency of ophthalmological manifestation and degree of immunodeficiency (n=271)

In our study, posterior segment diseases are most frequent (44%), followed by anterior segment diseases (31%), adnexal diseases (30%) and neuro-ophthalmological manifestations (6.6%). Overall, the most common disease is Retinal micro-vasculopathy 30.8% (28 out of 91), followed by anterior uveitis (9.9%), Keratoconjunctivitis sicca (9.9%) and blepharitis (8.8%). We have found, blepharitis (8.8%), conjunctivitis (5.5%) and molluscum contagiosum (5.5%) are frequent in adnexal diseases. Keratoconjunctivitis sicca (9.9%), anterior uveitis (9.9%) and keratitis (7.7%) are common in anterior segment disease. Retinal micro vasculopathy (30.8%), tubercular chorioretinitis (5.5%) and CMV Retinitis (3.3%) are common in posterior segment disease and optic atrophy (4.4%) is commonly found in neuro-ophthalmological manifestations. We found some patients have multiple segment involvement and again some have multiple diseases in the same segment at presentation in the study group (Table 4).

DISCUSSION

In this study, we have examined both eyes of total of 271 HIV-positive patients and evaluated the frequency of ophthalmological manifestations among them, regardless of the presence of ocular symptoms. Over one-third of our study populations have ophthalmological manifestation at the time of ocular screening. The estimated prevalence of HIV-related eye diseases in India is reported to be between 8-45 %

Table 4 — Distribution of different ophthalmic manifestations (n=91)

Structure Involved / Diseases	No of Patients	Total
Adnexa :		
Blepharitis	08 (8.8%)	27(30%)
Conjunctivitis	05 (5.5 %)	
Molluscum Contagiosum	05 (5.5 %)	
Conjunctival Microvasculopathy	04 (4.4 %)	
Lid Abscess	02 (2.2 %)	
Trichomegaly	01(1.1 %)	
EOM Palsy	02 (2.2%)	
Anterior Segment :		
Anterior Uveitis	09 (9.9 %)	28(31%)
KCS	09 (9.9%)	
Keratitis	07 (7.7%)	
Corneal Ulcer	03 (3.3%)	
Posterior Segment :		
Retinal Microvasculopathy	28 (30.8 %)	40(44%)
Tubercular Chorioretinitis	05 (5.5%)	
CMV Retinitis	03 (3.3 %)	
Vetritis	02 (2.2%)	
PORN	01 (1.1%)	
Toxoplasma Retinitis	01 (1.1%)	
Neuro Ophthalmology :		
Optic Atrophy	04 (4.4 %)	06(6.6%)
Retro-Bulbar Neuritis	02 (2.2%)	
Total	101	101

with a study population ranging from 100-112 participants^{1,2,6-8}. But we have found the overall frequency of ocular manifestations is 33.6% in our study population. A similar study was conducted in Mumbai, India where the overall prevalence of HIV-associated ocular disease was 17.5%, and 23.4% among those have CD4 counts <200 cells/ μ L⁶. We have screened patients at initiation of ART irrespective of CD4 cell count and symptoms. Nowadays ART has been initiated for all HIV-positive patients irrespective of CD4 T cell count , so the ocular involvement pattern is expected to be changing in India.

The majority of the patients (65.3%) came from a rural area but the urban population has more ophthalmic manifestation (41.5% of total urban populations). We have also found the majority of the patients (49%) are staying at home but disease frequency is more among skilled labor (43.8%). We have also found that the median age is higher among those who have Ophthalmic Manifestations in comparison to the patients without the same and the chances of developing ophthalmological manifestation among

Table 3 — Distribution of different structure involvement in co-relation with CD4 count (n=271)

CD4 Counts (/ μ L)	Adnexa	Adnexa Anterior segment	Adnexa Posterior segment	Anterior segment	Anterior Posterior segment	Posterior segment	No Involvement	Total	p-value
> 500	8(7.1%)	0	0	4(3.6%)	1(0.9%)	8 (7.1%)	91	112(100%)	0.00
200-500	13(10.5%)	1(0.8%)	1(0.8%)	14(11.3%)	0	14(11.3%)	81	124(100%)	
< 200	1(2.9%)	0	3(8.6%)	6(17.1%)	2(5.7%)	15(42.9%)	8	35(100%)	
Total	22	1	4	24	3	37	180	271	

males is higher in comparison with females. But no difference was found across religion and marital status of study populations. Pathai S,

*et al*⁶ showed there were no significant differences between the two groups in gender, age, marital status or occupation. But we have not found any study which showed an association between age, sex, occupation and residence-wise significance of Ophthalmic Manifestations, so further study needed.

In this study, we have found 17.4% of patients have binocular involvement. 16.2% have unocular involvement and the majority of the study population have no ocular involvement (66.4%). Our study showed, the majority of the HIV-positive patients (81.3%) who have ocular involvement presented with normal vision at the time of screening but 14.3% patients have low vision and only 4 patients out of 91 (4.4%) are blind. We have found that 77% of low vision patients and all 4 (100%) blind patients have both eye involvement. Our finding is similar with a study done by Listo BN, *et al*⁹ and Pathai S, *et al*⁶. Diminution of vision is rarely complained of by patients suffering from HIV infections because of the good vision in the better eye. So visual acuity cannot be taken as an indication of Ophthalmic Manifestations.

The most common involved structure is the posterior segment 48%, followed by the anterior segment 31% and adnexa 30% but 9% of patients have dual structure involved. This finding is corroborative with the study done by Joshi Purushottam, *et al*¹⁰ who also revealed that among ocular findings posterior segment lesions (32%) were most common and 9.7% of the cases had anterior segment involvement.

We have found, a large no of patients with Ophthalmic Manifestations are asymptomatic (46.2%). The most frequent symptom is Dim vision (46.9%). A similar finding was noted in the study done by Pathai S, *et al*⁶ where there is reporting of ocular symptoms was low (<10%) in groups of patients with and without ocular disease and 92.3% of patients are asymptomatic even though they have some form of HIV related Ophthalmic Manifestations. This may reflect that patients with HIV may not seek treatment for ocular conditions due to the absence of any symptoms.

In the present study, we have found that 12% of the study population have associated co-morbidity and most of them have tuberculosis. Listo BN, *et al*⁹ showed, a number of HIV patients with TB were also noted to have ocular manifestations but this was not statistically significant. But we have found, the patients with co-morbidity have more chances of developing Ocular Manifestations (75%) which is statistically significant. This is because different types of Tuberculosis are the major co-morbidity found in our

study and the occurrence of Tuberculosis is more in WHO clinical stages 3 and 4. Including our study, different studies shows clinical stage 3 and 4 are associated with more chance of developing ocular manifestations^{9,6,11}. This is the probable explanation for this significant association between co-morbidity and the Ocular Manifestations.

In our study, only 24.1% of stage 1 patients have Ocular Manifestation whereas 74.1% and 91.7% patients of Stage-3 and Stage-4 respectively have ocular involvement. This relation is statistically significant and suggestive of the increasing chance of the development of ophthalmological manifestation with advanced staging of HIV infection. This finding is corroborative by a study done by Listo BN, *et al* showing that patients in stage 4 had the highest prevalence of ocular manifestations (95.7%) followed by patients in stage 3 (91.5%). The least prevalence was noted in stage 1 (66.7%)⁹. Also in the study of Pathai S, *et al*⁶ it is shown that the prevalence of ophthalmic lesions associated with HIV was significantly higher in patients with WHO clinical stages 3 or 4. Those patients with advanced WHO clinical staging of HIV were nine times more likely to have ocular involvement. Similarly, it is reported by Jabs DA, *et al*¹¹ that the severity of HIV related eye diseases increases with advanced staging.

CD4-T lymphocyte counts have previously been said to be a reliable predictor of ocular complications of HIV infections¹². Our study showed the percentage of eye involvement is gradually increasing with decreasing CD4 count which is statistically significant. A similar finding was shown by Pathai S, *et al*⁶ that prevalence of ophthalmic lesions associated with HIV was significantly higher in patients with CD4 counts between 0-100 cells/ μ L. They found those with CD4 counts <100 cells/ μ L were six times more likely to have an ocular HIV-related lesion. Another study shows there was a significant association between current CD4 count of 0-100/ μ L, 101-200/ μ L and 500+/ μ L and Ocular Manifestations⁷. Our finding that 77.1% patients of less than 200/ μ L CD4 count have ocular involvement, is comparable with the result of the study by Pathai S, *et al*⁶, in which 76.9% of patients with ocular manifestations of HIV had CD4 counts <200 cells/ μ L. Bekele, *et al*¹³ shown that Ocular Manifestation was common in patients with a CD4-T cell count of <200 cells/ μ L. These findings are similar to other studies conducted in India¹³ and Senegal¹⁴. Thus CD4 count and WHO clinical stage may be important predictors of the presence of HIV-related eye disease in an ART-naïve population.

We have found, the majority of the patients with

adnexal and anterior segment lesion have CD4 count of more than 200/ μ L and most of the patients with posterior segment involvement have CD4 counts of less than 200/ μ L. A study done by Pratik Y Gogri, *et al*¹⁵ also showed that posterior segment lesions has a significant association with low CD4-count and most of the posterior segment lesions (72%) had CD4 count less than 200 cell/ mm^3 , corroborative with our study. So the chance of posterior segment involvement is increasing with decreasing CD4 count.

In our study, posterior segment diseases are most frequent (44%) followed by anterior segment diseases (31%), adnexal diseases (30%) and neuro-ophthalmological manifestations (6.6%). This finding is similar to the study by Joshi Purushottam, *et al*¹⁰, in which, posterior segment lesions (32%) were the most common.

Among the posterior segment diseases (44%), Retinal micro-vasculopathy (30.8%) is most common, followed by tubercular chorioretinitis (5.5%) and CMV retinitis (3.3%).

Similar findings were also shown in studies conducted by Joshi Purushottam, *et al*¹⁰. and Pratik Y, *et al*¹⁵. But Biswas J, *et al*⁷ showed a slightly different pattern where CMV retinopathy was more common. In most of the studies, increased frequency of CMV retinitis was noted as they have taken symptomatic patients with lower CD4 counts.

Among anterior segment diseases (31%) we have found, Kerato-conjunctivitis sicca (9.9%), anterior uveitis (9.9%) and keratitis (7.7%) are common. Blepharitis (8.8%), conjunctivitis (5.5%) and molluscum contagiosum (5.5%) are frequent in adnexal diseases and we have also found conjunctival microvasculopathy in 4.4%. Pratik Y, *et al*¹⁵ showed similar findings as our study. We have also found Kerato-conjunctivitis Sicca (9.9%) is as common as anterior uveitis among anterior segment findings which is corroborating with Liesegang TJ, *et al*¹⁶ which shows Keratoconjunctivitis sicca or dry eye occurs in 20-38.8% of HIV positive hosts in the later stages of AIDS.

We have found, Neuro-ophthalmological Manifestations (6.6%) of which Optic atrophy (4.4%) is commonly found. This frequency of Neuro-ophthalmic manifestations was lower than that reported by Pratik Y, *et al*¹⁵ (10%) Assefa, *et al*¹⁷ (9.6%), Sudharshan, *et al*¹⁸ (8.9%) and Biswas J, *et al*⁷ (9.3%). This may be due to that in the past most of the Indian studies were done among HIV-positive patients with eye symptoms and low CD4 counts but in this study, we have taken HIV-positive patients irrespective of ocular symptoms and CD4 counts before initiation of ART as per NACO guideline.

CONCLUSION

In India, current practice at several ART centers is to refer patients to Ophthalmologists only after complaints of ocular symptoms or abnormal ocular signs are noted by the Physicians. Our study emphasizes the need for routine baseline ocular screening examination before initiation of ART. For conditions like TB Chorioretinitis and CMV Retinitis where the lesion is mostly peripherally located within Retina, the patient may not experience a significant reduction in visual acuity but it is the utmost importance to carry out routine baseline ocular screening for all HIV-positive patients especially with an advanced degree of immuno-deficiency to halt disease progression and potentially blinding complications due to immune reconstitution once ART is commenced. The severity of Ocular Manifestations in HIV/AIDS in the form of visual impairment was higher in patients with low CD4- counts and advanced stages of HIV. So, when HIV infected patient comes to an ART Clinic multidisciplinary approach with proper ophthalmological evaluation is a must.

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