"OCULAR MANIFESTATIONS IN PATIENTS WITH HIV INFECTION AND ITS CORRELATION WITH CD4 COUNTS"

By

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Dissertation submitted to the

BLDE UNIVERSITY, BIJAPUR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

OPHTHALMOLOGY

Under the guidance of

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ACKNOWLEDGEMENT

It gave me great pleasure in preparing this dissertation and it gives me immense pleasure to take this opportunity to thank everyone who have helped me in making it possible.

I convey my profound sense of gratitude and indebtedness to my guide **Dr. M. H. Patil** **M.S,** Professor, Department of Ophthalmology ,BLDEU's Shri B.M.Patil Medical College, Bijapur, who with his immense knowledge and experience, has provided able guidance and constant encouragement throughout the course of my postgraduate studies and residency and in the preparation of this dissertation.

I express my heartfelt gratitude to **Dr.Vallabha K,** **MS, DOMS,** Professor and Head, Department of Ophthalmology , Shri B.M.Patil Medical College, Bijapur for his kind words and constant motivation throughout the course of this study.

I am deeply indebted and express my earnest thanks to **Dr.Sunil G.Biradar,**M.S, Professor , and **Dr.Raghavendra Ijeri ,M.S** , Assistant Professor, Department of Opthalmology , Shri B.M.Patil Medical College ,Bijapur for inspiring me to take up this topic and constantly giving me their encouragement and guidance .

My sincere thanks to **Dr.Shadakshari S Math** ,M.S, Associate Professor, **Dr.Ravi Jadhav** , DOMS, Senior Resident for being constantly involved thoroughout the study and providing timely suggestions and guidance for preparation of this dissertation work.

My heartfelt gratitude to **Dr.Snehalatha Hiremath** , MS,FREC, Raghudeep Eye Clinic for guidance, inspiration and support all through the course of my postgraduate studies and in the preparation of dissertation.

My sincere thanks are due to **Dr. M S Biradar** M.D. Principal, Shri B.M.Patil Medical College, Bijapur, for allowing me do this work, to access medical records, utilize clinical material and facilities in this institution.

My sincere thanks to **Dr.Shivakumar Hiremath,** Medical superintendant, Shri B.M.Patil Medical College, Bijapur for his support.

I acknowledge and thank **C.P.Venkatesh Memorial Trust**, Dharwad for their appreciation and support in this dissertation work.

My sincere thanks to all my Post-graduate colleagues , **Dr.Sushma Hosamani** , **Dr.Radhika** ,**Dr.Shravan Masurkar**, **Dr.Darshankumar U K**, **Dr.Shilpa Umarani** for their whole hearted support and timely help during the course of my dissertation.

I thank **Dr.Sumanth ,MD**, and **Dr.Shubha Jayaram ,MD** , Mysore Medical College, Mysore for their valuable help in statistical analysis of data.

I would also like to thank **Preeti Net Zone** for their meticulous work and timely help in the preparation of final manuscript.

I thank all my **PATIENTS**, who formed the backbone of this study without whom this study would not have been possible.

I would like to thank my **PARENTS** for their constant encouragement, love, sacrifice support and blessings in all the endeavours of my life and work.

Lastly, I am ever grateful to **LORD GANESHA** for everything .

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LIST OF ABBREVIATIONS

AIDS	-	Acquired Immunodeficiency syndrome.
ARN	-	Acute Retinal Necrosis
ART	-	Antiretroviral Theraphy
ATT	–	Anti Tubercular therapy
CDC	-	Centre for Disease Control and prevention
CD4	-	Cluster of differentiation
CME	–	Cystoid Macular Edema
CMV	-	Cytomegalovirus
CWS	–	Cotton wool spot
DNA	-	Deoxyribonucleic acid
HAART	-	Highly active antiretroviral therapy
HIV	-	Human Immunodeficiency Virus.
HPV	-	Human Papilloma Virus
HSV	-	Herpes Simplex Virus
HTLV	-	Human T cell Lymphotrophic Virus
HZO	-	Herpes Zoster Ophthalmicus
IRIS	-	Immune Recovery Inflammatory Syndrome
KCS	-	Keratoconjunctivitis Sicca
KS	-	Kaposi's sarcoma
LAV	-	Lymphadenopathy Associated Virus
NACO	-	National AIDS control organization.
NASBA	-	Nucleic acid sequence based assay
NFHS	-	National Family Health Survey
NHL	-	Non-Hodgkin`s lymphoma
NNRTI	-	Non Nucleoside Reverse transcriptase inhibitors
NRTI	-	Nucleoside Reverse transcriptase inhibitors
OI	-	Opputunistic infections

PCP	–	Pneumocystis carinii Pneumonia
PCR	-	Polymerase chain reaction
PHN	-	Post Herpetic Neuralgia
PI	-	Protease inhibitors
PORN	-	Progressive Outer Retinal Necrosis
RNA	-	Ribonucleic acid
SCC	-	Squamous Cell Carcinoma
SJS	–	Stevens Johnson syndrome
STD	-	Sexually transmitted disease
TB	-	Tuberculosis
VZV	-	Varicella Zoster Virus
WHO	-	World Health Organization

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ABSTRACT

Background

The Acquired Immunodeficiency syndrome (AIDS) , caused by Human Immunodeficiency Virus (HIV) , is the most important public health problem of 21st century. The prevalence rate based on NFHS III for Karnataka in 2006 is 0.69 and is second highest in India. It is a multisystem disorder with a lifetime cumulative risk of developing atleast one ocular lesion ranging from 50-100% in cases of AIDS. Ocular lesions are varied and affect almost all the structures of the eye and posterior segment lesions like cytomegalovirus retinitis can cause blindness. Infection with HIV results in selective loss of CD4T cells and serves as a predicting parameter for the occurrence of specific ocular infection . The purpose of this study was to evaluate the nature and incidence of ocular manifestations in patients with Human immunodeficiency virus and to correlate it with CD4 counts.

Objectives :

- To evaluate the nature and incidence of various ocular manifestations in patients with HIV infection and its relation to CD4 count of the patient.

Materials and Methods:

Patients attending/admitted to the hospital within the study period with sero-positivity for HIV 1 or HIV 2 or both were included in the study and subjected to detailed ophthalmic examination and laboratory tests. Documentation of relevant findings were done wherever feasible. Data was subjected for statistical analysis using InStat software version 5

Results:

The statistical analysis showed a significant correlation between lower CD4 counts and ocular manifestations. Prevalence of ocular manifestation is 34.86 %

.19.08% had anterior segment manifestations and 18.42% had posterior segment manifestations of HIV . 20 patients with ocular manifestations had a CD4 count less than 100cell/mm3.

Conclusion:

Overall ocular manifestations were found to be more common among patients with lower CD4 counts. This suggests that HIV related ocular disease is related to the degree of immunosuppression in HIV infected patients .Although the prevalence of ocular manifestations have significantly reduced in the HAART era , there has been an emergence of varied manifestations like Retinal detachment ,anaemic fundus ,cataract and uveitis among patients on HAART in the process of immune recovery .Ophthalmologists should routinely monitor HIV patients to understand the spectrum of ocular lesions as well as to timely treat them.

Keywords: HIV, Ocular manifestations , Prevalance, CD4 counts, Correlation, Immunosuppression ,HAART

INTRODUCTION:

The Acquired Immunodeficiency syndrome (AIDS) , caused by Human Immunodeficiency Virus (HIV) , is the most important public health problem of 21st century.The first cases of HIV/AIDS were reported in 1981 amongst a group of homosexual males in Philadelphia [1]. Since the beginning of the epidemic, almost 70 million people have been infected with the HIV virus and about 35 million people have died of AIDS. Globally, 34.0 million [31.4–35.9 million] people were living with HIV at the end of 2011[2].

The first Indian case of HIV was reported in a commercial sex worker from Chennai in 1986.[3] The national adult prevalence of HIV disease is 0.36% with around 2.51 million people being infected with this deadly virus according to the recent National AIDS control organization (NACO) estimates [4] . The prevalence rate based on NFHS III for Karnataka in 2006 is 0.69 and is second highest in India.

HIV/AIDS is undoubtedly a multisystem disorder but the lifetime cumulative risk of developing atleast one ocular lesion ranges from 50-100% in cases of AIDS. Biswas et al published first report of eye involvement in AIDS from India in 1995 [5]. Eye is one of the organs commonly affected by the primary or secondary pathologic processes in the multisystem involvement of AIDS. Ocular lesions are varied and affect almost all the structures of the eye. Ocular lesions in AIDS, especially posterior segment lesions like cytomegalovirus retinitis can cause blindness. But, it is important to note that anterior segment, adnexal or ocular surface lesions can also be vision threatening. [6]These ocular manifestations can be the presenting signs of a systemic infection in an otherwise asymptomatic HIV-positive patient. The severity of ophthalmic sequelae of HIV infection increases as immunocompetency decreases.

While the presumed HIV-related asymptomatic ocular lesions occur in the earlier stage, the relentless, destructive and blinding infections, especially opportunistic ones, occur in the late stage of AIDS.[7]

Infection with HIV results in selective loss of CD_4T cells initiated by the specific binding of HIV envelope glycoprotein , gp120 to the CD_4+receptor. Progressive depletion of CD_4+cells provides the best surrogate marker of immune dysfunction in HIV [8].The use of highly active antiretroviral therapy (HAART), which consists of a combination of nucleoside reverse transcriptase inhibitors, HIV protease inhibitors and non nucleoside reverse transcriptase inhibitors, has decreased plasma levels of HIV RNA and increased CD4+ T lymphocytes counts, improving the immune function of patients with HIV infection. The clinical presentation of HIV related diseases may be modified by HAART, which has dramatically improved the prognosis of HIV infection.[9] The predictive value of the $CD4^+$ T-cell count for ocular complications in HIV infection has been called into question by reports of CMV retinitis in patients with $CD4^+$ cell counts higher than 200 cells/mm^3. Thus, whether a reconstituted T-cell count will serve as a better predictor of specific ocular infection is under active evaluation. Despite these uncertainties, the $CD4^+$ cell count has remained the predicting parameter for the occurrence of specific ocular infection in patients who are HIV positive.[10]

The role of the Ophthalmologist in the diagnosis of AIDS is becoming increasingly important. Not only does the eye reflect systemic disease, but ocular involvement may often precede systemic manifestations. Hence the Ophthalmologist has an opportunity to make not only a sight saving, but also a life saving diagnosis of disseminated opportunistic infections .[11]

There have been many case reports and reviews from around the world on ocular adnexal and anterior segment manifestations in AIDS. But there is lack of information in the form of larger case series studies. There are also very few reports from India which further indicates that the epidemiology of ocular manifestations of HIV infection/AIDS in India is not well understood. The current study intends to evaluate the nature and incidence of ocular manifestations in patients with Human immunodeficiency virus and to correlate it with CD4 counts.

AIMS AND OBJECTIVES:

- To evaluate the nature and incidence of various ocular manifestations in patients with HIV infection and its relation to CD4 count of the patient.

REVIEW OF LITERATURE:

EPIDEMIOLOGY AND HISTORY [11,12,] :

AIDS was first recognized in the United States in the summer of 1981, when the Centre for Disease Control and prevention (CDC) reported the unexplained occurrence of pneumocystis carinii pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's Sarcoma in 26 previously healthy homosexual men in New York and Los Angeles. In 1983, Human Immunodeficiency Virus was isolated from a patient with lymphadenopathy, and by 1984 it was demonstrated clearly to be the causative agent of AIDS. By 1994, a million cases had been reported to the World Health Organization (WHO) and the pandemic has now affected all continents.

Since the beginning of the global pandemic, over 13 million under the age of 15 have lost their parents to HIV/AIDS. HIV infection / AIDS is a global pandemic, with an estimate of 38.6 million affected people in 2005.At the end of 2006, according to Joint United Nations Programme on HIV/AIDS, 45.3 million people are estimated to be living with HIV/AIDS (41.5 million adults and 3.8 million children below 15yrs). Out of which 90% of cases are in the economically productive age group of 15-45 yrs. Since the beginning of the epidemic, there have been as estimated 25million deaths due to AIDS. Women are becoming increasingly affected by HIV. Approximately 40% or 15 million of the 37.2 million adults living with HIV/AIDS worldwide are women. Once in every three children orphaned by HIV/AIDS is under age five. In addition, 4.1 million become newly infected and 2.8 million lose their lives to AIDS, making it the fourth leading cause of mortality worldwide.

In India the first case was detected in 1986 in Chennai, from which the figures have grown to 5.2 million among 15-49 yrs by 2005. National adult HIV prevalence is 0.9% with average of 0.5-1.5% .Maharashtra, TN, Karnataka, Andhra Pradesh, Manipur and Nagaland are states with infection rates >1% [13]. Although the disease was first encountered in homosexual men and injection drug users, the risk group includes transfusion recipients, female sexual contacts of infected men and prisoners. But it is being increasingly diagnosed in housewives and pregnant women now. Overall in the state, there has been a sharper decline in HIV prevalence among the younger women under age 25, indicating a possible decline in the incidence of HIV in general population. Districts in Northern Karnataka (Bidar, Gulbarga, Bijapur, Bagalkot, Belgaum, Dharwad, Gadag, Koppal, Raichur, Uttara Kannada, Haveri and Bellary) tended to have a relatively higher HIV prevalence among ANC attendees[14].

In 25 yrs, the AIDS has grown from a series of small outbreak in several groups scattered in US and Western Europe to a global public health calamity.

VIROLOGY – HUMAN IMMUNODEFICIENCY VIRUS [15]

HIV belongs to lentivirus subgroup of the family **retroviridae**. First identified as Lymphadenopathy Associated Virus (LAV), was renamed as Human T cell Lymphotrophic Virus III (HTLV – III). In 1986 **International committee on virus nomenclature** decided its new generic name Human Immunodeficiency Virus (HIV).

There are two types of HIV, type 1 and 2. Type 1 is more virulent pathogen than type 2 and seen worldwide. HIV -1 is responsible for a vast majority of infections globally.HIV-2 is very rare outside West Africa. However cases of HIV-2

have been described in other parts of Africa, Europe , America and Asia. HIV-1 sub types prevalent in India are A, B, C.

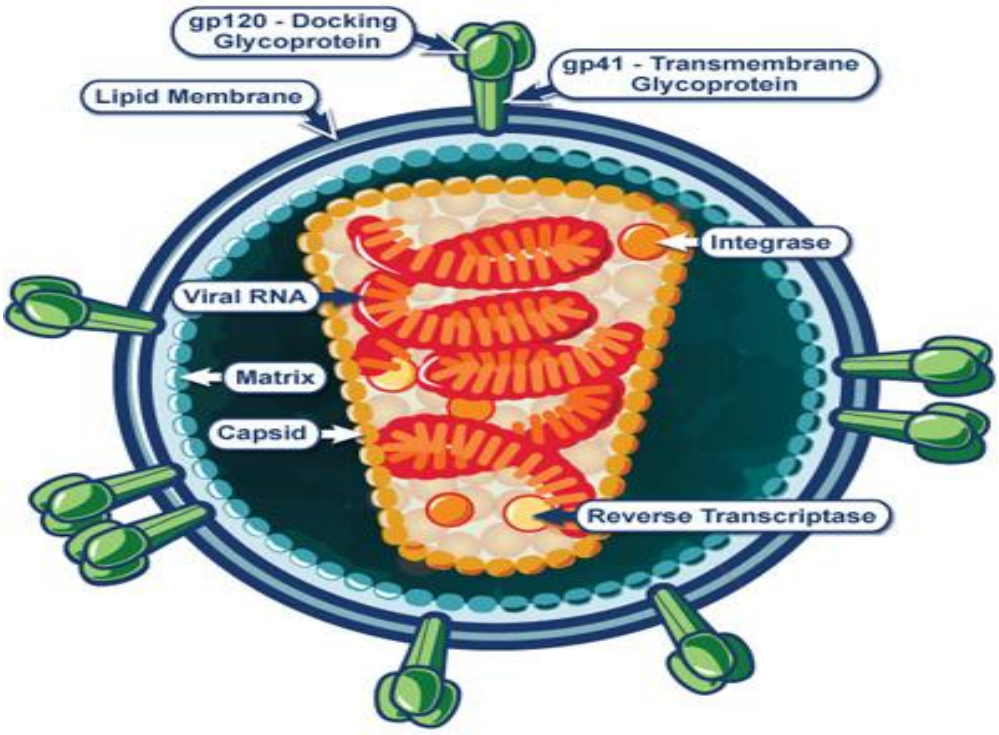
HIV 1 and 2 are each approximately 100nm in diameter and have a **single stranded RNA genome**. The virion has a cylindrical nucleo capsid that contains the single stranded RNA and viral enzymes including **proteinase, integrase** and **reverse transcriptase** . Enzyme reverse transcriptase is characteristic of retrovirus. Surrounding the capsid is a lipid envelope that is derived from the infected host cell and that contains three structural genes:

1. 'gag' gene (group antigen)

2. 'pol' gene (polymerase)

3. 'env' gene (envelope)

Structure of HIV virus



HIV 1 and HIV 2 are genetically similar in the gag and pol regions. The env regions are however different. This variation results in differences in the envelope glycoprotein of these viruses. Such heterogeneity leads to specific immune responses to these viruses, which necessitates different immune assays or western blot procedures for serologic diagnosis of HIV 1 and HIV 2.

In addition to the three structural genes, HIV contains six additional regulatory genes, **tat, rev, vif, vpr, ref** and **vpu.** Of these, two (tat and rev) are essential for viral replication, heterogeneity is noted in env and ref genes, resulting in differing cell tropism, variation in pathogenesis, disparable responses to therapy and potential challenges to develop a broadly cross reactive protective vaccine.

TRANSMISSION: [16,17,18,19]

Four principle modes of transmission of the virus are recognized.

(i) Sexual intercourse – vaginal or anal intercourse in either heterosexual or homosexual.

(ii) Transfusion of infected blood .

(iii) Use of contaminated needles or syringes or by skin piercing instruments which are contaminated with AIDS virus , but is rare.

(iv) Vertical – From an infected mother to her baby ,during pregnancy and delivery and after birth through breast feeding.

Transmission rates among different modes of exposure :

Type of Exposure	Efficiency in single exposure	% of Total Transmission
Blood transfusion	>90%	3-5%
Perinatal	30%	5-10%
Heterosexual	0.1 – 1.0 %	60-70%
Homosexual	0.1 -1.0%	5-10%
IV Drug abuse	0.5 – 1.0%	5-10%
Health Care	<0.5%	<0.1%

Although the efficacy of sexual mode of transmission is low, it accounts for the commonest mode of transmission, because of the absolute number of risk intercourse, is heavy.

PATHOGENESIS: [20]

Initial events in HIV infection include attachment of the virus to a distinct group of T cells and monocytes / macrophages that display a membrane antigen complex known as CD4.The T cells gradually decrease in number from the virus replication and the hallmark of HIV disease is ‘a profound immunodeficiency resulting primarily from progressive quantitative and qualitative deficiency of the subset of T cells – helper T cells or inducer T cells (CD4 cells).

Various stages of HIV replication are :

1. HIV **glycoprotein 120** attaches to CD4 receptor on CD4 cells, activated monocytes and macrophages and glial cells and it enters these cells.

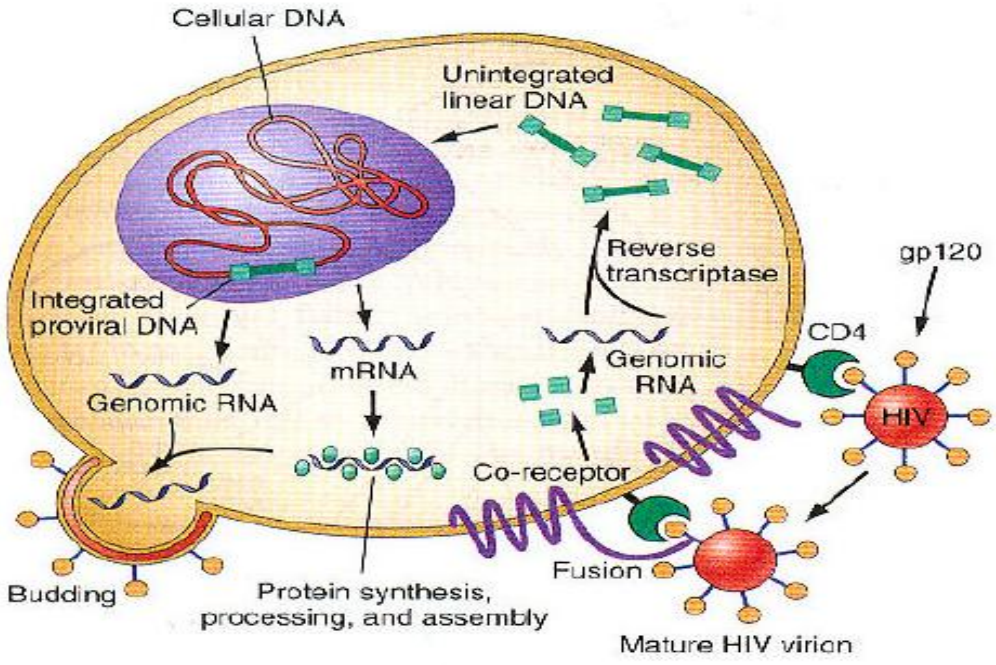
2. HIV uses enzyme **reverse transcriptase** to construct a DNA copy of its RNA genome.

3. Viral DNA then enters the nucleus of the cell and gets integrated into the host cell DNA with the help of **endonuclease**.

4. Regulatory proteins control transcription and are later translated into several large polyproteins and immature virion are so formed in the cytoplasm.

5. Immature virions containing the precursor polyprotein are cleaved by **viral protease enzyme** to result in the formation of mature virus which is budded out of the cell to infect new CD4 cell.

Various stages of HIV replication cycle



Rapid replication occurs with concomitant destruction of CD4 cells even in the initial asymptomatic phase of infection. It is estimated that viral turnover is very high; upto 10^9 virus particles every 1.5-2 days. In contrast, the infected macrophages, instead of undergoing lysis, harbor the virus and disseminate it throughout the body. However, their immune-related functions are altered – decreased migration response to chemo attractants, defective intracellular killing of various microorganisms such as

Toxoplasma gondii and Candida, reduced expression of class II molecules, which impairs the processing and presentation of antigen to T helper cells. Excessive production of tumour necrosis factor alpha leads to dementia, wasting syndrome and unexplained fever.

DISEASE COURSE : [17]

Natural history of HIV infection is divided as following stages

1. Acquisition of infection.

2. Primary HIV infection.

3. Asymptomatic HIV infection.

4. Early symptomatic HIV infection.

5. Late symptomatic HIV infection.

6. Advanced HIV disease.

The illness varies from one individual to another with several predictable stages that leads invariably to death. In general infected individuals initially experience an **acute primary infection**. Manifestations are varied and most often include the acute onset of fever, generalized lymphadenopathy, pharyngitis, erythematous maculopapular rash, arthralgia, myalgia, retro orbital headache, malaise, diarrhoea and vomiting. Opportunistic infections are rare during this phase, followed by a relatively **asymptomatic infection** that can include generalized lymphadenopathy. Usually it has duration of 10yrs, and CD4 cell count is usually above 500cells/mm3.

This progress to **early symptomatic** disease associated with progressive decline in T-helper cells, and eventually to advanced HIV disease with the development of opportunistic infections or malignancies. It lasts for about 1-2weeks and is characterized by symptoms typical of a non specific viral illness. The CD4 cell count continues downward with a range of constitutional symptoms including fever, unexplained weight loss, recurrent diarrhoea, fatigue and headache. Recurrent HSV infection and oral hairy leukoplakia may occur.

In **late symptomatic period** the risk of developing AIDS related opportunistic infections or malignancy substantially increases with CD4 count <200 cells/mm3.

Patients then invariably enter into an **asymptomatic phase** that can last for 2 or sometimes more than 10 years, during which the CD4+ T lymphocyte count varies from about 750 to 200 cells / cu.mm (normal count being 600 to 1400 cells / cu mm). It is followed by **advanced HIV disease**, which may last for up to three years, during which the CD4+ T lymphocyte decrease to less than 200 cells / cu mm. In advanced disease, CD4 count is <50 cells/mm3 with multiple opportunistic infections , and without ART death is inevitable.

DEFINITION AND CLASSIFICATION OF AIDS [21]

Expanded WHO Case Definition for AIDS.

An adult or adolescent (>12yrs of age) is considered to have AIDS if a test for HIV antibody gives a positive result and one or more of the following conditions are present.

• >10% of body weight loss or cachexia with chronic diarrhea or chronic fever or both intermittent or continuous for at least one month.

• Cryptococcal meningitis

• Pulmonary or extrapulmonary tuberculosis

• Kaposi's sarcoma

• Candidiasis of oesophagus.

• Clinically diagnosed life threatening or recurrent episodes of pneumonia with or without etiological confirmation.

• Invasive cervical cancer.

• Pneumocystis carinii pneumonia

• Disseminated M.avium infection

• CMV disease

• HIV associated dementia

• Toxoplasmosis

• Immunoblastic lymphoma

• Chronic cryptosporidiosis

• Disseminated histoplasmosis

WHO clinical staging system for HIV infection.

Stage I:

Only a small number of people have a recognizable acute illness ,as initially HIV infection is clinically silent or asymptomatic. Few patients may develop mild viral fever like illness.

Stage II:

As immunosuppression develops, the CD4 count falls and viral load increases. There is increasing susceptibility to a small range of clinical illnesses. Clinical manifestation may consist of mild weight loss, skin and oral problems recurrent sinusitis or herpes zoster.

Stage III:

With further immunosuppression, the susceptibility widens to select group of common and more virulent infection such as TB and bacterial pneumonia.Common symptoms in this stage are weight loss more than 10%, chronic diarrhea and prolonged unexplained fever.

Stage IV:

With more profound immunosuppression, when the CD4+ T lymphocyte count falls below 200, the opportunistic infections develop and the individual is considered to have advanced disease.

DISEASE PROGRESSION AND SURVIVAL:

Disease progression and survival with HIV is variable such as Rapid Progressors, Slow Progressors and Non Progressors. It may be rapidly progressive over 2yrs or hardly progress at all over 15 yrs. However older age and low socio-economic status adversely affect survival.

DIAGNOSIS [16-19,21-25]

HIV infection is diagnosed by blood tests that detect HIV antibodies. The tests usually being done are :

A.Specific tests.

B.Serological tests

The **specific tests** for HIV infection are :

a)**Antigen detection** : The p24 antigen is the earliest marker to appear in blood by about 2weeks, following a single massive infection and are routinely used for screening.

b) **Virus isolation** : Once infected with HIV, the virus persists for life in blood and body fluids within the CD4+T lymphocyte. Reverse transcriptase activity and presence of viral antigen indicate viral replication and are commonly done routinely.

c) **Detection of viral nucleic acid** : It is detected by Polymerase chain reaction (PCR) .They are useful for diagnosis ,including during window period as results become positive after 72 hours of infection. It is also used for monitoring prognosis and to test resistance to ART.

The various types of PCR include DNA PCR , RT PCR, bDNA PCR and Nucleic acid sequence based assay NASBA.

d) **Antibody detection** : Diagnosis is based on detecting serum antibodies to viral proteins, core p24 or envelope gp120,gp41. It is the simplest and most commonly employed technique for diagnosis.

The **serological tests** are :

I) Screening tests

II) Serological test

I) **Screening tests** : These tests are sensitive, specific and less expensive and hence used for screening.

a) **Elisa test** : It contains antigens from both HIV1 and HIV2 with a high specificity , and moderate sensitivity. It serves as an extremely good screening test and is most commonly employed.

b)**Rapid test** : Test results are obtained within 30 minutes

- Dot blot assay
- Particle agglutination
- HIV spot and Comb test

c) **Simple test** : These require about 1-2 hours and does not require expensive equipment

II) **Supplemental tests** :

a) Western blot test : This is based on the fact that specific antibodies, with different well characterized molecular weights are produced in response to multiple HIV antigens.

Antibodies to p24, p41 and gp 120/gp160 gives conclusive evidence of HIV infection. It is a good confirmatory test, however it is expensive, cumbersome and often not readily available. The test is also considered positive if a band is noted against at least two of above proteins.

b**) Indirect immunoflourescence assay**

c) **Radio Immuno Precipitation Assay** (RIPA), **Passive haemagglutination** assay and **Dot immunobinding** assay also are available.

The **non specific tests** for HIV infection are :

1.Total and differential leukocyte count

2.CD4+T cell assay

3.Platelet count

4.IgG and IgA levels

5.Skin test for cell mediated immunity

6.Tests for opportunistic infections and tumors

TREATMENT :

Indications for antiretroviral therapy (ART)[16]

I. Acute infection syndrome

II. Chronic Infection

A. Symptomatic disease

B. Asymptomatic disease

1. CD4 T cell count <350 /mm3 decreasing

2. HIV RNA >50,000 copies / ml or increasing

III. Post exposure prophylaxis

HIV has the ability to rapidly develop resistance if any drug is used alone. Hence current guidelines recommend a minimum of 3 antiretroviral drugs to be used in combination. The triple drug regimen or combination of Protease inhibitors with non neucleoside reverse transcriptase inhibitors is commonly referred to as HAART (Highly Active Antiretroviral Therapy).

Various steps in replicative cycle of HIV may be targeted. Currently available for clinical use are : [26]

- Reverse transcriptase inhibitors - nucleoside (nRTI)

- Reverse transcriptase inhibitors – non nucleoside (nnRTI)

- Protease inhibitors.

- Fusion inhibitors.

NRTI'S and **NNRTI'S** inhibit reverse transcriptase and this prevents the virus from infecting the cell. **PI'**s inhibit protease, an enzyme which cleaves viral proteins and is important for the final assembly of virions. PI's are the most potent anti-retroviral drugs. **Fusion / Entry inhibitors** represent the new class of anti-retrovirals. This injectable drugs inhibit HIV fusion with the CD4 cell membrane and is intended for use in patients who have failed with other regimens.

Combination ART

None of the drugs has been shown to eradicate HIV infection, but when used in combination they may decrease viral replication, improve immunologic status and delay infectious complications and prolong life.

Investigational ART agents

- Compounds that bind to gp 120 so as to inhibit viral adsorption.

- C×CR4 and CCR5 inhibit viral entry.

- NCP7 block viral assembly.

- Proviral DNA integration inhibiting agents.

- HIV and RNA transcription blocking agents.

CLASSES OF ANTIRETROVIRAL DRUGS

Reverse Transcriptase Inhibitors -nRTIs	Reverse Transcriptase Inhibitors-nnRTIs	Protease Inhibitors - PI	Fusion Inhibitors
Zidovudine Stavudine Lamivudine Didanosine Zalcitabine Emtricitabine Abacavir Tenofovir	Nevirapine Efavirenz Delavirdine	Iridinavir Nelfinavir Ritonavir Saquinavir Lopinavir Amprenavir Atazanavir Fosam prenavir	Enfuvirtide T-20

CD4+ T LYMPHOCYTE COUNT AS A PREDICTOR OF RISK [27]

For years, the CD4+ T Lymphocyte count proved a reliable predictor of the risk of ocular complications of HIV infection. Recently, however the use of Highly Active Anti Retroviral Therapy (HAART) has allowed substantial and sustained albeit incomplete, repopulation of T lymphocytes to occur in many patients. Such observations have raised the question of whether reconstituted T lymphocyte populations are in fact functional, and more specifically, whether the current or the lowest CD4+ T Lymphocyte count is a better predictor of the risk of HIV associated disorders. The CD4+ T lymphocyte count reflects the immune status and low CD4+ T lymphocyte count indicates the poor immune system. Absolute Lymphocyte Count (ALC), CD8+ T lymphocyte count, and the ratios among all these also reflects the immune status of the HIV patients. Serial evaluation of these counts are necessary in all these patients to assess the course of disease and to know the effect of treatment.

CD 4 count and associated manifestations of HIV

CD4+ T Lymphocyte count	Disorders
< 500 cells / cu.mm	Kaposi's sarcoma Lymphomas
<250 cells / cu.mm	Pneumocystosis Toxoplasmosis Herpes Zoster Ophthalmicus
< 100 cells / cu.mm	Retinal or conjunctival microvasculopathy CMV retinitis Keratoconjunctivitis sicca Cryptococcosis Microsporidiosis HIV encephalopathy Progressive multifocal encephalopathy

OPHTHALMIC MANIFESTATIONS OF HIV DISEASE :

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,[28,29] subsequent studies have described several AIDS related conditions in the eye and orbit. 70–80% of adult AIDS patients will experience an ocular complication at some point of their illness[28,30] .Studies have reported 13.3% cases presented with ocular findings alone who were later diagnosed as having HIV. Orbital and adnexal findings include tumors of the periocular tissues and external infections. Anterior segment manifestations consist of keratitis, keratoconjunctivitis sicca, iridocyclitis, and other complications. Posterior segment findings include a HIV associated retinopathy and a number of opportunistic infections (OI) of the retina and choroid. HIV has also been related to neuroophthalmic manifestations, such as visual field defects, papilloedema, and diplopia. The occurrence of ophthalmic complications associated with HIV infection is significantly lower in the pediatric age group. Partial immune system recovery following initiation of effective antiretroviral therapy (ART) may modify clinical presentation of ophthalmic OI and can affect response to treatment. In addition, in one eye, several infections may occur at the same time, rendering diagnosis and therapeutic intervention more difficult.

The clinical presentation of HIV related diseases may be modified by HAART, which has dramatically improved the prognosis of HIV infection. All areas of the visual system can potentially be affected in patients with HIV infection or AIDS. Cytomegalovirus (CMV) retinitis, which can lead to blindness, is the most common infectious ocular complication and may affect 30% of severely immunocompromised

individuals. Since the advent of HAART, the incidence of CMV retinitis has decreased significantly. However, in HAART-naïve patients or in those who are immunocompromised while receiving ART, CMV infections can still occur. CD4+ T Lymphocyte proved to be a reliable predictor of ocular complications of HIV infection. In patients with early-stage HIV disease (CD4 count >300 cells/µL), ocular syndromes associated with immunosuppression are uncommon. Nonetheless, eye infections associated with sexually transmitted diseases (STDs) such as herpes simplex virus, gonorrhea, and chlamydia may be more frequent in HIV-infected persons. Therefore, clinicians should screen for HIV in the presence of these infections. All patients with HIV disease should undergo routine ophthalmologic examinations, since proper diagnosis and treatment may help to maintain vision and prolong life.

Reported Ocular Manifestation of HIV Disease Grouped by Anatomic Location:

I.**Orbital Manifestations** –Orbital cellulitis, Orbital lymphoma

II. **Ocular adnexae and Anterior segment**

A. Infectious diseases :Molluscum contagiosum ,Herpes zoster ophthalmicus ,Herpes simplex virus vesicular lesions, Tuberculosis (cutaneous lesions) ,Cryptococcosis (cutaneous lesions)
B. Neoplasms - Kaposi's sarcoma, Lymphoma, Squamous cell carcinoma
C. Others -Atopic dermatitis, Blepharitis/meibomitis , Trichomegaly ,Stevens Johnson syndrome

II**. Conjunctiva**

A. Infectious diseases-. Molluscum contagiosum (rare) ,Gonorrhea, Syphilitic chancre ,Tuberculosis, Cryptococcosis ,Pneumocystosis (rare), Microsporidiosis

B. Neoplasms -Kaposi's sarcoma , Ocular surface squamous neoplasias, Conjunctiva intraepithelial neoplasia , Squamous cell carcinoma

C. Others- Dry eye , Microvasculopathy , Stevens Johnson syndrome

III. **Cornea**

A. Infectious diseases- Molluscum contagiosum, Varicella-zoster virus-associated keratitis Herpes simplex virus-associated keratitis ,Cytomegalovirus keratitis, Gonorrhea, Syphilitic keratitis ,Tuberculosis, Cryptococcosis, Microsporidiosis

B. Others- Keratitis sicca ,Stevens Johnson syndrome, Peripheral corneal ulceration, Phospholipidosis ,Intracorneal deposits (possibly associated with hyperlipidosis), Endothelial deposits secondary to Rifabutin.

IV. **Episclera/sclera**

A. Infectious diseases -Varicella-zoster virus-associated scleritis ,Tuberculosis

V. **Anterior uvea**

A. Infectious diseases -Varicella-zoster virus-associated anterior uveitis, Herpes simplex virus-associated anterior uveitis ,Cytomegalovirus-associated iritis (rare) .Human immunodeficiency virus-associated anterior uveitiS, Syphilitic anterior uveitis, Tuberculosis ,Cryptococcosis ,Toxoplasmic iritis

B. Neoplasms- Lymphoma

C. Other- Immune recovery uveitis, Uveitis associated with medications ,Rifabutin- associated uveitis, Cidofovir-associated uveitis

VI. **Neuro-ophthalmic abnormalities**

They can also be grouped into those caused due to the disease itself and those related to the management.

V. **Posterior segment**

HIV retinopathy,CMV retinitis, Acute retinal necrosis, Progressive outer retinal necrosis,Ocular syphilis , Ocular tuebrculosis ,Toxoplasmosis, Candidiasis , Cryptococcal chorioretinitis , Histoplasmosis, Pneumocystis choroiditis

I. ORBITAL MANIFESTATIONS :

Orbital manifestations of HIV infection are rare. Few cases of orbital cellulitis and orbital lymphoma have been reported. Most of the orbital cellulitis were related to Aspergillus infection .Other organisms implicated are Rhizopus arrhizus, Toxoplasma gondii, and Pneumocystis carinii. Children may present with recurrent episodes of orbital/peri-orbital cellulitis [36,37]. Primary non-Hodgkin`s lymphoma (NHL) of the orbit and ocular adnexa is a rare disease. It accounts for only 1% of all NHL. In general, the risk of developing NHL is higher in HIV infected patients as against the 16.1 per 100,000 men in general population. The reported cases of lymphoma responded well to radiotherapy. However, high doses may be correlated to late ocular complications[38,39].

II. EYELIDS AND OCULAR ADNEXAL MANIFESTATIONS :

1.VIRAL INFECTIONS

A. MOLLUSCUM CONTAGIOSUM

It is caused by DNA Pox virus and affects about 5%-33% of HIV infected patients [40] typically affects two age groups – Children [41] and Young adults and has

also been reported as the initial manifestation of HIV disease [42] while in a general population of 10,000 people, about 24 new cases of molluscum contagiosum have been reported each year in adults .It is characterised by involvement of skin and mucous membrane , translucent pink or pearly white, wart like nodule or papule on the skin of lids with central umbilication that is pathognomic due to presence of central soft, white, cheesy material (consists of viral infected cells). In HIV positive individuals these lesions are characteristically larger in number and size, often confluent, bilateral, have an aggressive course and are resistant to therapy [43].Rarely, conjunctival or corneal involvement or dissemination can occur. The lash line should be carefully examined in all cases of chronic conjunctivitis so as to not miss a molluscum lesion.

Molluscum can be treated by topical agents like trichloroacetic acid ,phenol or serial applications of liquid nitrogen. Incision with or without curettage, excision and cryotherapy are equally effective. Dessiminated lesions can be treated by oral Acyclovir. Institution of HAART with restoration of immunity leads to complete resolution of lesions and limitation of infection but the phenomenon of immune reconstitution following HAART can cause new presentations like severe conjunctival inflammation till regression of lesions occurs [44].

B.HERPES ZOSTER OPHTHALMICUS (HZO):

Herpes Zoster is caused by varicella zoster virus(VZV), member of the herpes virus group. Primary infection occurs in early childhood, as chicken pox, a self-limiting generalised exanthema that rarely involves the eye and heals without sequela. Subsequently the virus migrates to the trigeminal ganglion where it remains quiescent for years. If cell mediated immunity is reduced as in infection with Human

Immunodeficiency Virus (HIV), cancer,lymphoma or immunosuppressive therapy, the virus becomes activated and travels down the branches of the trigeminal nerve causing a typical vesicular rash .In younger individuals, HZO may be the initial manifestation of HIV infection [45] . Any patient younger than 50 years of age,presenting with HZO, is potentially a suspect of having HIV infection or any other immunosuppressive condition [28,46]. The ophthalmic division of the trigeminal nerve is involved more frequently than other branches, hence the name Herpes Zoster Ophthalmicus (HZO). The ophthalmic division branches into the lacrimal, nasociliary and frontal nerves. Involvement of the frontal nerve is common. When the nasociliary nerve is affected, the patients may present with vesicles at the tip of the nose, known as Hutchinson`s sign. Studies have shown ophthalmic involvement in 99% of patients with this sign [47] .

Characteristic prodromal symptoms include headache, generalized malaise and fever [48]. It occurs early in the course of HIV infection when the CD4 count is more than 200 cells/µl. It is therefore not considered an AIDS defining illness although its occurrence in a young person should raise the possibility of immune suppression.

Ocular complications result from inflammation, nerve damage and tissue scarring [49,50]. Herpes zoster ophthalmicus presents as vesicobullous rash and may be associated with keratitis, scleritis, uveitis, retinitis or encephalitis [45] . Herpetic neuralgia (PHN) refers to debilitating pain and itching in the involved branch of the nerve persisting many months after healing of the acute lesion. It is due to irritation of nerve endings by the resulting scar tissue.The severity of the skin rash is an important prognostic parameter of subsequent ocular involvement[51] .Significant entropion or trichiasis may result from herpes zoster, as the virus can cause permanent contraction scars of the deep dermal tissues of the eyelids [47]. A variant of HZO known

as zoster sine herpete can present with conjunctivitis, uveitis, episcleritis, scleritis and corneal hypoesthesia without skin lesions. About 50% of patients with HZO develop anterior uveitis. The uveitis can lead to elevated intra ocular pressure, heterochromia iridis and sector iris atrophy.

A study by Hodge et al , showed a relative incidence risk ratio of 6.6/1 in HIV positive patients compared to HIV negative patients [52]. Reports suggest that it affects 5–15% of HIV positive patients and may have a high rate of painful and sight threatening complications [30,45].

Diagnosis of HZO is mainly clinical.Virus culture,Tzanck smears, PCR for VZV DNA,flourescent antibody testing and antigen detection by direct immunoflourescence can be used for confirmation.

Treated with intravenous Acyclovir 10mg/kg , 3 times a day for 5 days followed by oral Acyclovir 800mg five times daily for least 3–6 weeks. Other drugs include Famcyclovir and IV Foscarnet .This limits the duration of skin rash and reduces the prevalence of inflammatory eye complications. Adults with an acute, moderate-to-severe skin rash may receive acyclovir orally and bacitracin in ointment form for skin lesions.

Patients with iridocyclitis and/or stromal keratitis may be treated with topical steroids. Systemic steroids and antivirals may prevent loss of sight from uveitis and keratitis. Addiotionally topical cycloplegic should be used in uveitis. In cases of retinitis, choroiditis, or cranial nerve involvement, intravenous acyclovir and oral prednisone are indicated. Options for treatment of PHN if it develops , include Topical lidocaine cream plus tricyclic antidepressants, Amitriptyline 50 mg nocte or Carbamazepine 200 mg every night.

C. VIRAL KERATITIS:

Herpes Simplex Virus (HSV) and Varicella Zoster Virus(VZV) are the most common etiologic agents of infectious keratitis [43]. AIDS patients can present with simultaneous HSV 1 and 2 ocular infections unlike in seronegative patients. Young and associates showed an atypical presentation in AIDS patients with a predilection for marginal as opposed to central epithelial keratitis in non-HIV patients, also a relative resistance to treatment, more frequent and lengthier recurrences [53].

Herpes simplex virus (HSV) can cause painful and often recurrent corneal ulcerations with a characteristic branching or dendritic pattern on slit lamp exam.It is often associated with corneal scarring and iritis. Keratitis due to varicella zoster is usually associated with HZO and complications include subepithelial infiltrates, dendritic and geographic epithelial keratitis, stromal keratitis, disciform keratitis, uveitis and secondary glaucoma. Corneal complications occur in 65% of individuals with HZO and dendritic ulcer occurs in 51% of cases. Neurotrophic keratitis occur in 25 % [54].Corneal stromal involvement has been reported infrequently in individuals with AIDS due to the T- lymphocyte dysfunction [55]. HAART induced immune recovery can increase the risk of recurrence of viral keratitis, especially stromal keratitis [56].

Treatment is along the same lines as in non-HIV patients with trifluorothymidine and cycloplegic drugs, with debridement of the ulcer using a cotton-tip applicator. Oral acyclovir (400 mg twice daily for 1 year) decreases the risk of recurrent HSV keratitis by 50% [57] , topical antivirals and cycloplegics are used. Long term suppressive oral Acyclovir therapy (400mg, twice daily for a year according to HEDS) may also benefit HIV- infected individuals with a history of HSV disease, in light of increased recurrence rates [58].

CYTOMEGALOVIRUS(CMV) KERATITIS :

CMV retinitis is the commonest AIDS related opportunistic infection of the eye, but rarely involves the anterior segment as anterior uveitis [59]. It can be transmitted by blood, saliva,breast milk and mucous membrane contact and usually remains asymptomatic or causes transient conjunctivitis in immunocompetent persons. CMV epithelial keratitis resembles VZV dendrites. Corneal endothelial deposits are seen in about 80% of eyes with CMV retinitis [60]. They appear as linear or stellate lesions and form a reticular pattern, best visualized on retroillumination, commonly in the inferior cornea. It is composed of fibrin and macrophages, with no active CMV infection. Stromal keratitis is noted when stromal keratocytes are infected. Restoring immunity by HAART prevents CMV infection.

D. BACTERIAL KERATITIS:

The clinical presentation of bacterial keratitis in HIV- infected individuals differs from that in general population as the lesions are usually bilateral, involve multiple pathogens and carry a higher risk of perforation [43]. Paucity of inflammation among immunosuppressed, contributes to the delay in diagnosis and treatment.

Predisposing risk factors for bacterial keratitis in HIV patients are the preexisting keratoconjunctivitis sicca, viral keratitis and the use of crack cocaine by HIV infected individuals . The risk of infection with ‘normal flora’ may be greater for severely immunosuppressed individuals [55]. Staphylococcus aureus, Staphylococcus epidermidis and Pseudomonas aeruginosa are the most frequently implicated bacteria. Klebsiella oxytoca, Streptococcus, Bacillus, Micrococcus, Capnocytophaga and most recently Acanthamoeba have also been reported, with some cases of recalcitrant infection requiring keratoplasty and even evisceration of the globe [61].

NEISSERIA GONORRHOEA INFECTION:

HIV infection can modify the typical host response to gonococci resulting in more severe ocular signs and symptoms [62]. It is usually transmitted to the eye by accidental auto inoculation. It causes pseudomembranous or membranous conjunctivitis with ulceration, scarring and perforation in one or both eyes. Gram staining and culture help in indentification of the etiology. Topical therapy alone will be ineffective. Systemic treatment with Ceftriaxone or other appropriate antibiotics must be used to treat gonococcal conjunctivitis.

MYCOBACTERIAL DISEASE:

Mycobacterium tuberculosis , an acid fast bacillus , is the commonest systemic opportunistic infection associated with AIDS, even though ocular tuberculosis is not that common [63,64] with a reported prevalence of only 0.2% of eyes in an autopsy series of individuals with AIDS.

The anterior segment manifestations of ocular tuberculosis are ulcers, tubercles, granular masses or pedunculated polypoid tumours of conjunctiva and eyelidsor localized masses resembling chalazion [55]. An association between corneal phlyctenulosis and tuberculoprotein hypersensitivity is also suggest. TB may cause interstitial keratitis with or without stromal infilterates, sclerokeratitis and scleritis (nodular variety being more common than diffuse). It can present as granulomatous type of anterior uveitis, even and the inflammatory reaction correlates with the level of CD4+ T cell count. Mycobacterium avium, a species of nontuberculous mycobacteria, was reported to be the cause of endophthalmitis [65] with an intense inflammatory reaction and hypopyon in an AIDS patient who had a history of disseminated M. avium infection.

Treatment is along the lines of that in the general population with systemic antitubercular therapy according to the modified DOTS (Directly Observed Treatment Short course) regimen. Specific ocular treatment should be instituted too. There have been reports of scleral TB responding favourably to additional topical (2 hourly) and subconjunctival (every 3 days) Streptomycin sulfate along with ATT, with healing of lesion [55]. HIV infected individuals require therapy of longer duration and with additional drugs.

SPIROCHAETAL INFECTIONS:

The incidence of syphilis which had reached a low point in mid 1950s showed a steady rise again in the early 1980s which coincided temporally with the start of AIDS epidemic. Previous infection with syphilis is strongly associated with increased risk of HIV infection which is postulated to be due to disruption of mucosal epithelial barrier in syphilitic ulcers, which contain mononuclear cells that are the targets of HIV infection [55] .Ocular manifestations of syphilis in HIV infected individuals are similar to those seen in seronegative patients except that they tend to be more severe, aggressive and relapsing.

In the anterior segment , chancres of the conjunctiva (primary syphilis), conjunctivitis (granulomatous type in secondary syphilis) and gummata (tertiary syphilis) are seen [66]. It is the most common bacterial cause of uveitis in HIV patients with an incidence of 0.6%. It consists of panuveitis in conjunction with anterior uveitis [67]. Eighty five percent of HIV-positive patients with ophthalmic syphilis have co-existing neurosyphilis. Hence all patients with syphilitic uveitis must undergo CSF analysis to rule out neurosyphilis .Isolated episcleritis and scleritis are uncommon but can present in the secondary or late syphilis [68].

Diagnosis with direct examination under dark field microscopy, rapid plasma reagin or FTA test or biopsy can be used in suspicious lesions. Treatment is similar to that of neurosyphilis with high dose IV Penicillin G (12-24 million units per day for 14 days) or Benzathine penicillin (2.4 million units IM weekly for 3 weeks). Extensive follow-up subsequently for atleast 2 year is recommended because of the high rate of relapse.

E.FUNGAL INFECTIONS:

Fungal corneal ulcers are rare in the absence of preceding trauma, ocular surface disease or corticosteroid therapy among general population. However HIV/AIDS patients can develop spontaneous fungal infections and are generally more severe [43]. One study found that 81.2% of individuals in Africa who presented with fungal keratitis were HIV infected [69]. Candida and Cryptococci are the most prevalent ocular fungal pathogens among HIV positive hosts. Candida species are particularly common in intravenous drugs users and causes keratitis. Cryptococcus commonly causes posterior segment pathology but can sometimes cause conjunctivitis, limbal infection, iris granulomas and scleral ulceration [70]. Fungal keratitis have a more acute and protracted course , result in bilateral involvement and often perforate in the HIV infected population .Spontaneous fungal keratitis secondary to Candida parapsilosis and Candida albicans has been observed with advanced HIV disease and a history of antecedent trauma [71,72].Defects in cellular immunity also may play a role in susceptibility to corneal infections.

Other fungi causing keratitis are Fusarium or Aspergillus species. These filaments fungal infection are seen in association with trauma with vegetable matter. In a study , 81.2% cases with fungal keratitis were found to be HIV positive with

Fusarium solani being the most common organism accounting for 75% cases with fungal keratitis .Histoplasma and pneumocystis can rarely cause anterior segment manifestations. The risk factor for Pneumocystis carinii associated infection of conjunctiva found in one patient was the long term use of aerosolized Pentamidine prophylaxis against P.carinii pneumonia [73]. Culture or biopsy of lesions is important in HIV positive individuals with ocular surface infections to differentiate between bacterial and fungal etiology [43].

The treatment consists of oral itraconazole, oral albendazole or topical fumagillin[74,75,76] .

F. PROTOZOAL INFECTIONS

MICROSPORIDIAL KERATITIS

Microsporidia are spore forming, obligate intracellular protozoan parasites. They occur when the CD4+ T cell counts drop to about 100 cells/cu.mm [77]. 5 species have been indentified in HIV positive patients with two main clinical presentations of ocular microsporidiasis : a necrotizing stromal keratitis in immunocompetent individuals and an epithelial keratoconjunctivitis in immunocompromised patients. The keratoconjunctivitis in AIDS patients is thought to be rare. Patients may complain of a sandy feeling in the eyes and, and the cornea often has multiple tiny lesions unilateral or bilateral superficial punctate epithelial keratitis, white intraepithelial infiltrates, mild anterior chamber reaction and conjunctival follicular hypertrophy [75] . Punctate epithelial keratitis have been reported to be caused by Encephalitozoon hellem.

Definitive diagnosis is by Giemsa or Gram stain and spores from conjunctival scrapings or corneal biopsies stained with Masson trichrome or Giemsa stain. Immunoflourescence and electron microscopy can help confirm the diagnosis. Ocular Microsporidiasis should be suspected in all HIV positive patients with persistently negative cultures for epithelial keratitis.

Microsporidial infection may resolve with immune reconstitution. It is treated by topical Fumagillin 70mg/ml eye drops. Albendazole (400 mg, twice daily, orally) is given as an adjunct for co-existing systemic infection. Although HAART has been shown to alleviate and resolve microsporidial keratconjunctivitis [78], reactivation has been reported as a part of Immune Recovery Inflammatory Syndrome (IRIS).

TOXOPLASMA INFECTION

Toxoplasma gondii causes necrotizing retinochoroiditis with secondary anterior uveitis, but parasites do not extent beyond the neural retina. In AIDS patients, it can also develop a primary anterior uveitis without retinal involvement. Iris nodules with severe anterior segment inflammation with tissue destruction are noted. Inflammation responds well to anti-parasitic therapy but not to corticosteroids alone[79].

2. NEOPLASMS

KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is a highly vascularized, painless mesenchymal tumour,[80] caused by HHV 8. Symptoms include ocular irritation, trichiasis or interference of vision by the lesion [81,82] .It appears as multiple purple-to-red nodules affecting the eyelids or conjunctiva in up to 20-30% of HIV positive patients and in

rare cases the orbit [83]. It is most common in the inferior fornix and may be confused for pyogenic granuloma or subconjunctival haemmorhage [84]. The low prevalence in India may be attributed to the lower proportion of cases associated with homosexual behavior and low incidence of human herpes virus 8 [85,86] .

The main postulated mode of transmission is sexual [87] although vertical transmission from mother to child is thought to be common in sub-Saharan Africa [88,89] where the disease is endemic. Multiple factors may interact with HIV to cause Kaposi Sarcoma. This includes deregulated expression of oncogenes, decreased immune surveillance and release of Cytokines and Growth factors by the action of HIV upon infected cells. Latency Associated Nuclear Antigen (LANA) encoded by HHV-8 genome is a protein that interacts with tumour suppressor genes in a manner that promotes oncogensis.

Histologically, it has a complex arrangement of capillary channels and vascular spaces ("slits") without endothelium. Malignant spindle cells are arranged around these incomplete vascular spaces. Dugel and associates have classified adnexal KS lesions clinically and histopathologically into three stages. Stage I and II lesions are flat (less than 3 mm in height), patchy and of less than four months duration.Stage I consists of flat dilated vascular channels with moderate inflammatory infiltrate but without spindle cells or slit spaces. Stage II has plump endothelial cells that line thin, dilated vascular channels with few foci of immature spindle cells and early slit vessels. Stage III lesions are nodular, greater than 3 mm in height and greater than four months in duration. It has densely packed spindle cells with hyperchromatic nuclei and mitosis. This staging may have prognostic value regarding the course of disease and response to therapy [90]. Complete and partial resolution of Kaposi's sarcoma has been observed with HAART [91]. The clinical response correlates

with an increase in CD4 cells and a decrease in plasma HIV-1 RNA levels. There are reports of decreased incidence of AIDS-related Kaposi's sarcoma with the widespread use of HAART but IRIS can cause lethal Kaposi's sarcoma [92].

Treatment is aimed at reducing pain and disfigurement. Local measures are used in minimal cutaneous Kaposi Sarcoma. When it causes discomfort due to mass effect, secondary corneal changes or disfiguring, suitable treatment can be planned. Treatment options include local excision, radiotherapy, cryotherapy or systemic chemotherapy (Vinblastine, Bleomycin, Doxorubicin, Interferon alpha-2a. Radiation theraphy is effective in treating eye lid and conjunctival lesions but can lead to loss of lashes, irritation, conjunctivitis, conjunctival keratinization,cicatricial ectropion and retinopathy. Systemic agents are warranted in extensive cutaneous disease, visceral disease or lymphoedema.Intralesional Vinblastin or interferon alpha have produced good results [93]. Associated systemic KS is best treated with systemic chemotherapy [50] .

SQUAMOUS CELL CARCINOMA (SCC) :

Squamous cell carcinoma of the conjunctiva is the third most common neoplasm associated with HIV presenting at a younger age and is usually more aggressive. HIV testing should therefore be carried out in all cases of conjunctival tumours for patients living in high-risk areas such as Africa, as it may be the first sign of HIV-positivity [94]. A study by Agaba in Uganda showed a correlation between conjunctival squamous-cell carcinoma and HIV infection. Fair skin pigmentation, UV radiation and atopic eczema are the main risk factors for this form of SCC.The most common presentation is that of a friable white or pigmented nodule at the limbus of the eye [95]. Most commonly noted clinical characteristics of conjunctival SCC are

corneal overriding (90%), fast growth rates (83%) , tumors larger than 1cm (17%), changes in conjunctival colour (66%), and nasal location (66%) [95]. It rarely invades the eyeball or adjacent structures and death is uncommon. An aggressive form of SCC has recently been described in young adults less than 50 years of age in whom the disease progresses relentlessly, invading the eyeball, orbit and adjacent adnexal tissue [96] and metastasising to regional lymph nodes [97].

High titres of Human Papilloma Virus (HPV) type 16, 18 have been found in association with this tumour, raising the possibility that it may be caused by an infectious agent. It is not common in Indians due to lesser prevalence of the causative agent – Human Papilloma Virus. Theories abound that HIV directly induces neoplastic change in tissue by secreting viral oncogenes that inactivates tumour suppressor gene products secreted by host tissues, thereby promoting oncogenesis. Integration of viral genome into host tissue is also postulated to lead to neoplastic transformation. HIV induced immune suppression may reduce immune surveillance thereby priming the tissue for malignant transformation [98]. HPV is known to increase the activity of Transforming growth factor Beta (TGFβ) which promotes differentiation and neoplastic transformation of cells. Pan activation of humeral immune system and increase in Cytokine release leads to a chronic inflammatory state that facilitates malignant transformation [99].

If the tumour is diagnosed early before invasion of eyeball or conjunctiva, wide excision has 100% cure rate. A tumour that is fixed to the eyeball should be treated by enucleation of the eye to prevent lid invasion and subsequent systemic spread through vascular and lymphatic route. Early diagnoses followed by wide excision or enucleation can relieve pain and improve the quality of life. Margin free surgery followed by cryotherapy or radiation has 100% cure rate. Recurrent lesions

are treated with topical Mitomycin C, 5FU or interferon Alpha [100]. Along with the conventional modalities, HAART has been shown to cause complete regression of invasive conjunctival SCC in an HIV infected patient [101]

NON-HODGKIN'S LYMPHOMA (NHL):

It accounts for 3.5–5% of AIDS-defining illnesses [55]. It is usually seen in patients with CD4+ T cell counts of <50 cells/cu.mm. It can affect eyelids and conjunctiva, presenting as rapidly enlarging erythematous lesions with prominent vitreous cells and anterior chamber reactions [102] with or without subretinal exudation. Treatment is by radiotherapy and/or chemotherapy (Vinblastine, Interferon alpha)

BACILLARY ANGIOMATOSIS:

It is vascular proliferative forms of infection with Bartonella organism with increased risk among patients with CD4 count less than 200cells/cumm. It is to be differentiated from Kaposi sarcoma , as it often mimics it but is more lethal.

OTHER MANIFESTATIONS

KERATOCONJUNCTIVITIS SICCA (KCS):

Keratoconjunctivitis sicca also called dry eye syndrome, which results from deficiency of any of the tear film layers. Apparently, it is not related to CD4+ counts or associated with the severity of HIV [103] . Dry eye occurs in 20–38.8% of HIV infected hosts in the later stages of AIDS[55]. Etiology is multi-factorial and is due to the combined effects of HIV mediated inflammatory destruction of primary and accessory lacrimal glands and to the direct conjunctival damage due to HIV itself. Autoimmune etiology has been attributed to keratoconjunctivitis sicca and tends to occur at higher CD4+T cells count. Affected individuals are more susceptible to

bacterial keratitis. Typical symptoms are dryness, burning and a sandy-gritty eye irritation that gets worse as the day goes on. Crusting, discharge or stye formation are also noted. Management options include artificial tears, long-acting lubricants and punctual occlusion in severe cases.

CONJUNCTIVAL MICROVASCULOPATHY:

Conjunctival microvascular changes are commonly seen in 70-80% of patients of HIV patients .These include asymptomatic segmental vascular dilatation , narrowing, microaneurysm formation, comma shaped vascular fragment and visible granularity to flowing blood column [104].These are more common near the inferior limbus. The severity of the microvasculopathy has been correlated to increased zeta sedimentation ratios and fibrinogen levels [105].

The cause is postulated to be due to increased plasma viscosity, endothelitis or immune complex deposition. No treatment is required.

PRESEPTAL CELLULITIS :

Staphylococcus aureus is the most common cause of cutaneous and systemic bacterial infection in HIV positive patients. It is found twice more commonly in the nasal mucosa of HIV patients. Treatment is similar to that in immunocompetent individuals.

BLEPHARITIS:

Blepharitis is more common and more serious in HIV infected individuals. Blepharitis and eye lid ulcer have been reported as the initial manifestations of HIV disease [106].New onset chronic relapsing episodes of blepharitis , which began months to years after starting indinavir theraphy have also been reported.

TRICHOMEGALY :

Acquired trichomegaly or hypertrichosis have been described, especially in the late stages. Exact cause is unknown although drug toxicity , elevated viral load have been suggested to play a role. It has to be treated if annoying or of cosmetically unacceptable.

STEVEN JOHNSON SYNDROME (SJS) :

HIV infected patients are frequently exposed to many medications, especially nevirapine which is capable of causing hypersensitivity to toxic reactions. Altered cell mediated immunity may also lead to increased risk of SJS as a response to infectious agents as well.Associated dry eye may aggravate the problems associated with SJS in HIV paitents.

CONJUNCTIVITIS :

Non specific, culture negative conjunctivitis has been reported to be present in <1% of patients with HIV. Rarely Cryptococcus or Cytomegalovirus can be present. Grams stain and culture are essential before labeling it as non infective and biopsy can be used in unresponsive cases.

POSTERIOR INTRACORNEAL INFILTRATES:

Posterior intracorneal infiltrates have been reported in HIV infected hosts with concomitant cytomegalovirus retinitis and in children on prophylactic rifabutin. The infiltrates are distributed primarily in the inferior cornea. The cause is still under investigation. They may be caused by direct deposition of immune complexes or viral particles, toxicity of medication or even the direct effect of opportunistic infections [107].

CORNEAL PHOSPHOLIPIDOSES:

Vertex keratopathy or corneal phospholipidosis can be caused by antiviral such as ganciclovir , acyclovir or atovaquine. Patient may be asymptomatic or complain of mild irritation, foreign body sensation or photophobia. Characteristic whorl like pattern of gray white opacities is seen at the level of the corneal epithelium.

ANGLE CLOSURE GLAUCOMA:

Acute angle closure glaucoma has been described in association with uveal effusion syndrome in patients infected with HIV. B scan ultrasonography can be used for confirmation. Treatment includes cycloplegics, aqueous suppressants, hyperosmolar agents and surgical drainage of suprachoroidal fluids.

SECONDARY CATARACT :

A study from Sudan reported a young HIV positive patients in their early twenties ,with lens opacities that morphologically resemble juvenile cataract and were operated . These patients had no associated conditions such as anterior iritis that would have accounted for their cataract. HIV virus were isolated in lens tissue of patients with cataract. They recommended that early surgery is important to prevent development of complications and to assure visual recovery.

III.ANTERIOR UVEA

IRIDOCYCLITIS:

Inflammation of the uveal tract (iris, ciliary body and choroid) is a common anterior segment manifestation of HIV. It is seen in up to 88% of HIV patients in Zimbabwe. It tends to be the initial manifestation in some and is mild,associated with

ocular toxoplasmosis,fungal keratitis , viral infections, tuberculosis and syphilis, They present with pain, photophobia, reduced vision and redness of the involved eye. Clinical signs of anterior uveitis include cells in the anterior chamber, keratic precipitates, posterior synechiae, and hypopyon. Clinical signs of posterior uveitis include vitritis, chorioretinal infiltrates, vascular sheathing, and retinal hemorrhages. This presentation requires a thorough ocular examination in order to rule out anterior or posterior segment infection [28] .It may be associated with retinal or choroidal infection with multiple opportunistic organisms, such as cytomegalovirus, herpes simples virus, varicella zoster virus, Candida species, Cryptococcus species, Toxoplasma gondii, Treponema pallidum and Mycobacterium species [108]. Encysted T. gondii organisms have been found in an iris biopsy specimen from an AIDS patient presenting with iridocyclitis [109]. Iridocyclitis may also be associated with Reiter`s syndrome, which is defined by the classic triad of arthritis, urethritis, and conjunctivitis that appears to be more common in patients with HIV infection.

PCR of the aqueous humor or vitreous is used for identification of those organisms. Vitreous samples have a higher sensitivity [109,110,111] .

The treatment of iridocyclitis depends on the specific infectious agent. In the cases associated with medications, the dose should be tapered or the drug should be discontinued. Topical corticosteroids are usually indicated, but must be used carefully whenever a infectious cause is suspected [30] .

IATROGENIC/POST-TREATMENT MANIFESTATIONS OF HIV/AIDS

IMMUNE RECOVERY UVEITIS (IRU):

Immune recovery uveitis involves mainly the anterior uvea and vitreous, occurring in patients on HAART on their path to immune recovery, and is often

associated with a marked disturbance of visual function and is severe enough to cause hypopyon. The reported incidence among people with AIDS who receive HAART varies from 0.109 per person-year to 0.83 cases per person year [35,112]. Karavellas et al have reported the anterior segment complications of IRU as anterior and posterior sub-capsular cataract, persistent post operative anterior chamber inflammation with posterior synechiae and large visually important inflammatory deposits on intra ocular lens [113]. Other complications include optic disc edema, cystoids macular edema, epiretinal membrane formation,vitreomacular traction syndrome , retinal neovascularization.

Other iatrogenic manifestations can be a) Drug-induced uveitis caused by Rifabutin and Cidofovir causing a predominantly anterior uveitis. b)Stevens Johnson syndrome (SJS) due to drugs, especially Nevirapine, and also as a response to infectious agents due to altered cell-mediated immunity [106,107]. People with larger CMV retinitis , are at increased risk for IRU, presumably because there are more viral antigens in the eye. IRU can also occur as a result of heightened inflammatory reaction against pathogens including T.gondii, M. avium complex and Leishmania species [114]. Corticosteriods may be used with recurrence of macular edema and other complications .

DRUG INDUCED UVEITIS :

Another group of disease has been attributed to the toxic effect of drugs like Rifabutin and Cidofovir. In both instances, predominantly anterior form of uveitis develops with marked discrepancy between symptoms and morphological changes. Rifabutin is characterized by severe pain and cidofovir by marked inflammation.

Refabutin :

It is a semisynthetic rifamycin derivative, active against M.avium infections. Anterior uveitis and vitreous inflammatory reactions have been also described in association. It is seen in patients who receive a daily dose of 300-1800mg . Risk of Rifabutin induced IRU increases when administered concurrently with antifungal azole agents, clarithromycin and some protease inhibitors. The inflammation is explosive in onset with development of hypopyon. Treatment consists of topical corticosteroids with or without reduction of rifabutin dosage. Isolated corneal endothelial deposits have also been seen in HIV infected children receiving rifabutin theraphy [115].

Cidofovir :

It is a nucleotide analogue used to treat CMV retinitis. The manifestations are varied, non granulomatous anterior uveitis occurs in 26-44% of individuals taking intravenous cidofovir. Posterior synechiae and hypotony occurs in 0-20% of treated individuals. It is suggested that hypotony is caused due to direct damage to the non pigmented ciliary body epithelium , from high concentrations of the drug[116] . There appears a direct relationship between cidofovir associated uveitis and CD4 counts suggesting that better immune function allows development of inflammation. Treated with topical corticosteroids and mydriatic agents, without stopping cidofovir. However in cases with severe hypotony cidofovir has to be invariably stopped. Topical ibopamine 2% , a prodrug of catecholamine and dexamethasone 0.1% has been suggested in such cases.

IV.NEURO-OPHTHALMIC MANIFESTATIONS:

Histological studies have shown that up to 75%-90% of HIV/AIDS patients have brain damage, including the optic nerve. Sixty percent of HIV patients with neurological symptoms have some form of neuro-ophthalmological deficit. Many factors, such as CNS infection by HIV alone or with other co-infecting pathogens, neoplasms, inflammatory processes etc may contribute to the neuro-ocular manifestation in HIV/AIDS patients [117,118] and are found in 6% of AIDS patients [119]. They may present at different stages though Bhatia noted that involvement of the brain usually occurs in the final stages of HIV/AIDS. Along with the HIV ongoing replication, neurotoxins are produced to cause apoptosis in specific neural tissues that lead to axonal loss, neuronal damage, and finally, neuro-ophthalmologic abnormalities.

Various neuro-ophthalmic manifestations include optic nerve disease (oedema, inflammation, and atrophy, papilloedema due to raised intracranial pressure, retrobulbar neuritis, cortical blindness, pupillary defects, cranial nerve palsies, ocular motility disorders and visual field defects [30,118]. Optic neuropathy, papilledema, and cranial nerve palsies are the most commonly found cases. Optic neuropathies can be caused by viral, bacterial or fungal infections, commonly found are CMV and Cryptococcus neoformans invasion. It may be attributed to compression, infiltration, infection, vaso-occlusion and inflammation [9] or to direct HIV infection [118].

Cryptococcal meningitis can be the cause of papilledema. Nerve palsies are associated with cryptococcal meningitis and intracellular toxoplasma cysts [9]. The most common infection is cerebral toxoplasmosis since it has a predilection to the central nervous system [9,120]. Symptoms include headache, fever, lethargy and seizures

[120]. Moraes reported that neurological involvement might occur independently of ocular manifestations and vice versa. A study by Guiloff [121] suggested that of those patients who present with neuro-ophthalmic manifestations of HIV/AIDS, 40% are due to opportunistic infection.

NEURO-OPHTHALMIC COMPLICATIONS OF HIV

Malignancy/OI	Ocular Symptoms
Orbital lymphoma	- Proptosis - Visual loss through a mass effect - When the tumor is more indolent, pain and diplopia may be the first signs of lymphoma
CNS lymphoma	Depending on its location, may produce a variety of abnormalities, including visual field defects, ocular motility disturbances, or uveitis
Orbital infection with Aspergillus organisms	-Proptosis - May involve the adjacent sinuses in an aggressive manner
Progressive multifocal Leukoencephalopathy (PML)	- Visual field defects - Cortical blindness
CNS toxoplasmosis	Depending on its location, may produce visual field abnormalities or ocular motility disturbances
Cryptococcal meningitis	- Papilledema may be seen in patients who have increased intracranial pressure associated with cryptococcal meningitis - Sudden visual loss is thought to be secondary to optic neuropathy or occipital cerebral involvement - Motility disturbances with diplopia

V. POSTERIOR SEGMENT MANIFESTATIONS :

HIV-RETINOPATHY :

HIV retinopathy, also referred to as HIV-related ocular micro-angiopathic syndrome, is a non-infectious microvascular disorder characterised by cotton wool spots, microaneurysms, retinal haemorrhages, roth spots, telangiectatic vascular changes and areas of capillary non-perfusion [122,123].Microvasculopathy is the most common ocular manifestations of HIV and is found in 70% of persons with HIV/AIDS [124,125]. It clinically manifests as cotton wool spots (CWS), intraretinal haemorrhages and microaneurysms, particularly around the posterior pole. Most patients with retinal microvasculopathy are asymptomatic. However, it may be the initial cause of other ocular complications in HIV-positive patients, such as CMV infection, retinal and optic nerve damage and various vision abnormalities, including abnormal color vision, reduced contrast sensitivity, and visual field abnormalities [126] .The severity of vascular damage correlates well with the multiple opportunistic infections in AIDS patients [127] .A study by Kuppermann et al [128] suggested that it is a late manifestation of AIDS and a decreasing CD4+ count correlates with the occurrence of HIV-related retinopathy, especially less than 200 cells/mm^3 [86,129] .

The aetiology of this retinopathy has been postulated to be due to HIV infection of the endothelium of the retinal microvasculature (possibly cytomegalovirus induced), and deposition of circulating immune complexes. Although common in the retina, it may affect conjunctiva and optic disk. In support of this ,HIV have been isolated from human retina and antigen were detected in retinal endothelial cells. Microvascular abnormalities include loss and degeneration of pericytes, swollen endothelial cells, thickened basement membranes, shrunken

capillary lumina in retinal vessels and tubuloreticular structures, all of which are found in almost all HIV-positive patients [129,130]. Reduced leukocyte density in macular capillaries, lead to retinal hypoxia, and increased polymorphonuclear leukocyte rigidity, which causes microvascular damage by releasing proteases, toxic oxygen radicals, and also influence microvascular blood flow. Even without retinopathy or optic nerve disease, obvious thinning of the retinal nerve fiber layer is found in HIV-positive patients [131,132] .Other factors, such as damage from immune complexes and hemorrhagic abnormalities, can also contribute to the vascular alterations. Both the structural proteins and the regulatory proteins of HIV itself play a role in the viral ocular infection. HIV gp120 can activate apoptosis in endothelial cells and change the function barrier of the microvascular endothelial cell monolayer by increasing vasopermeability .Also, HIV Tat protein, a transcriptional activator of viral gene expression produced early in the infection, has been shown to induce changes of the tight junction proteins in the retinal pigment epithelium (RPE), which is responsible for altering the blood-retinal barrier and subsequent HIV trafficking into the eyes . Schmetterer et al also suggested that abnormal retinal hemodynamics in this group may be involved in the pathogenesis of HIV-related microvasculopathy. A study by Cunningham and associates suggested the possibility that occult herpetic infection may be a contributing factor to ischemic maculopathy, as well as alterations in blood flow in the setting of microvascular abnormalities [133].

Cotton wool spots

Cotton-wool spots (CWS) are the most common ocular micro-angiopathic manifestations of HIV/AIDS .However, they are non-specific and may be seen in variety of conditions such as diabetes, hypertension, leukaemia, anaemia and systemic lupus erythematosis [24,134]. Cotton wool spots are caused by a circulatory disturbance

within tiny areas of the retina and occlusion of pre-capillary arterioles is commonly located in the superficial retina [125,9,135] related to the high levels of circulating immune complexes found in the condition. While HIV retinopathy resembles the manifestations of diabetic and hypertensive retinopathy,but it lacks the hard exudates. CWS in HIV positive patients are boomerang-shaped and are more eccentric. They can be mistaken, due to their colour, for the infective lesions of cytomegalovirus retinitis . Unlike these CMVR infective lesions CWS are transient, not visually-threatening, and tend to disappear within 6-12 weeks. Pepose et al further suggested that the deposition of immune complexes causes axoplasmic stasis, ischaemia and, consequently, CWS formation.

Retinal haemorrhages

Retinal haemorrhages appear as flame-shaped areas when they affect the nerve fibre layer and as dot-and-blot patterns when they affect the deeper layers of the retina [136]. Retinal haemorrhages are seen less frequently than CWS and are estimated to occur in approximately 30% of persons with advanced HIV/AIDS. Intraretinal hemorrhages, including Roth`s spots, may be present in AIDS patients. They are commonly innocuous and may occur within different layers of the retina. The histopathological findings of retinal vessels resemble that of diabetic retinopathy, with pericyte necrosis, endothelial cell swelling and thickened basement membranes[137]. It is suggested that the vascular injury includes immunoglobulin deposition, direct infection of the endothelial cells with HIV and hyperviscosity due to increased red blood cell aggregation, fibrinogen and increased polymorphonuclear leukocyte rigidity.

Telangiectatic vascular changes

Retinal telangiectasias are known as a group of rare, idiopathic anomalies of the retinal vasculature characterised by irregular dilation, microaneurysms and vessel failure and may be found in HIV-infected persons .

Branch retinal artery and retinal vein obstructions have been seen in HIV infected patients [138,139]. There are some reports of ischemic maculopathy ,which can be severe, however the condition is apparently uncommon. The presence of opacification of the superficial retina, resulting in a cherry red spot, or intraretinal hemorrhages near the fovea may suggest the diagnosis. Bilateral involvement , with an abrupt onset is noted. Fluorescein angiography should be done on HIV infected patients with unexplained vision loss.

CYTOMEGALOVIRUS RETINITIS:

Individuals with advanced HIV/AIDS may be affected by a number of opportunistic infections of the retina and choroid like cytomegalovirus retinitis. According to the various reports CMV retinitis is the most important ocular opportunistic infection among 15-40% of patients who are HIV-positive [140]. It can be an initial AIDS-related ocular opportunistic infection in 1.8-3% patients. The cross sectional prevalence of CMV retinitis is 20% in HIV positive patients with CD4+ T cells <200cells/μl, which increases to 30% with CD4+ T cells <50 cells/ μl. This suggests that there is increased risk of development of CMV retinitis with decline in CD4+ T cells count. Use of antiviral drugs can delay its onset in patients with lower CD4+T cell count [128]. The virus is usually acquired in childhood and may remain latent for life.

There are three clinical forms of CMV retinitis. The classical form (pizza pie retinopathy or cottage cheese with ketchup) is characterized by confluent retinal necrosis with hemorrhage ,mostly in the posterior retina over several weeks. Untreated lesions progress to full-thickness necrosis with resultant retinal gliosis and pigment epithelial atrophy. Patients often have loss of visual field (scotomas) or visual acuity. The indolent form is recognized as a granular lesion in the peripheral retina, often with little or no hemorrhage. Patients may notice floaters, or they may be asymptomatic. Approximately 15% of infected patients are often asymptomatic despite the presence of extensive or vision-threatening CMV retinitis [137,141] . Neither form have much vitreous inflammatory reaction overlying the lesion. A third, uncommon presentation is frosted branch angiitis [142]. Cytomegalovirus necrosis can sometimes be confused with CWS, however, CMV lesions tend to enlarge and coalesce over time, forming large, wedge-shaped areas of involvement . In the HAART era, zone 1 involvement and retinal detachment remain the most common causes of visual acuity loss among patients with CMV retinitis. Cataract and CME also are common causes of loss of visual acuity, primarily in those patients with HAART-induced immune recovery. Profound loss that is irreversible is said to occur via three mechanisms, namely, direct damage to the macula and optic nerve, retinal detachment which may occur even after CMV retinitis has resolved and immune recovery uveitis .

Treatment protocol :

Evaluation of the patient's anti-HIV regimen should be the initial step in developing a treatment plan. Maximal suppression of HIV RNA with a subsequent increase in CD4 count will improve the response to anti-CMV therapy.

CHOOSING THE TREATMENT MODALITY FOR CMV RETINITIS

Consideration	Effect on treatment choice
The location and extent of CMV retinitis (i.e., sight threatening or peripheral) and the status of the fellow eye	If the patient has sight-threatening CMV retinitis or bilateral disease, parenteral therapy should be used.
Whether the disease is newly diagnosed or relapsed	If the patient is experiencing a relapse, combination therapy with two parenteral agents has produced the best result
The immune status of the patient	The immune status of the patient will determine whether an implant is required
Whether the patient is HAART naïve or whether HAART has failed	HAART should be initiated in naïve patients, and the regimen should be optimized in patients with failing HAART.
The presence of other conditions that can affect medication choice	For example, for patients actively using drugs, the implant may facilitate treatment
Other medications with overlapping toxicities	Overlapping toxicities may help decide between ganciclovir vs foscarnet. For example, if a patient has neutropenia that is unlikely to resolve, ganciclovir should be avoided
Adherence to follow-up	For patients with poor adherence, the implant may facilitate treatment.
Patient's preference and quality-of-life concerns	Quality-of-life issues may sway a patient away from parenteral therapy

Currently approved treatments for CMV retinitis include ganciclovir, cidofovir, foscarnet, valganciclovir, and fomivirsen.

Ganciclovir is available in intravenous and oral forms and as an implant that can be placed in the vitreous. The ganciclovir implant releases ganciclovir into the eye for about 6 to 8 months before it needs to be replaced. It should be used with systemic therapy whenever possible . It is given in an induction dose of 5mg/kg IV q12h for 14-21 days , with maintainance dose of 5mg/kg IV qd. Neutropenia is the most common side effect.Oral form is available at a strenght of 1g .

Valganciclovir is a monovalyl ester of ganciclovir and acts as a prodrug; it is given orally and has higher bioavailability than oral ganciclovir.It is started with an induction dose of 900g PO bid for 21 days, and maintainance dose of 900mg PO daily. Neutropenia is the most common side effect.

Cidofovir and foscarnet, both intravenous medications, should be avoided in patients with renal insufficiency (creatinine clearance <55; creatinine >1.5) and should not be used concomitantly with other nephrotoxic agents.Cidofovir induction dose is 5mg/kg IV once weekly for 2 weeks ,as infusion IV over 1 hour and maintainance dose of 3-5mg /kg IV every other week. Cidofovir must be administered with probenecid (2 g 3 hours before and 1 g 2 and 8 hours after cidofovir dose) and adequate hydration.Foscarnet is given as 90mg/kg IV qd for 14-21 days over 2 hours, and maintained as 90-120mg/kg IV qd over 2 hours.

Fomivirsen, an anti-sense molecule, is approved for intravitreous injection in patients with relapsed CMV retinitis but has been associated with pigmentary retinopathy.

Prophylaxis for CMV Retinitis

Patients receiving oral ganciclovir prophylaxis or therapy for extraocular CMV should be evaluated every 3 months as treatment may mask the development of

symptoms of retinitis. Oral ganciclovir (1000 mg tid) has been approved as prophylaxis for CMV retinitis in severely immunocompromised patients (CD4 counts <50 cells/mm3), although it is rarely used. It is not clear which patients will derive maximum benefit from oral ganciclovir prophylaxis, and there is interest in developing a rational strategy of targeted prophylaxis to decrease the chance of development of resistance to ganciclovir.Presumably, oral valganciclovir with improved bioavailability will also offer effective prophylaxis. There have been a few cases of reactivation of CMV after discontinuation of secondary prophylaxis despite high CD4 cell counts, reinforce the need for continued monitoring.

HIV RETINITIS :

HIV may cause peripheral chronic multifocal retinal infiltrates with associated low-grade vitritis and retinal vasculitis. These patients present most commonly with floaters followed by blurred vision. Other symptoms include photopsia, photophobia, tearing and foreign body sensation. These lesions are grey white or yellow, irregular in shape and < 200μm in dimension located in mid periphery or anterior retina. Unlike CMV, the lesions are stationary or progress very slowly and are not associated with retinal hemorrhage. Retinitis in inflammed eyes usually occurs in patients with higher CD4+ counts and is more commonly due to Acute retinal necrosis(ARN), toxoplasmosis, syphilis or late stages of Cryptococcus infection. Retinitis in quiet eyes occurs in patients with lower CD4+ counts and is more commonly due to CMV and Progressive outer retinal necrosis(PORN). The etiology is uncertain but HIV infection is presumed, as treatment with anti-retroviral agents cause regression and vitreous cultures are negative for organisms other than HIV. Patients must be evaluated for syphilis which may cause a similar clinical picture.

NECROTIZING HERPETIC RETINOPATHY:

Necrotizing herpetic retinopathy (NHR) is a continuous spectrum of posterior segment inflammation induced by herpes viruses, most commonly Varicella Zoster virus. Incidence of NHR in HIV-positive patients after HZO is reported to be 4%-17% [90]. Its two most recognizable clinical patterns are Acute Retinal Necrosis (ARN) and Progressive Outer Retinal Necrosis (PORN). Usually, the ARN occurs in healthy persons or AIDS patients with only mild immune dysfunction and elevated CD4+ counts, whereas the PORN usually develops in those who are severely immunocompromised. In addition to VZV, HSV and CMV have been isolated in patients with ARN, and HSV in eyes with PORN

Acute retinal necrosis (ARN):

Acute retinal necrosis is a progressive necrotic herpetic viral retinitis. It may occur due to varicella zoster virus (VZV), Herpes simplex virus (HSV) or CMV. However, VZV appears to be the most common causative organism [10]. It presents similarly in immune-competent and immune-compromised individuals and causes bilateral loss of vision. ARN is characterised by a peripheral retinal whitening that progresses to necrosis within several days and retinal detachments with proliferative vitreoretinopathy commonly occur [143] .Central retinal vein occlusion as the initial presentation of herpes zoster ophthalmicus has also been reported. Researchers have suggested that the pathophysiological mechanisms is the virulence of the virus after its reactivation which is particularly significant in immune-compromised patients, and severity is determined by the level of immuno-compromise .Intravenous acyclovir is useful in immunocompetent individuals,but it is recalcitrant to treatment in HIV-infected patients. The currently recommended treatment involves standard induction

dosages of ganciclovir or foscarnet, with adjunctive high-dose intravenous acyclovir (15 mg per kilogram every 8 hours).

Progressive outer retinal necrosis (PORN):

Progressive outer retinal necrosis is a form of rapidly progressive necrotising herpetic retinitis. While the VZV has been reported as the major etiological agent for PORN, HSV Type 1 has also been implicated [104,144]. It is most often bilateral, characterized by severe visual loss, which can occur within weeks. PORN is characterized by retinal lesions, which are often multiple, punctate white spots that coalesce. The presentation can be deceptive because there is typically an absence of dense vitritis. Hemorrhage and inflammation are rarely seen. However, the disease can result in permanent bilateral blindness within a few days. The exact pathophysiological mechanism is not currently clear, however, severe immune compromise and previous herpetic infection is necessary for presentation of the condition [10]. Risk factors for PORN include a low CD4+ cell count and recurrent, recent or current cutaneous, cerebral or visceral VZV or HSV infection.

The optimal treatment has not been established and prognosis is poor even with high doses of combinations of ganciclovir, foscarnet (both intravenously and intravitreally), and acyclovir. Patients often develop retinal detachments.

OCULAR TUBERCULOSIS :

Although pulmonary tuberculosis is the commonest systemic opportunistic infection seen in AIDS cases in India, a study found only 1% cases with presumed ocular tuberculosis . The association between tuberculosis and HIV infection has been attributed to two processes i.e people with latent TB acquire HIV infection which

increases the risk of reactivation of the TB by a hundred-fold, or people with HIV infection acquire TB infections and their immune-suppression puts them at high risk of developing active TB. Intensifying the TB crisis is the emergence of multi-drug resistant TB. Babu RB et al has reported the incidence of ocular tuberculosis to be 1.95% in HIV/AIDS patients . A similar incidence of 2.8% of choroidal granuloma in HIV positive patient with tuberculosis has been reported by Beare NAV et al .

Lewallen S. and associates have reported abnormal eye findings in 22% of tuberculosis patients with HIV/AIDS. It can have varied presentations like choroidal granuloma (52%) , subretinal abscess, panophthalmitis etc and almost all have associated pulmonary tuberculosis. Ocular tuberculosis can occur even at CD4+T cell counts greater than 200cells/µl. The frequent ocular manifestation is granulomatous uveitis, which is usually accompanied by choroiditis [145]. Beare et al [146] suggested that choroidal granuloma is not diagnostic of ocular TB, however, its presence can confirm its diagnosis in the presence of other signs. It usually presents as multifocal choroidal tubercles with discrete yellow lesions mainly at the posterior pole. It may be associated with variable vitreous inflammation and an exudative retinal detachment.Occasionally , it may present as a big solitary posterior pole granuloma like mass.Massive choroidal invasion may lead to secondary retinal necrosis and blindness and is associated with very poor prognosis.

Diagnosis is based on clinical appearances and confirmed by histopathology and Polymerase Chain Reaction Test (PCR). First choice of treatment is Rifampicin 600mg PO , daily(> 50 kg body weight)+INH 300mg PO daily + Pyrazinamide .Ethambutol 15 mg/kg PO daily is added if resistance is suspected.

OCULAR SYPHILIS

Bacterial chorioretinitis occurs infrequently and is usually considered in patients with advanced HIV disease and posterior segment infection that is unresponsive to suspected viral, fungal or protozoan causes . Ocular syphilis is the most common intraocular bacterial infection [147]. Its resultant retinitis is found in 1% to 2% of patients who are HIV positive Syphilis in AIDS may develop when CD4-counts are greater than 200 cells/μl and runs a more rapid and aggressive course.

Clinical findings of ocular syphilis in AIDS may include iritis ,retrobulbar optic neuritis, perineuritis, papillitis, neuroretinitis, retinal vasculitis, necrotizing retinitis , which may be clinically indistinguishable from CMV, and exudative retinal detachment. Vitritis can be present as a primary manifestation of ocular syphilis with HIV infection [148].Visual loss is most frequently due to uveitis and secondarily due to optic nerve disease. Involvement can be either unilateral or bilateral and can involve the central nervous system (CNS) in up to 85% of cases [149,150].

Diagnosis is by Rapid plasma reagin tests (RPR), Venereal Disease Research Laboratory (VDRL) tests, Fluorescent treponemal antibody absorption test (FTA-ABS) etc. Treatment of ocular syphilis includes 12– 24 million units of IV aqueous Penicillin, administered for 10 days in AIDS patients. Tetracycline, erythromycin and chloramphenicol are options for patients allergic to penicillin. Some authors believe that HIV positive patients may require maintenance therapy, because ocular symptoms may recur.

TOXOPLASMOSIS :

Toxoplasma gondii has been found to affect about 10% of HIV/AIDS patients . The organism that causes toxoplasma retinochoroiditis has been found to be

relatively rare and accounts for 1% of AIDS-related retinal infections with varied prevalence among geographic regions and populations. Ocular toxoplasmosis can be the first manifestation of T.gondii infection.

The organism exists in three forms; sporozoites, bradyzoites and tachyzoites. Sporozoites or oocysts result from the parasite's sexual cycle in the cat intestine and are eliminated by the cat and undergo sporulation to become infectious. Bradyzoites are slowly multiplying organisms contained in tissue cysts and are localised to muscle and brain and may live in host cells for months to years . Once ingested, gastric enzymes of the host degrade the cyst wall and liberate them. Tachyzoites are rapidly dividing organisms which are found in the host tissues during the acute phase of infection and are responsible for tissue destruction. Human infection results from ingesting food contaminated with oocysts or uncooked food containing bradyzoites. Once the host is infected, the tissue cysts can persist for life. In the presence of inadequate immunity, bradyzoites can produce lesions when they disintegrate in the form of the tachyzoites which continue to multiply.

Infection presents as multifocal retinochoroiditis with less frequent vitritis than in immune-competent individuals [113] . It can be differentiated from other retinitis by the presence of intense, "fluffy" areas of retinal whitening with accompanying vitritis, sometimes referred to by the analogy "headlights in the fog" with retinal whitening being the headlight and the fog being the overlying vitritis. There is associated inflammatory reaction in the form of iritis, vitritis, choroiditis, multifocal or diffuse necrotizing retinitis, papillitis or retrobulbar neuritis or outer retinal toxoplasmosis. It is often bilateral, multifocal and not associated with chorioretinal scars. Toxoplasmosis retinitis among immunocompromised can be differentiated from CMV retinitis as it presents with less haemorrhage and more iritis and vitritis.

Infection responds to the standard anti-parasitic drugs (Pyrimethamine, Clindamycin, Sulfonamides) in most cases, but there are reactivations and progression of disease when therapy is stopped. Severe retinal necrosis can lead to retinal tears or detachment.

CANDIDIASIS:

The most common fungal organism implicated in fungal retinitis is candida. Histoplasmosis and aspergillus infection tend to affect the choroid more often . Candida retinitis is commonly seen in intravenous drug abusers and is characterised by a fluffy white "mound" of retinal infiltrates, which may enlarge to involve the vitreous as well [136,137]. It may break through the retina into the vitreous and cause candidal endophthalmitis. Usually,overlying vitritis or itreous abscesses may also be seen. Once the diagnosis is confirmed, the patients should receive intravenous amphotericin.

CRYPTOCOCCAL CHORIORETINITIS:

Cryptococcal ocular infection in immune-suppressed individuals is due to infection by yeast, Cryptococcus neoforman. Cryptococcus choroiditis is uncommon while its CNS involvement is more common .Typical cryptococcal lesions are located in the choroid and retina and appear as multiple discrete yellowish spots varying in size from 500- 3,000µm in diameter [150,151] . Infection may also cause papilloedema due to increased intracranial pressure from meningitis. In addition, the associated abducens nerve palsy, headaches and papilloedema are the clinical signs that help differentiate from other causes of multifocal choroiditis. There is usually a significant visual loss associated with the condition either due to optic neuropathy , involvement of the chiasma , tract or cortical blindness . The course of visual loss can range from

profoundly rapid in hours if due to invasion and necrosis of the optic nerve tissue or slowly progressive of weeks to months if due to chronic papilloedema .

HISTOPLASMOSIS :

It is caused by Histoplasma capsulatum. It is a rare manifestation in HIV/AIDS. Ocular histoplasmosis patients remain asymptomatic. Viterous appears clear and the lesions appear as atrophic spots in mid periphery and posterior pole. Choroidal neovascularisation may be present in 5% of cases.

PNEUMOCYSTIS CHOROIDITIS :

Pneumocystis jiroveci is an unusual fungus that exhibits some protozoan characteristics.It is the cause of P jiroveci pneumonia (PCP), the most common systemic infection in patients with HIV disease. Pneumocystis ocular involvement was first suspected in 1982 when a patient with advanced HIV disease and PCP had evidence of the organism in the ganglion and plexiform layers of the retina on histopathologic study.

Pneumocystis choroiditis is clinically characterized by multiple pale yellow-white choroidal lesions, usually in both eyes [152].The lesions generally are round or ovoid and of variable size, and may coalesce to form large regions of confluent involvement with resultant choroidal necrosis. If this process involves the foveal area, loss of central vision may occur.The lesions are referred to as “frothy vacuolar eosinophilic choroidal infiltrates which contain cystic and crescentic organisms”. Fluorescein angiography of the choroidal lesions reveals early hypofluorescence and late staining with minimal evidence of dye leakage. Of note is the almost total lack of

an associated inflammatory response in the retina, vitreous, and anterior segment. Treatment is the same as that for PCP.

OCULAR MANIFESTATIONS IN THE PEDIATRIC GROUP

A global summary of HIV/AIDS epidemic dating from December 2003 from UNAIDS/WHO estimates that there are 2.5 million children under 15 years world wide living with HIV/AIDS, and 700,000 were newly infected with HIV in 2003. Approximately 500,000 children died from the disease in 2003 [153].

The most frequent mode of transmission of HIV in the pediatric group is mother to child transmission. The incubation period tends to be shorter in children. Some bacterial infections are more common in this age group than in adults, whereas cryptococcosis and toxoplasmosis and Kaposi Sarcoma are less frequent.

The occurrence of ophthalmic complications associated with HIV infection is significantly lower in the pediatric group. The first reports of eye complications in children related to HIV infection are from 1982. CMV retinitis occur far less frequently and it is diagnosed predominantly in patients with CD4 cells counts below 20cell/mm^3, owing to the immature immune status and less frequent exposure to CMV in pediatric HIV-infected patients. The reason for this fact is still unclear, but may be related to an altered immune response to HIV in children. The most frequent manifestation in the pediatric group is dry eye syndrome, which occurs in approximately 20% of patients and anterior uveitis in India . Kestelyn et al and other authors have described perivasculitis /sheathing of the peripheral fundus vessels(38%), which were bilateral ,affecting veins more than the arteries and extending sometimes to posterior pole without invading it ,as a common finding in children with AIDS.Nutritional status is probably the most important factor that

contributes to the high prevalence of ocular involvement in HIV-positive children in developing countries.

The authors also described a possible link between lymphocytic interstitial pneumonia, parotitis, lacrimal gland involvement, and perivasculitis of the retinal vessels as the expression of the same immunopathological process in different sites. Purdy et al. reported three cases of bilateral progressive outer retinal necrosis due to varicella-zoster virus in children with HIV infection. All three lost vision in both eyes [154].

MATERIALS AND METHODS:

The study titled "OCULAR MANIFESTATIONS IN PATIENTS WITH HIV INFECTION AND ITS CORRELATION WITH CD4 COUNTS " carried out on patients tested HIV positive and attending / admitted in B.L.D.E.U'S Shri B.M.Patil Medical College, Hospital and Research centre, Bijapur .

Study Design : A cross sectional one year study

Study period : 1st October 2011 to 31st October 2012

Method of collection of data :

Sample Size:

With proportion of ocular manifestation in HIV of 80% [155,156] with 15% allowable error at ,95% confidence interval , sample size for this study is 43 using the following statistical formula

$$n = \frac{(1.96)2 \times p \times q}{L2}$$

Therefore, a minimum of 43 cases having ocular manifestations will be included in the study.

Statistical analysis :

- Data expressed as mean ± SD and analyzed by One-Way Analysis of Variance (ANOVA), linear regression, correlation-coefficient (r) and Tukey Kramer multiple comparisons test for significance at $P < 0.05$ using Graph Pad (InStat) software,version 5.
- Association between ocular manifestations of HIV/AIDS & CD4+T cell count was analysed using Chi-square ($\chi 2$) test.

Selection criteria :

Inclusion criteria:

- Patients attending/admitted to the hospital within the study period with sero-positivity for HIV 1 or HIV 2 or both.
- All age groups
- Both genders

Exclusion criteria:

- H/O Ocular disease prior to detection of HIV status or from childhood.
- Cases where ocular lesion is likely to be drug induced

Methodology :

In this cross-sectional study, all cases diagnosed as having HIV depending on the detection of antibodies in their blood against HIV-1/HIV-2 by using two different ELISA kits were included after obtaining informed consent. All cases notified as having HIV in OPD's and In-patient wards and all patients reported positive at the voluntary counselling and testing centre were included in the study. All mobile and out patients were examined in the OPD , while immobile and bed ridden patients were examined at the bedside and reviewed in OPD at the time of discharge and the necessary tests if any were completed.

These patients were further subjected to a detailed history taking, including occupation, socio-economic status, presenting complaints, ocular complaints, duration of illness, past history. Treatment history including blood transfusion and history of treatment taken for other diseases were enquired. In family, history of similar complaints in the members, and HIV status of the spouse and children were elicited.

Personal history including IV drug use and sexual history of any promiscuity and duration of HIV disesase since first diagnosis was noted. Thorough general examination and systemic examiantion was done.

The CD4 count was done by automated flow cytometry analyser FACS calibur (Beckton Dickinson). BD FACS Calibur is capable of measuring the scatter and the fluorescence parameter and gives information about the size and granularity of the cell. It can measure both absolute CD4 + T-lymphocyte count as well as % CD4 count. Three-color direct immunofluorescence reagent was used to identify and determine the percentages and absolute counts of mature human T lymphocytes (CD3) and helper/inducer (CD3+CD4+) T-lymphocyte subsets in erythrocyte-lysed whole blood. Absolute counts were enumerated from a single tube using TruCOUNT tubes.

Detailed ocular examination was done in all patients. Visual acuity was recorded by Snellen's test chart .In those whom visual acuity could not be tested due to poor general condition, were reviewed in OPD at the time of discharge for evaluation. Anterior segment evaluation with slit-lamp biomicroscopy, ocular motility, and pupil examination were done. Patients were dilated with Phenylephrine 5% and Tropicamide 0.8% combination eye drops. Direct and indirect ophthalmoscopy was performed to study the posterior segment of the eye. Colour vision and corneal sensations were noted. Corneal staining and examination on slit-lamp under cobalt blue filter were carried out wherever indicated.Intra ocular pressure was recorded with Applanation tonometer .

Documentation of relevant findings of anterior segment with slit-lamp camera and fundus photographs with fundus camera was done wherever feasible.The diagnosis was made on clinical grounds, though if feasible relevant confirmatory tests

were carried out. The relevant treatment for ocular complaints was instituted, along with the consultation with the physician for systemic condition, when required.

RESULTS:

The present cross sectional study was carried out on all HIV positive patients , who presented to or were referred to Ophthalmology Out Patient Department during the study period October 2011-October 2012.

Table 1. Age distribution of HIV patients

Age in years	Number of patients	Percentage %
10-20	2	1
21-30	36	24
31-40	56	37
41-50	31	20
51-60	20	13
>61	7	5
Total	152	100

Mean ± SD : 16.66 ± 13.2

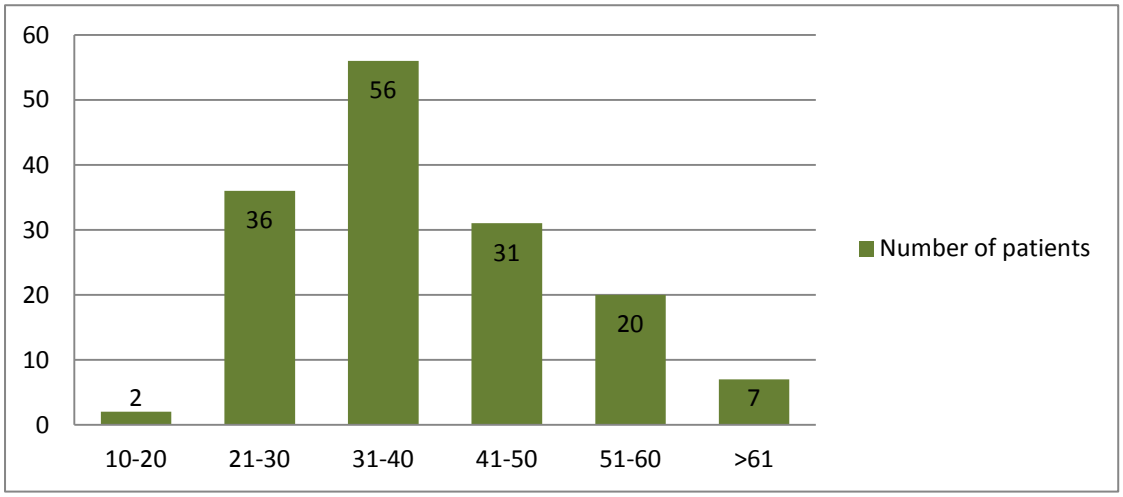


Figure 1.Age distribution of HIV patients.

A total of 152 patients were examined during the study period . Among these, 56 patients (37%)were in the age group of 31-40 years, followed by 21-40 (24%), 41-50 (20%) ,51-60 (13%) >61 (5%) and 10-20 (1%). The lowest and the highest age at presentation irrespective of absence of ocular or systemic complaints was 18 years and 70years respectively. In our study, the mean age of the patients was found to be 16.66 years with a SD of 13.2 years(Table 1).

Table 2. Gender distribution of HIV patients

Gender	Number of patients	Percentage %
Female	69	45.39
Male	83	54.60
Total	152	100

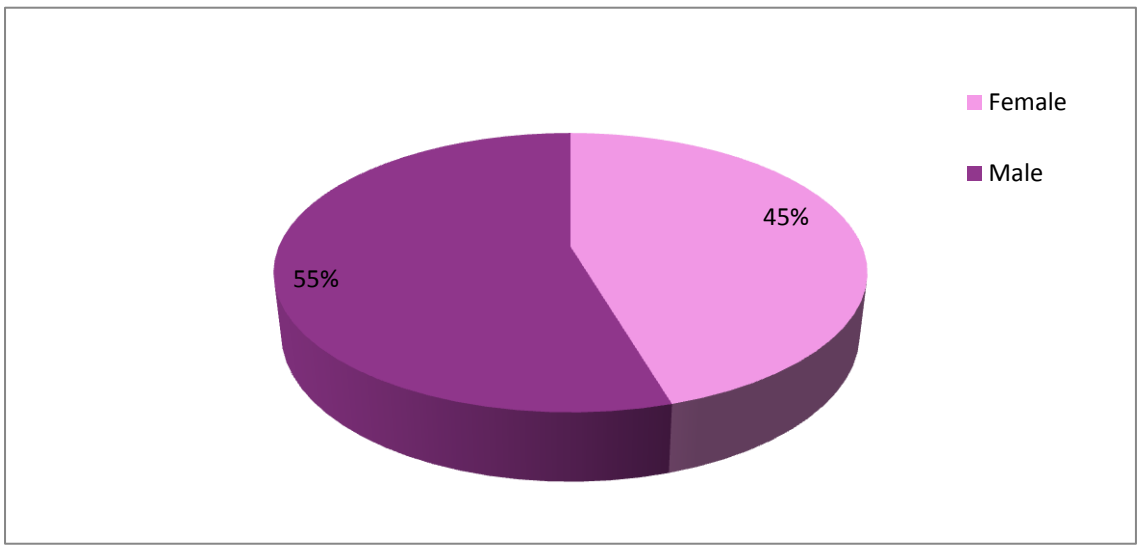


Figure 2: Gender distribution of HIV patients

Among the 152 patients , our study found a male to female ratio of 1.20:1, with 68 (45.39%) female patients and 84 (54.60%) male patients (Table 2).The ratio was 1.21:1 among patients with ocular manifestation of HIV.

Table 3. Age and Gender distribution of HIV patients

Age in years	Males	%	Females	%	Total number of patients	%
10-20	0	0	2	3	2	1
21-30	14	17	22	32	17	11
31-40	30	36	26	38	58	38
41-50	22	27	9	13	40	26
51-60	12	15	8	11	22	14
>61	5	6	2	3	12	8
Total	83	100	69	100	152	100

Mean±SD Males 23.75 ± 9.708, Females 24 ± 2.808

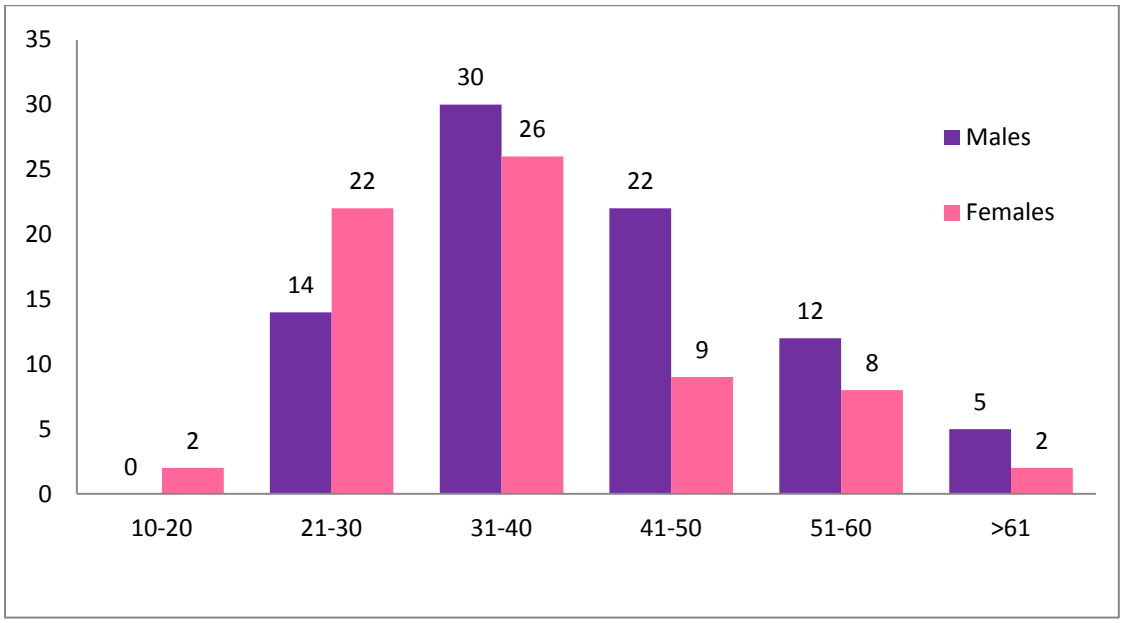


Figure 3: Age according to gender distribution of HIV patients

Considering the distribution of age according to the gender of the patient, we noted that , 66 out of 83 males and 57 out of 69 females and were in the sexually active age group of 21-50 years(Table 3). The mean age was 23.75±9.708 years in males and 24±2.808 years in females.

Table 4. Marital status of HIV patients

Marital status	Number of Patients	Percentage %
Married	143	94.07
Unmarried	9	5.92
Total	152	100

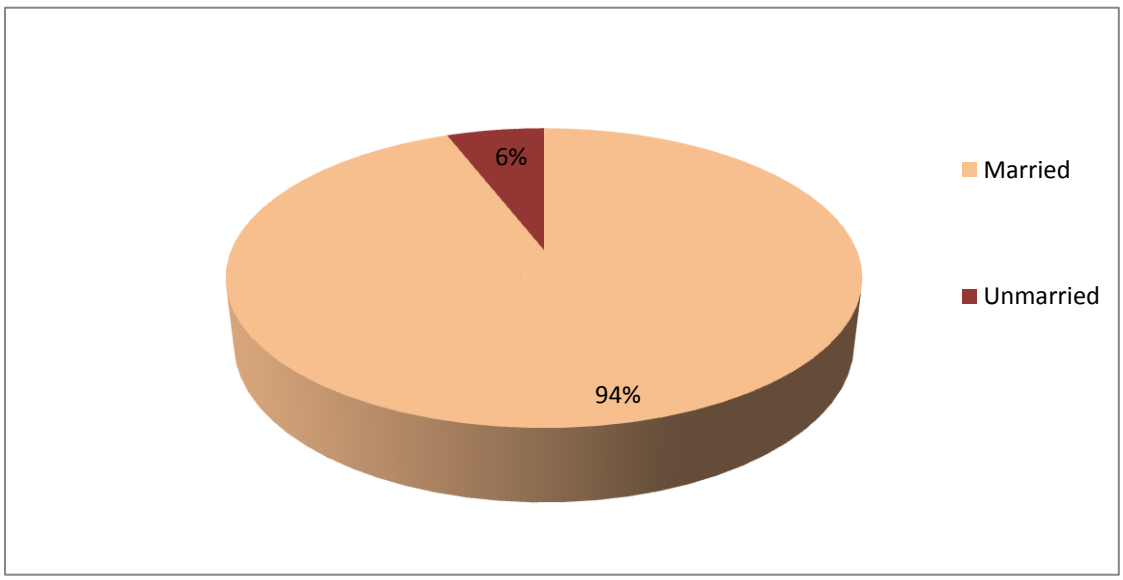


Figure 4 : Marital status of HIV patients

A minority of 9 patients(5.92%) with HIV were unmarried and the remaining 143 patients were married for variable periods(Table 4).

Table 5.Route of exposure to HIV infection

Route of Exposure	Number of patients	Percentage %
Transsexual	142	93.42
IV drugs	8	5.26
Needle prick	0	0
Blood transfusion	0	0
Transsexual+IV drugs	2	1.32
Total	152	100

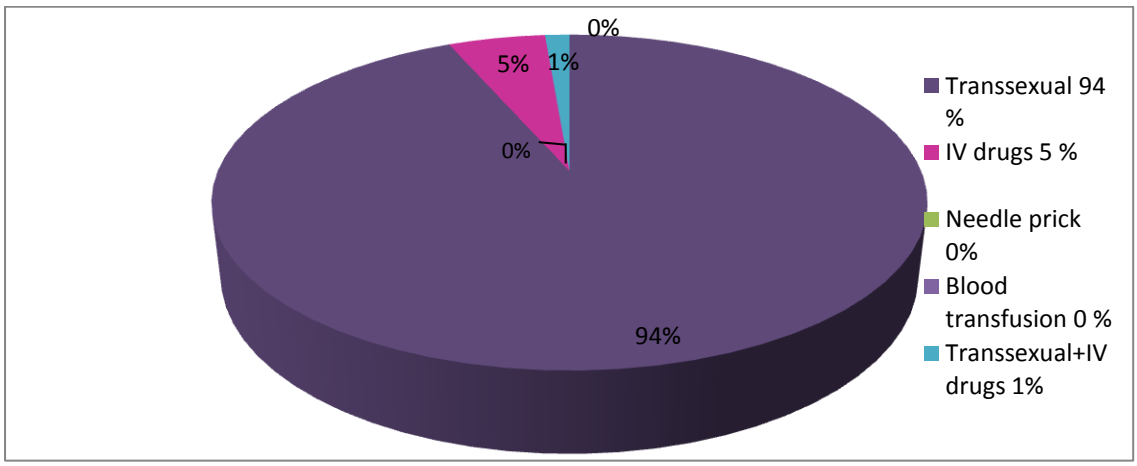


Figure 5: Route of exposure to HIV infection.

Out of 152 patients , a majority of 142 patients(93.42%)had acquired HIV infection by Trans-sexual mode of contact, 8 patients gave history of drug abuse and 2 patients had aquired through combined transsexual and IV route (Table 5).

Table 6. Education of HIV patients

Education	Number of patients	Percentage %
Educated	76	50
Uneducated	76	50
Total	152	100

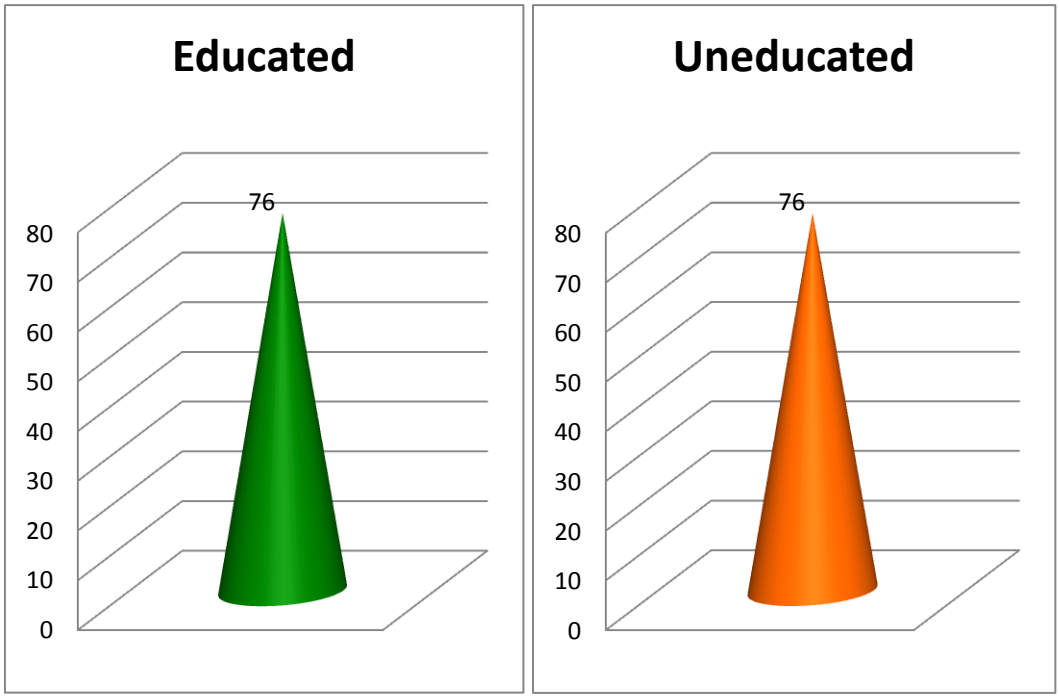


Figure 6 : Education of HIV patients .

Considering the educational background of the patients in our study we noted an equal number of patients in the educated and uneducated group with 76 patients(50%) each. Among the educated patients 61 patients had completed high school education and 47 patients had completed Secondary school education in our study(Table 6) .

Table 7. Residency of HIV patients

Residency	Number of patients	Percentage %
Urban	36	23.68
Rural	116	76.32
Total	152	100

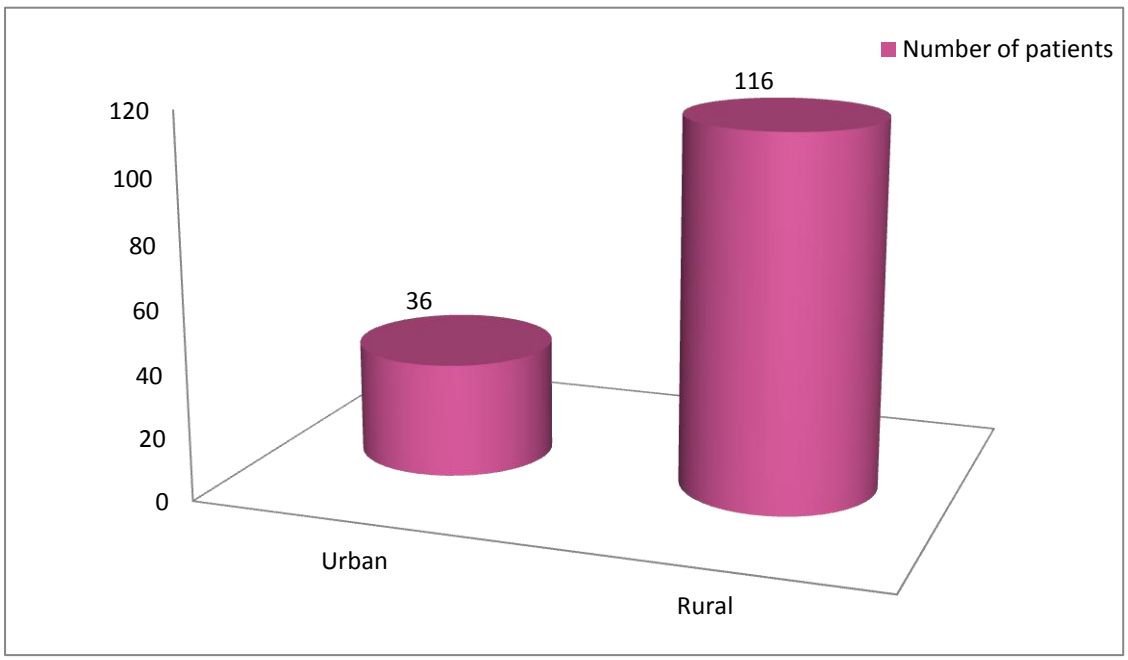


Figure 7: Residency of HIV patients .

In our study, a majority of 116 patients (76.3%) were from rural areas and 36 patients (26.68%) were living in urban cities(Table 7).Among the urban dwellers, 13 patients were uneducated and remaining 23 were educated with 6 among them having completed high school education . In rural areas 63 patients were uneducated ,53 patients were educated, however only 20 among them had completed upto high school education.

Table 8. Occupation of HIV patients

Occupation	Number of patients	Percentage %
Employed	121	79.60
Unemployed	31	20.40
Total	152	100

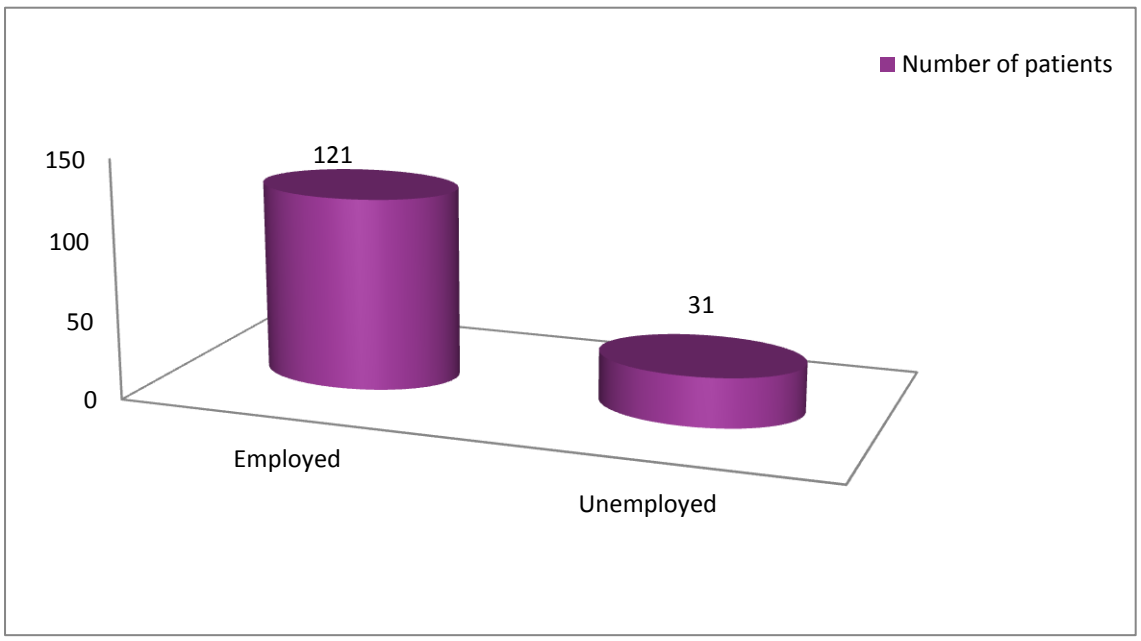


Figure 8: Occupation of HIV patients

Majority of 121 patients(79.6%) in our study were employed and remaining 31patients(20.40 %) were unemployed (Table 8). Farmers 46 patients (30.26%) were most commonly affected by HIV. Among those who were unemployed , all were females , among them one was a unmarried mentally disabled female of 18 years and remaining 30 were housewives.

Table 9.Duration of HIV in patients

Duration of HIV in years	Number of patients	Percentage %
Newly detected	45	29.6
<1 yr	42	27.6
1-5 yr	41	27.0
6-10 yr	21	13.8
≥10	3	2.0
Total	152	100

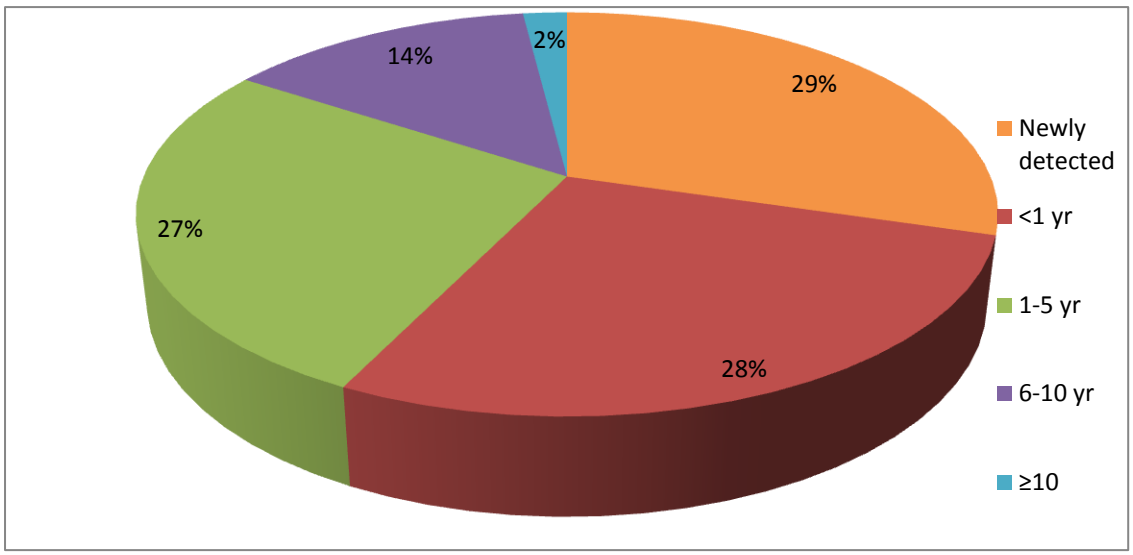


Figure 9: Duration of HIV in patients.

41 patients (26.97%) in our study were newly detected cases of HIV infection after evaluation following admission for various complaints.Among 111 patients who were known case of HIV , 33 patients(21.71%) had a duration of illness less than one year.The shortest duration was 2 days in 2 patients and longest was 18 years in one patient(Table 9).

Table 10. Systemic manifestation in HIV patients

Systemic manifestations	Number of patients	Percentage %
Present	120	78.95
Absent	32	21.05
Total	152	100

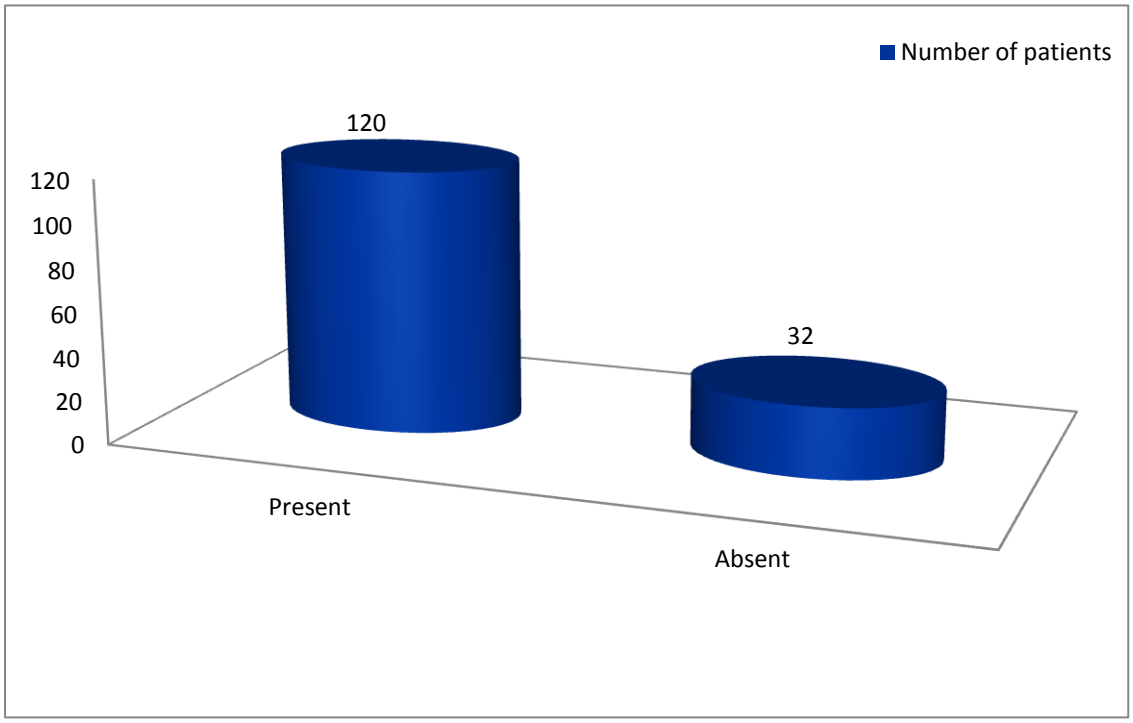


Figure 10: Systemic manifestation in HIV patients.

The systemic manifestations were present in 120 patients (78.95%) in our study (Table 10).The most common systemic involvement amongst our study was various manifestations of Tuberculosis seen in 40 patients(26.32%) including pulmonary, abdominal , extrapulmonary TB and TB meningitis. It was also the most common manifestation among patients with ocular manifestations of HIV.The second most common system affected was the gastrointestinal system presenting as acute gastroenteritis due to various etiology in 12 patients (7.89%).

Table 11. HIV patients and HAART theraphy

HAART	Number of patients	Percentage %
Yes	84	55.26
No	68	44.74
Total	152	100

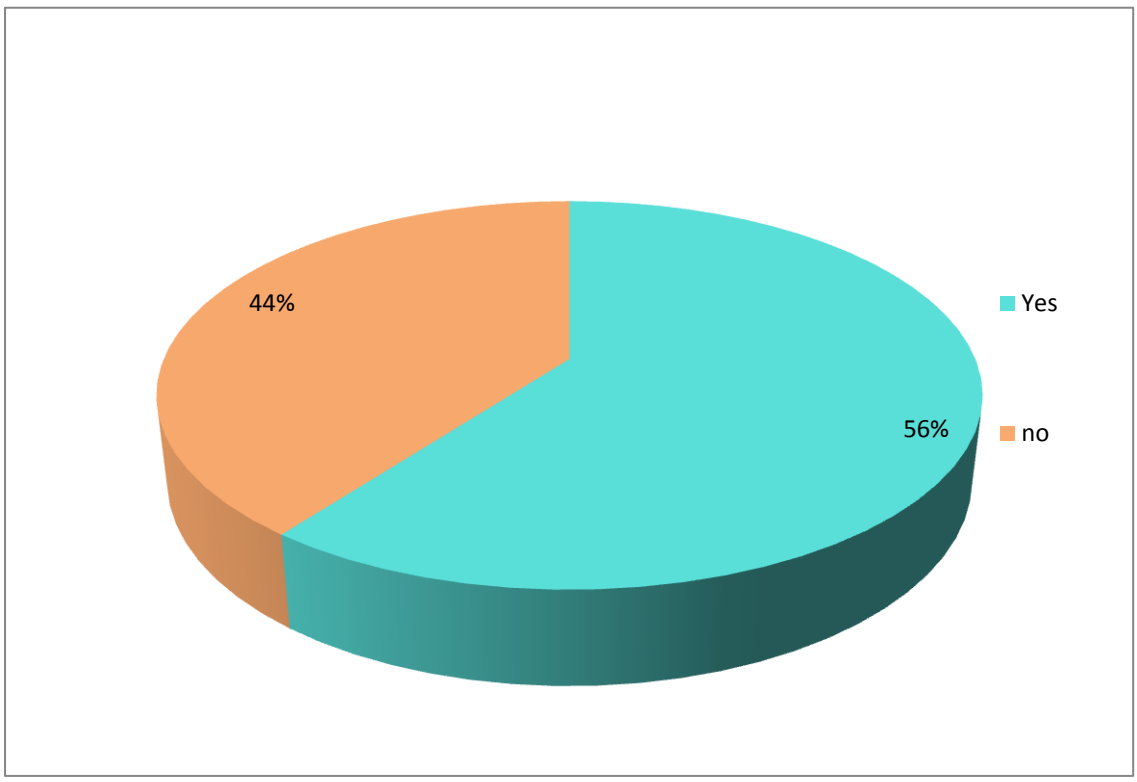


Figure 11 : HIV patients and HAART theraphy.

A majority of 84 patients (55.26%) were already initiated with HAART for various indications at the time of presentation and the remaining 68 (44.74%)were not on treatment at the time of presentation in our study(Table 11).

Table 12. Visual status in HIV patients

Vision	Right eye	Percentage(%)	Left eye	Percentage(%)
6/6(Good)	86	56.58	89	58.55
6/6p-6/12 (Mild)	23	15.13	22	14.47
6/18-6/36(Moderate)	27	17.76	19	12.50
6/60 or less(Severe)	12	7.89	18	11.84
Could not be assessed	4	2.63	4	2.63
Total	152	100	152	100

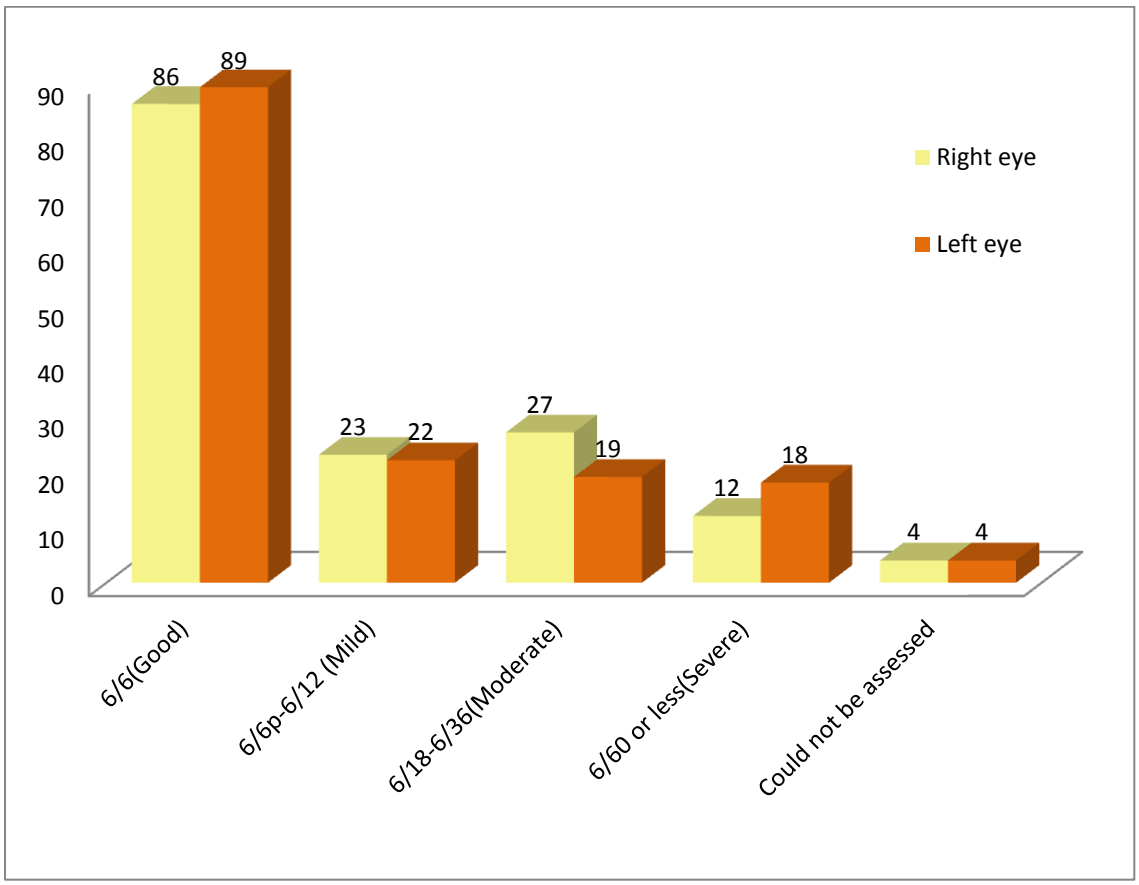


Figure 12 : Visual status in HIV patients.

In our study , majority had good vision 6/6 in 86 patients (56.58%) in right eye and 89 patients (58.55%) in left eye.Mild visual impairment(6/6p-6/12) was noted in 15.13 % in right eye and 14.47% in left eye.Moderate visual impairment (6/18-6/36)

was present in 17.76% in right eye and 12.5 % in left eye , severe visual deterioration (6/60 or worse) was seen in 7.89% in right eye and 11.84% in left eye. Also vision could not be assessed in 4 patients due to poor physical status and non co-operation(Table 12).

Table 13. Ocular Manifestations in HIV patients

Condition	Number of patients	Percentage %
Patients with ocular manifestations of HIV	53	35
Patients without ocular manifestations of HIV	99	65
Total	152	100

Prevalence : 35%

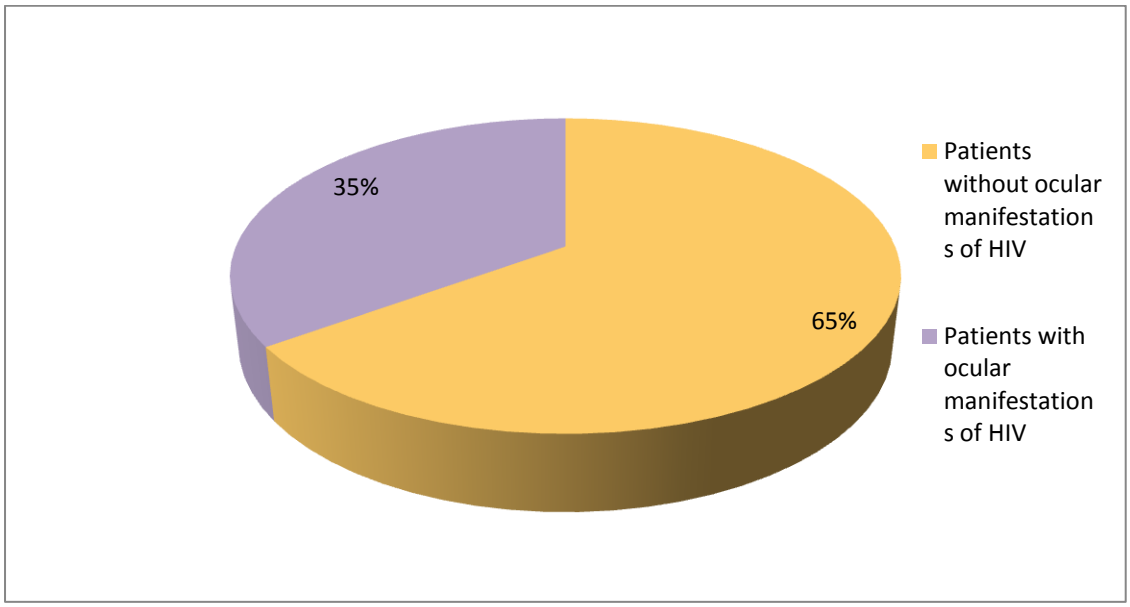


Figure 13: Ocular Manifestations in HIV patients

Among a total of 152 patients , 53 patients had one or other ocular manifestation related to HIV with a prevalence of 34.86 % i.e approximately 35% in our study(Table 13) . 29 patients (19.08%) had anterior segment manifestations , 28 patients(18.42%) had posterior segment manifestation and 4 patients (2.63%)had both anterior as well as posterior segment manifestations(Table 14)

Table 14. Ocular manifestations in different segments of the eye in HIV patients

Ocular manifestations	Number of patients	Percentage %
Anterior Segment	29	19.08
Posterior Segment	28	18.42
Anterior +Posterior segment	4	2.63

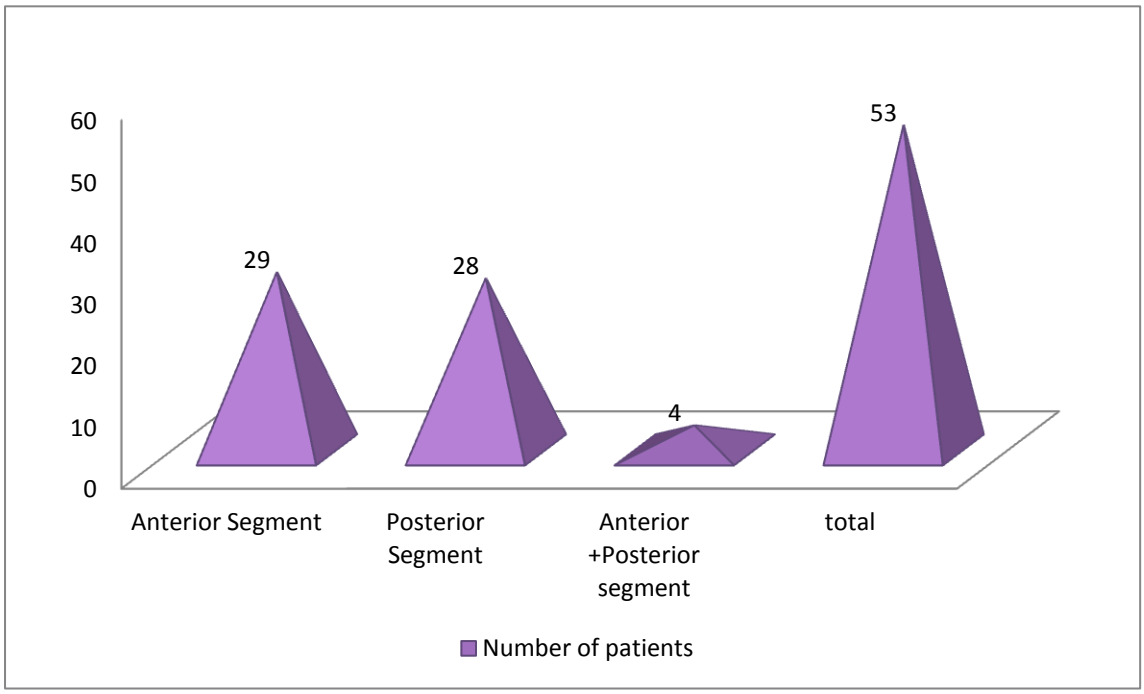


Figure 14: Ocular manifestations in different segments of the eye in HIV patients

In our study , we noted the presence of more than one ophthalmic finding either involving the same segment or the different segment in one or both eyes in few cases, and were counted separately. The most common anterior segment manifestation in our study was Blepharitis present in 10 patients (6.58%) with 6 patients have acute blepharitis and 4 patients having chronic mebominitis . The most common posterior segment manifestation was HIV retinopathy , noted in 17 patients(11.18%) (Table 15)

Table 15. Ocular manifestations in each segments in HIV patients

Location	Disease	Number of patients	% incidence
Anterior segment and adnexa	Blepharitis	10	6.58
	Multiple pustules on lid	2	1.32
	Multiple papules over lid	1	0.66
	Molluscum contagiosum	1	0.66
	SCC of lid	1	0.66
	Corneal opacity	4	2.63
	Herpes Zoster Ophthalmicus	2	1.32
	Cataract	6	3.95
	Uveitis	2	1.32
Neurophthalmic	6^{th} nerve palsy	1	0.66
	Esotropia	1	0.66
	Nystagmus	1	0.66
Posterior segment	HIV retinopathy	17	11.18
	CMV retinitis	5	3.29
	Choroidal infilterate	1	0.66
	Papilloedema	4	2.63
	Retinal detachment	2	1.32
	Anaemic fundus	5	3.29

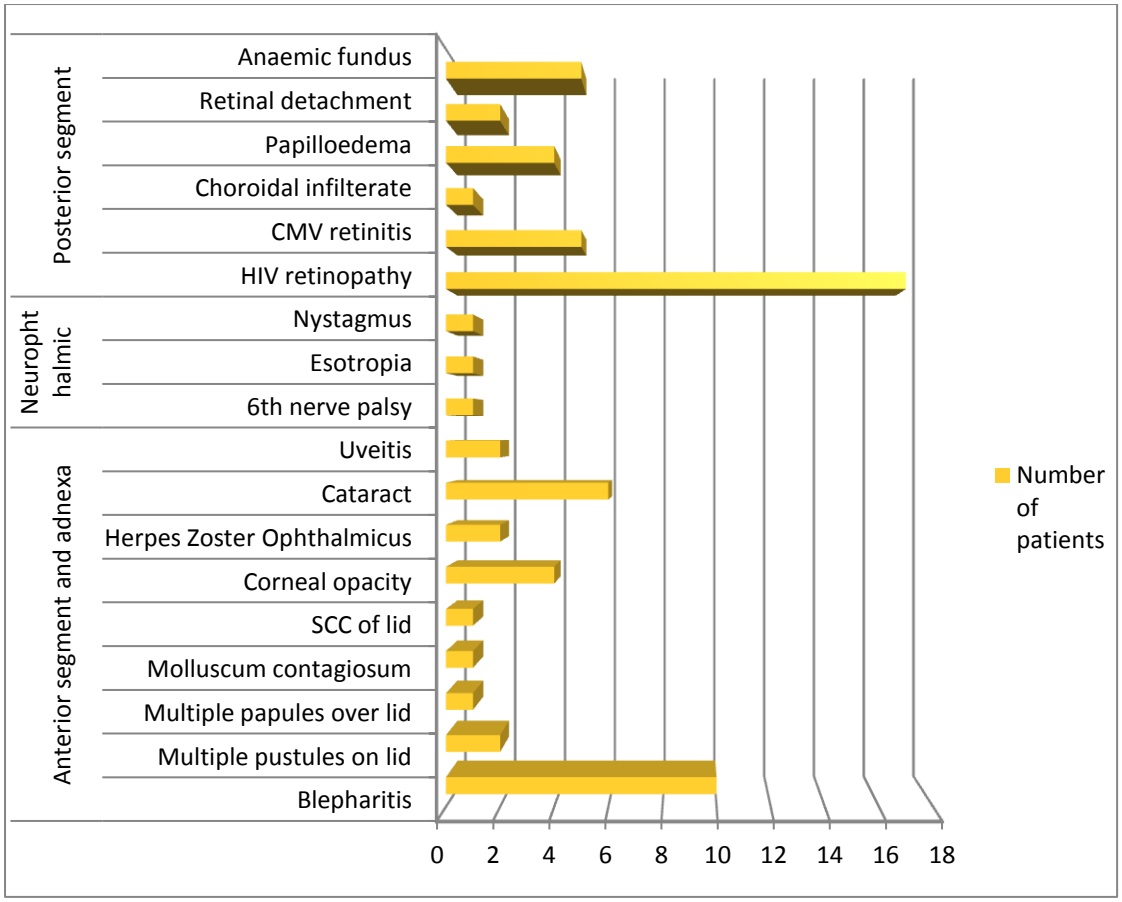


Figure 15 : Ocular manifestations in each segments in HIV patients.

In our study , cataract was second most common anterior segment manifestation , present in 6 patients (3.95%), followed by corneal opacity in 4 cases (2.63%) , 2 cases of pustules over lid , 2 cases of Herpes zoster ophthalmicus and, 2 cases of uveitis (1.32%). We also noted 1 case each of molluscum contagiosum , multiple papules over lid, SCC of lid (0.66%). Neuroophthalmic manifestations included one case each of 6^{th} nerve palsy, esotropia and nystagmus(0.66%) (Table 15).

In our study , second most common posterior segment manifestation were CMV retinitis and Anaemic fundus with 5 cases(3.29%) each, followed by papilloedema present in 4 patients (2.63%) ,Retinal detachment in 2 patients (1.32%) and one case of choroidal infiltrate (0.66%)(Table 15).

Table 16. Distribution of patients based on CD4 counts

CD4 counts in	Number of patients	Percentage %
0-100	37	24
100-200	27	18
200-300	24	16
300-400	21	14
400-500	15	10
500-600	16	10
600-700	10	7
700-800	1	0.7
>800	1	0.7
Total	152	100

Mean ± SD : 500 ± 273.86 , Median CD4 Counts: 266.66 , Range : 284.49 - 710.51.
Two tailed p value = 0.0007

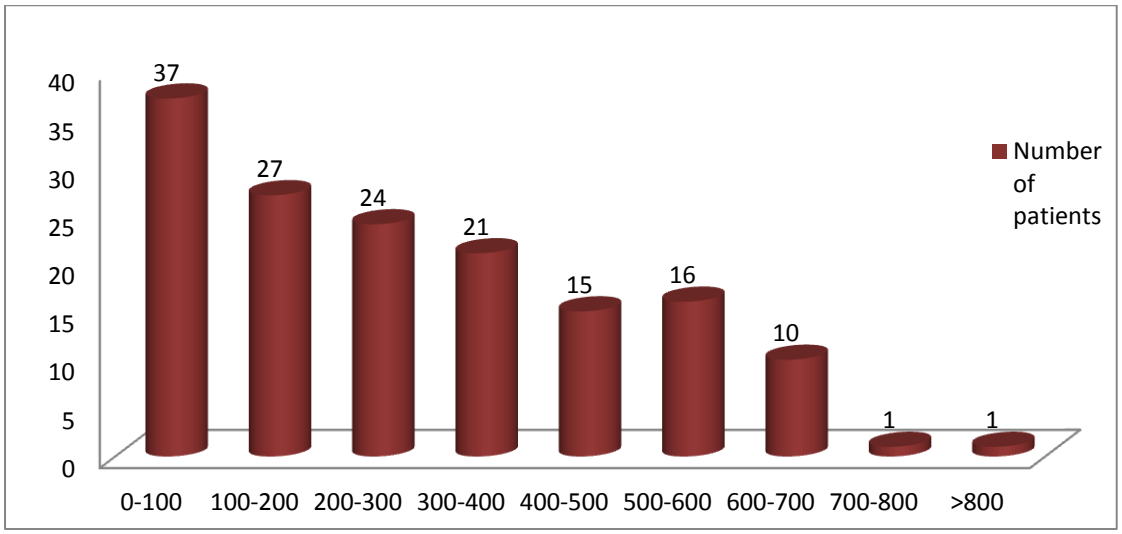


Figure 16. Distribution of patients based on CD4 counts

Table 16 shows the CD4 dsitribution amongst the patients in the study. Severe depletion was seen in 37 study subjects(24%) with cell count less than 100cells/mm^3 . The CD4 count ranged from 14 cells/µl in 2 patients to 1420 in one patient. The mean CD4 count was 500+273.86 and median CD4 count was 266.66 cell/mm^3. The CD4 count showed a highly significant result with a p value of 0.0007

Table 17: Correlation of ocular manifestation with CD4 counts in HIV patients

CD4+ T cell count (cells/ml)	Total no. of patients	Total number of patients with ocular manifestation	Percentage
1-100	37	20	54.1
101-200	27	14	51.9
201-300	23	14	60.9
301-400	22	4	18.2
401-500	15	0	0
501-600	16	4	25
601-700	10	1	10
701-800	1	0	0
801 and above	1	0	0
Total	152	57	37.5

Chi-square test, P=0.002

NOTE: 4 patients had both anterior segment and posterior segment manifestations

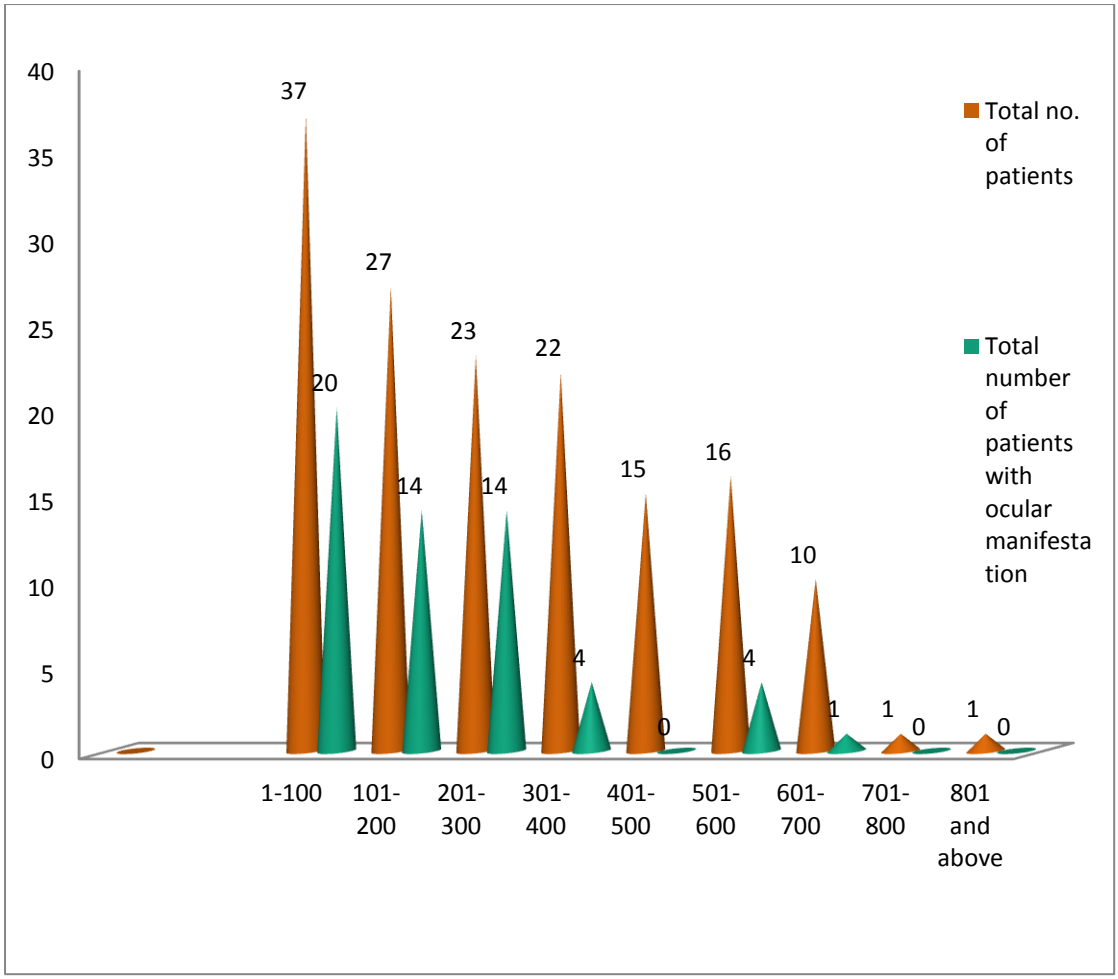


Figure 17 : Correlation of ocular manifestation with CD4 counts in HIV patients

In our study , the majority of 20 patients (54.1%) with ocular manifestations had a CD4 count less than 100cell/mm^3. 14 patients (51.9%) with ocular manifestations had a cell count in the range of 101-200 cell/mm^3 and 14 patients (60.9%) with ocular manifestations had 201-300 cells/mm ^{3}.Among the remaining patients with manifestations ,CD4 count was between 300-700 cell/µl. However only one patient each had counts in the range of 700-800cells/mm ^{3} and > 800cells/µl , but did not develop any ocular manifestation.(Table 17). The p value suggested a very significant result .

Table 18 : Ocular manifestation of AIDS in relation to duration of disease

Duration of diseases	Total No of patients	Patients with ocular manifestations	Percentage %
Newly detected	41	11	27
<1 yr	33	11	33
1-5 yr	52	21	40
6-10 yr	23	7	30
≥10	3	3	100
TOTAL	152	53	35

Chi-Square : 84.871; with degree of freedom -8; P<0.0001.

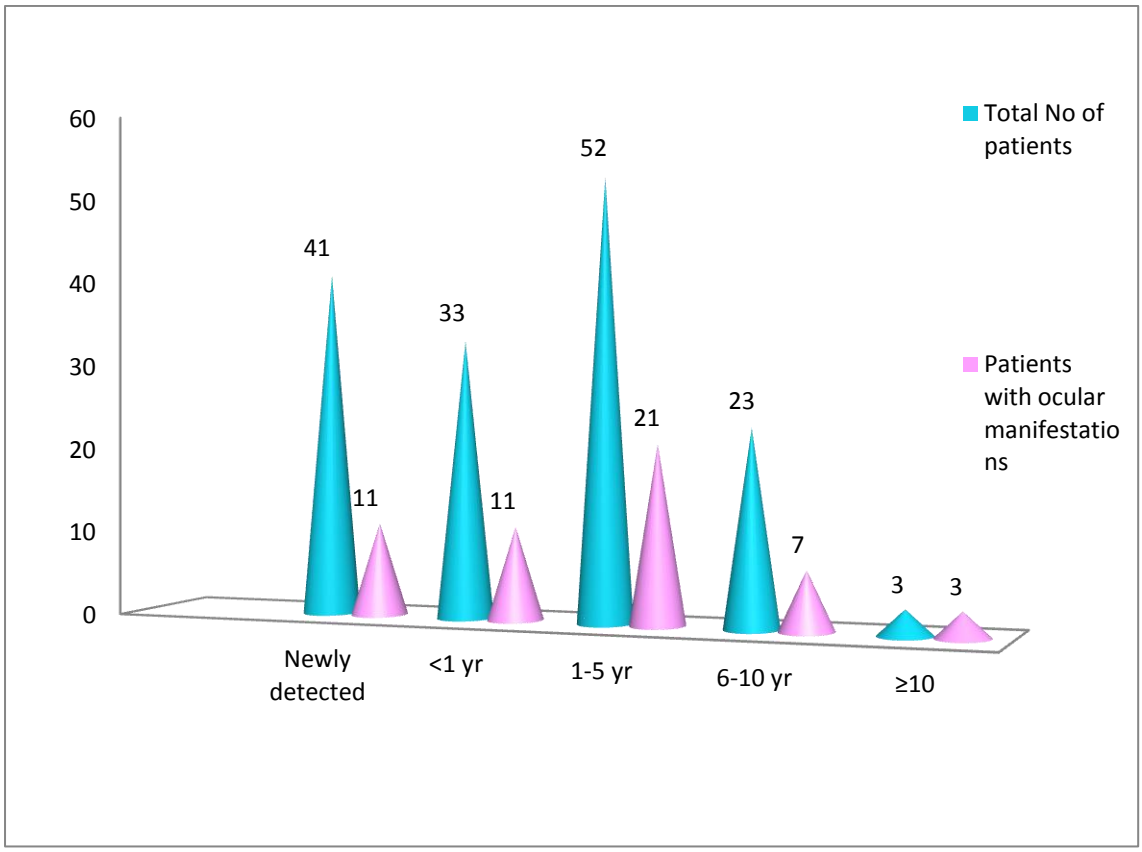


Figure 18 : Ocular manifestation of AIDS in relation to duration of disease

Analysis of ocular manifestation of AIDS in relation to duration of disease, suggest that there is a significant trend between the disease duration and ocular manifestations. Ocular manifestation increased with increase in duration of disease

period from 1-5 years(Table 18). Among 53 patients, a total of 43 patients developed one or other ocular manifestation of HIV within 5 years of disease . Beyond 5 years of disease duration , ocular manifestations reduced considerably and was noted to be present in 10 patients only in our study. Chi square analysis showed a significant result with a p value of <0.0001.

Table 19: Correlation of Visual status in HIV patients and CD4 count

Vision	CD4 count									P value
Right eye	1-100 (n=37)	101-200 (n=27)	201 -300 (n =24)	301-400 (n=21)	401-500 (n=15)	501-600 (n=16)	601-700(n=10)	701-800(n=1)	>800(n=1)	
6/6 (Good)	16	13	18	12	13	6	7	0	1	< 0.01**
6/6p-6/12 (Mild)	7	4	4	4	1	2	0	1	0	< 0.01**
6/18-6/36 (Moderate)	6	6	1	4	0	8	2	0	0	<0.001***
6/60 or less (Severe)	6	3	0	1	1	0	1	0	0	<0.001***
Could not be assessed	2	1	1	0	0	0	0	0	0	< 0.05 ns
Left eye	1-100(n=37)	101-200 (n=27)	201-300(n=24)	301-400 (n=21)	401-500 (n=15)	501-600(n=16)	601-700(n=10)	701-800(n=1)	>800(n=1)	
6/6 (Good)	19	15	18	13	10	6	7	0	1	<0.001***
6/6p-6/12 (Mild)	4	5	3	4	1	4	0	1	0	<0.001***
6/18-6/36 (Moderate)	3	3	2	4	2	4	1	0	0	<0.001***
6/60 or less (Severe)	9	3	0	0	2	2	2	0	0	<0.001***
Could not be assessed	2	1	1	0	0	0	0	0	0	>0.05ns

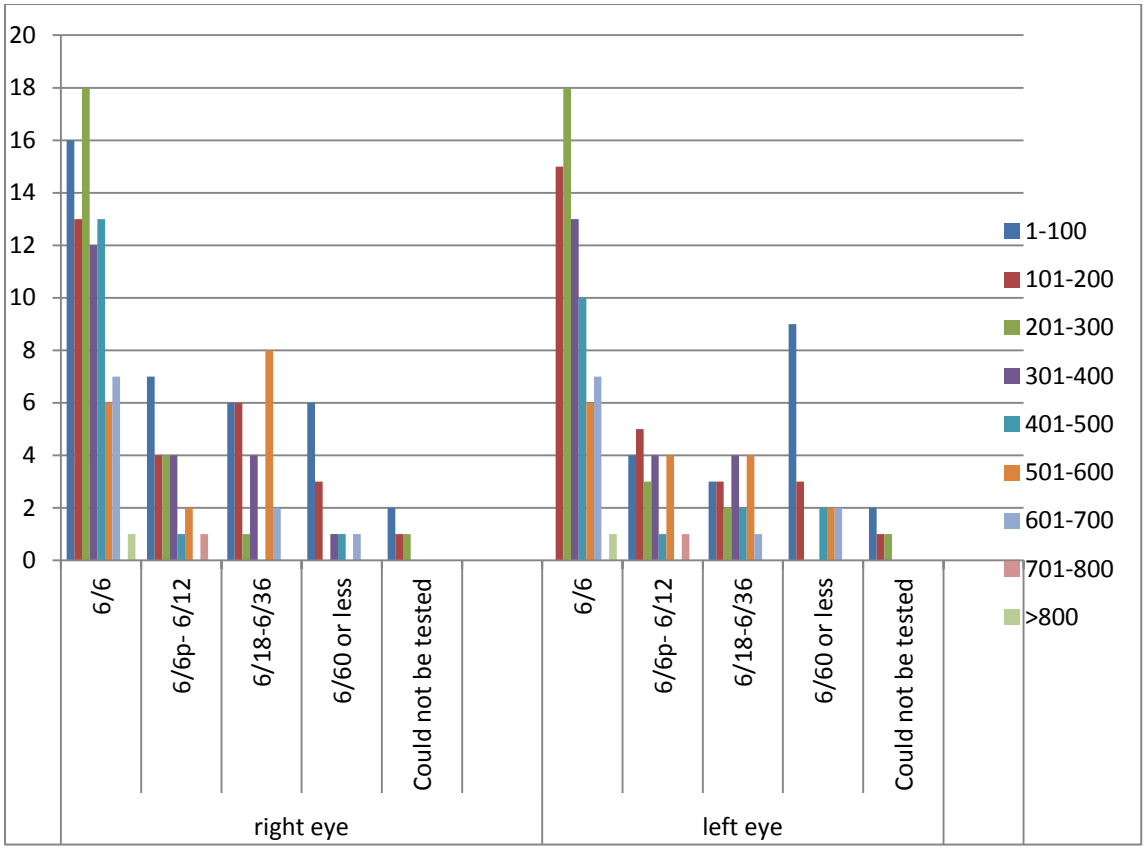


Figure 19 : Correlation of Visual status in HIV patients and CD4 count

Correlation of visual status in HIV patients and CD4 counts(Table 19), showed that right eye is affected more than the left eye. Severe and moderate visual impairment was more significant than the mild and good vision. In 12 out of 27 patients who had moderate visual impairment in right eye had a CD4 count less than 200 cell/mm ^{3}. 9 out of 12 patients who had severe visual impairment in right had a CD4 count less than 200 cells/mm^3. In other words statistically significant vision problems were observed in HIV patients with lower CD4 counts . Significant association was also noted among patients with left eye mild to severe visual deterioration and CD4 count. Highly significant p value of <0.0001 was noted in the study in patients with CD4 counts lesser than 200 cell/mm 3 and mild to severe visual impairment in left eye.

Table 20 .Correlation of HAART with ocular manifestations in HIV patients

Ocular manifestations	Patients not on HAART treatment(n= 68)	Patients on HAART treatment(n= 84)	Total number of patients (n=152)	P value
Blepharitis	3	7	10	<0.05*
Multiple pustules on lid	0	2	2	<0.01**
Multiple papules over lid	1	0	1	<0.05*
Molluscum contagiosum	0	1	1	<0.05*
SCC of lid	1	0	1	<0.05*
Corneal opacity	2	2	4	>0.05ns
Herpes Zoster Ophthalmicus	2	0	2	<0.01**
Cataract	1	5	6	<0.001***
Uveitis	0	2	2	<0.01**
6th nerve palsy	1	0	1	<0.05*
Esotropia	0	1	1	<0.05*
Nystagmus	0	1	1	<0.05*
HIV retinopathy	8	9	17	<0.0001****
CMV retinitis	1	4	5	<0.001***
Choroidal infilterate	0	1	1	<0.05*
Papilloedema	1	3	4	<0.01**
Retinal detachment	0	2	2	<0.01**
Anaemic fundus	1	4	5	<0.001***

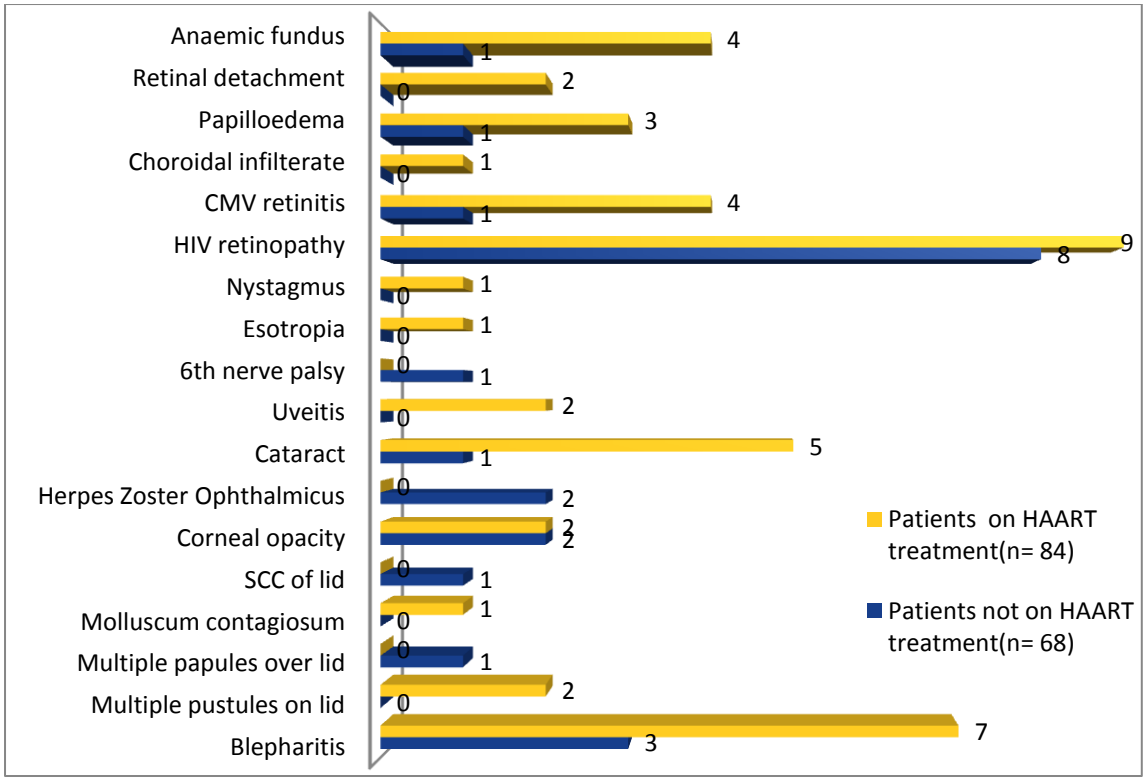


Figure 20 : Correlation of HAART with ocular manifestations in HIV patients

In our study , when ocular manifestations were correlated with HAART treatment it was noted that though Blepharitis (6.58 %)was the most common anterior segment manifestation in HIV patients , it was found to be more common among patients with HAART therapy with a significant p value of <0.05. A similiar finding was also noted among patients with cataract , multiple pustules on lid, molluscum contagiosum and uveitis ,being more common in patients on HAART theraphy. It was also noted in the study that HAART treatment had no impact on corneal opacity. Multiple papules over lid , SCC of lid and HZO was found most commonly in patients who were not on treatment with significant p values(Table 20). Among neuroopthalmic manifestations, 6th nerve palsy was significantly associated with patients not on treatment.

In our study , the presence of HIV retinopathy was the most common posterior segment manifestaion (11.18%). However, it was noted to be almost evenly spread about among both groups of patients. The rest of the posterior segment manifestations were noted to be present more among patients on HAART with variable significance levels(Table 20). Findings in the study suggested that most patients on HAART had posterior segment manifestations.

Table 21: Correlation of each ocular manifestation with CD4 Counts

Ocular manifestation	CD4 Counts									
	1-100 (n=37)	101-200 (n=27)	201-300 (n=24)	301-400 (n=21)	401-500 (n=15)	501-600 (n=16)	601-700 (n=10)	701-800 (n=1)	>800 (n=1)	P value
Blepharitis	3	3	2	1	0	1	0	0	0	>0.05 ^{ns}
Multiple pustules on lid	0	0	2	0	0	0	0	0	0	<0.05*
Multiple papules over lid	0	1	0	0	0	0	0	0	0	<0.05*
Molluscum contagiosum	0	0	0	0	0	1	0	0	0	<0.05*
SCC of lid	1	0	0	0	0	0	0	0	0	>0.05 ^{ns}
Corneal opacity	1	1	1	0	0	1	0	0	0	>0.05 ^{ns}
Herpes Zoster Ophthalmicus	0	1	0	1	0	0	0	0	0	>0.05 ^{ns}
Cataract	2	1	2	1	0	0	0	0	0	>0.05 ^{ns}
Uveitis	1	0	1	0	0	0	0	0	0	<0.05*
6th nerve palsy	0	0	0	1	0	0	0	0	0	<0.05*
Esotropia	1	0	0	0	0	0	0	0	0	<0.05*
Nystagmus	1	0	0	0	0	0	0	0	0	>0.05 ^{ns}
HIV retinopathy	3	5	6	1	0	1	1	0	0	>0.05 ^{ns}
CMV retinitis	5	0	0	0	0	0	0	0	0	<0.05*
Choroidal infilterate	1	0	0	0	0	0	0	0	0	>0.05 ^{ns}
Papilloedema	1	1	0	1	0	0	1	0	0	>0.05 ^{ns}
Retinal detachment	0	2	0	0	0	0	0	0	0	>0.05 ^{ns}
Anaemic fundus	2	1	1	1	0	0	0	0	0	>0.05 ^{ns}

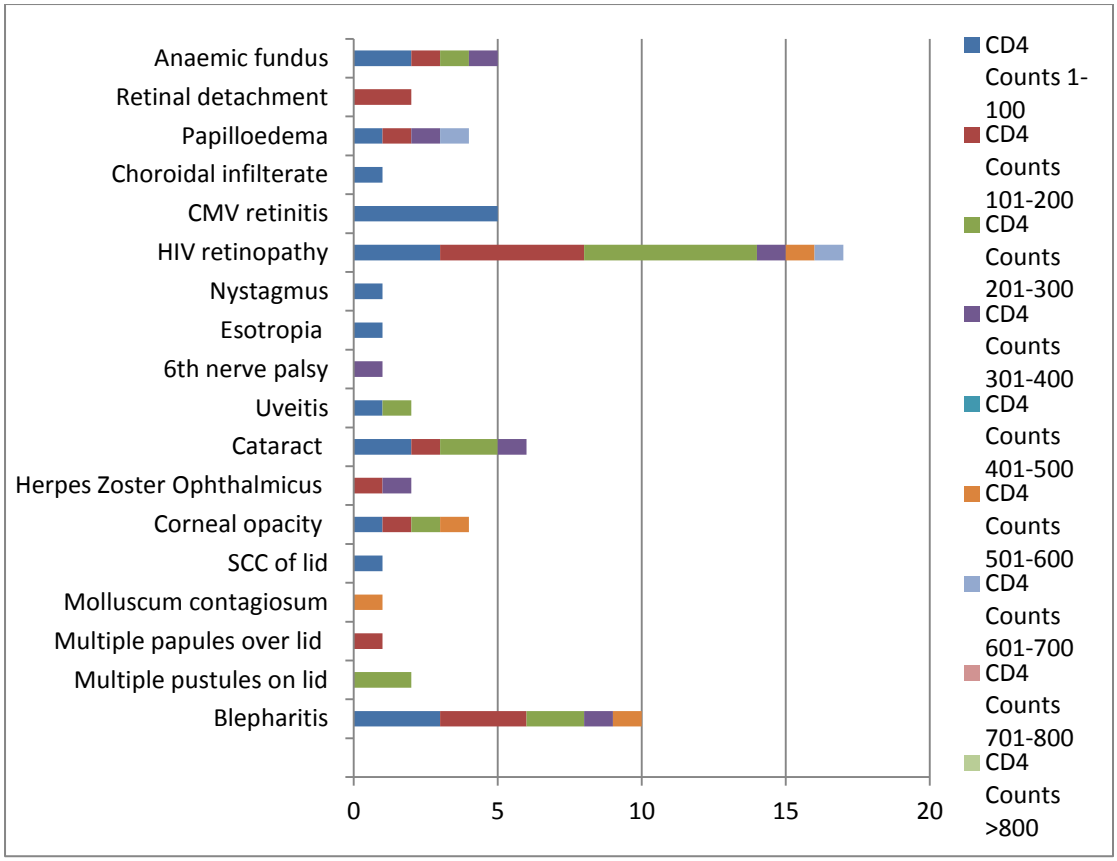


Figure 21 : Correlation of each ocular manifestation with CD4 Counts.

In our study , correlation of ocular manifestation and CD4 counts(Table 21) showed that presence of Blepharitis , SCC of lid , Corneal opacity , HZO and cataract were independent of the CD4 counts. Presence of multiple pustules and papules over lids was more common among patients with CD4 counts between 101-300 cells/mm3 and molluscum contagiosum among CD4 counts between 501-600 cells/mm3 with a significant p value of <0.05. Uveitis was noted to be present among patients with CD4 counts between 0-300 cells/mm3 with significant p value <0.05. The neuroopthalmic manifestation of esotrophia and nystagmus was common among low CD4 counts of <100 cells/mm3 and 6th nerve palsy was noted to be present in patients with CD4 counts 301-400 cells/mm3 with a significant p value of <0.05(Table 21).

In our study , low CD4 count <100 cells/mm3 was noted among patients with CMV retinitis with a significant p value<0.05.The rest of the posterior segment manifestations like HIV retinopathy , choroidal infilterate, papilloedema, retinal detachment and anemic fundus showed a non specific correlation with CD4 counts(Table 21).

DISCUSSION:

The present study was conducted on 152 patients who were known to be positive for HIV infection with or without AIDS on treatment / without treatment during the study period October 2011 to October 2012.

I: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF PATIENTS:

Age distribution :

In terms of age distribution, in the current study 75% of HIV and 77.36% patients with ocular manifestation are found between the age group 21-50 which is in accordance with the observations made by Dinesh et al [7] who reported around 74% and Jyotirmay Biswas et al at 76% [85] . Lower distribution levels were observed by Gharai S [157] at 52% . Further in the current study incidence was 89% in extended age period 21-60. In other words ~14% of incidences were observed at the age between 51-60. Results of all these study highlights that the disease is predominant during sexually active period. Significant incidences even in the age group between 51-60 could be due to increased survival rate of HIV patients, probably with the better treatment or with good medical care. The observed result is of great concern since it has a tremendous influence on the cultural as well as economic status , hence affecting not only the family members but also the society at large.

Table 22 : Age distribution of various studies

Author	Year	Age in years (21-50)
Dinesh et al	1999	74 %
Jyotirmay Biswas et al	2000	76%
Gharai S et al	2008	52%
Present study	2013	77.36%

Sex distribution of HIV patients in various studies

In the present study 55% of patients were males while 45% females suggesting the ratio of M:F as 1.20:1 of HIV and. Among patients with ocular manifestations, the ratio of M:F was 1.21:1. Almost a close result was obtained in a study conducted by Yared Aseefa et al [158] who reported a ratio of 1.23:1 and Juliet OS et al [159] 1.4:1. Results are in accordance with the observation made by Biswas J et al[85] and that of Gharai S et al [157] suggested a ratio of 3:1 between M:F as all reported a higher male prevalence . A higher ratio of 7:1 and 9:1 was observed by JABS et al [160] and Dinesh et al [7]. Wide variation in the sex distribution pattern suggest wide variation in culture conditions, where females have restricted sexual partners while not so with males. Differences could be either due to the differences in socio-economic status as well as the migration of males for occupation to distant places for the family maintenance.

Table 23: Sex distribution of various studies

Study	**Year**	**M:F RATIO**
Yared Aseefa et al	2004	1.23:1
Juliet Otiti Singeri et al	2010	1.4:1
Biswas J et al	2000	3.34:1
Gharai S et al	2008	3:1
Jabs et al	1995	7.33:1
Dinesh K Sahu et al.	1999	9:1
Present study	2013	1.21:1

Distribution of cases by mode of transmission:-

The present study shows the most common risk of exposure is the trans-sexual route which is observed in 93.42%participants, 5.26 5 through IV drugs and 1.32 %patients had aquired through combined transsexual and IV route. However we did

not get any case which suggested blood transfusion or needle prick as probable mode of acquiring HIV in our study. Biswas J et al have similarly reported that 75% of the patients had acquired HIV infection by transsexual route [85]. A similar study by Pathai S et al [161] has reported relatively higher percentage of transmission through trans sexual route in 96.7% of the patients, blood transfusion and intravenous drug abuse in 1.3% of the patients. Sexual route 73% was the most common route of transmission as reported by Dinesh K Sahu et al [7] .This series shows transsexual route of transmission as the major route of acquiring HIV, however percentage affected is slightly more than that suggested by numerous other reported studies. This excessively high rate of transsexual transmission could be because of the rampant practice of the socially tabooed "devadasi " system in places in and around Bijapur. Thus, patients should be educated about the disease and counselled appropriately to prevent the transmission of this deadly virus by creating awareness and health education and eliminating the practice of Devadasi system.

Table 24. Mode of HIV transmission in various studies

Study	**Year**	**Transsexual mode %**
Biswas J et al	2000	75%
Pathai S et al	2009	96.7%
Dinesh K Sahu et al	1999	73%
Present study	2013	93.42%

Systemic manifestations :

The systemic manifestations were present in 78.95% in our study .The most common systemic involvement amongst HIV patients as well as in patients with ocular manifestations in our study was various manifestations of Tuberculosis seen in

26.32% and 22.64% respectively, including pulmonary, abdominal , extrapulmonary TB and TB meningitis. The second most common system affected was the gastrointestinal system presenting as acute gastroenteritis due to various etiology in 7.89% . A study by Bemnet Amare et al reported nearly 46.8% had either current or a previous history of tuberculosis (pulmonary and extra-pulmonary) [162]. Similar observation with tuberculosis(pulmonary) as the first most common systemic association was noted in 50% patients in a study by Biswas J et al [85]. Pathai S et al in a study have reported similar findings in which 53% of the patients had either current or a previous history of tuberculosis [161] . The reason for the comparatively low prevalence rates found in our study compared to previous studies could be attributed probably to the general awareness among people about HIV and earlier screening as well as free HAART treatment being provided by the Government of Karnataka, which has made it easier for the lower socio economic groups to have access to the medications . However , our findings are consistent with the fact that systemic manifestations when present , were mostly tuberculosis as observed by various other studies.

Table 25. Systemic manifestation in HIV in various studies

Study	**Year**	**Tuberculosis %**
Bemnet Amare et al	2011	46.8%
Biswas J et al	2000	50%
Pathai S et al	2009	53%
Present study	2013	26.32%

II. OCULAR MANIFESTATIONS :

Prevalance of ocular manifestations

In the present study , out of 152 patients with HIV, 53 patients had ocular manifestations; 34.86% of the patients have ocular manifestations which is in accordance with the study by Pavana K A et al at 37.6% [163] and by Biswas J et al who reported ~ 40% [85] .Gharai S et al [157] report of ~45% prevalence of ocular manifestations in their study . However studies conducted by JABS et al [160], & Dinesh Sahu et al [7], observed an incidence of 50 and 58% of prevalence respectively .The decreased prevalence in the present study could be due to effective HAART therapy and due to increased awareness among general public and health care practitioners , thus seeking early consultation with an ophthalmologist.

Table 26 : Prevalance of ocular manifestations in various studies

Study	Year	Ocular manifestations %
Pavan KA et al	2012	37.6 %
Biswas J et al	2000	40%
Gharai S et al	2008	45%
Jabs et al	1995	50%
Dinesh Sahu et al	1999	58%

Prevalence of various ocular manifestations in HIV patients

Anterior segment manifestations

In the present study , anterior segment manifestations were encountered in 19.08 % and the most common anterior segment manifestation in our study was blepharitis noted in 6.58% . A study by Pavan KA et al [163] reported 7% involvement of anterior segment and adnexa in HIV patients. Their study also suggested lid

infections as the most common manifestation as noted in our study . Biswas J et al also suggested that severe blepharitis, styes and lid ulceration may be the initial involvement in AIDS[164] . Cataract was second most common anterior segment manifestation , present in 3.95% . Corneal opacity was noted in 2.63% , 2 cases of pustules over lid . Herpes zoster ophthalmicus was noted in 1.32% in accordance to observations noted by Biswas J et al [85] around 1 % and similar results were also reported by Gharai S et al[157] and Dinesh SK et al [7] . Active uveitis or evidence of uveitis as posterior synechie, old KP's and iris atrophy was present in 1.32% . Other studies by Biswas J et al [85] reported 3% and Dinesh S K et al [7] reported 4.2%. We also noted 1 case each of molluscum contagiosum , multiple papules over lid, SCC of lid at 0.66% . Similar observation was noted in the study by Pavana K A et al who reported 3 cases of molluscum contagiosum of lid among 553 patients [163] . We did not encounter any case of Kaposi Sarcoma in our study which could be due to the lower prevalence of homosexual behaviour and the low incidence of the human Herpes virus 8, which are known to be associated with Kaposi's sarcoma. Finding in our study were keeping in with the observations made in anterior segment in various other reported studies.

Neuroophthalmic manifestations :

Neuroophthalmic manifestations were noted in 0.66%, which included one case each of 6th nerve palsy, esotropia and nystagmus. Study by Pavana KA et al [163] reported 5.78% of the patients with neuro-ophthalmic manifestations. Several reported studies , report the presence of gaze palsies, nystagmus , optic neuropathies and visual field defects and have attributed it to CNS involvement and HIV encephalopathy. Our observation was unique as we noted isolated 6th nerve palsy

following HZO , which is considered to be relatively uncommon even though combined 3rd , 4th and 6th nerve palsies are reported in 7-31% of cases.

Posterior segment manifestations :

In our study Posterior segment manifestations were present in 18.42%. The most common posterior segment manifestation was HIV retinopathy , noted in 11.18% . Similar observations were reported in studies by Lewallen et al [165] and Biswas J et al [166] at 13% and 12.8 % respectively. Another study by Purushottam J et al reported a higher prevalence at 32 % [167] . This disparity can be explained probably by the selection of patients with AIDS in their study , while patients were seen earlier by us. The findings in our study was in accordance with the observations made by numerous other reported studies.

Table 27: Prevalance of HIV retinopathy in various studies

Study	**Year**	**HIV retinopathy %**
Lewallen et al	1994	13
Biswas J et al	1999	12.8
Purushottam J et al	2012	32
Present study	2013	11.18

CMV retinitis and Anaemic fundus were present in 3.29% each. Biswas et al in a study have reported CMV retinitis in 17 % of the patients [85]. Jabs DA et al reported 22.7% cases of CMV retinitis [160]. Pathai S et al, found CMV retinitis in 8.7% of the patients with HIV infection enrolling for HAART therapy in India[161] . Our findings were in accordance with the findings reported by Chiou et al [168] which observed HIV retinopathy as the most common ocular finding and CMV retinitis was the most commonly seen opportunistic infection. It has also been reported in various studies

that the patients with CMV retinitis at the time of enrollment during their study had a significantly greater mortality than those without CMV retinitis with relative risk of 2.3 [169,170]. Holland et al observed that the introduction of HAART has markedly reduced the incidence of CMV retinitis, but has not eliminated new cases all together [171]. Similarly in our study we noted that 1 patient with CMV retinitis died within 3 months from the time of diagnosis. The lower prevalence in our study can be explained by observations made by earlier reported studies that suggest marked reduction of CMV retinitis with the introduction of HAART.

Table 28: Prevalence of CMV retinitis in various studies

Study	**Year**	**CMV retinitis %**
Biswas J et al	2000	17
Jabs D A et al	2007	22.7
Pathai S et al	2009	8.7
Present study	2013	3.92%

Other posterior segment manifestations :

Current study noted papilloedema present in 2.63% ,Retinal detachment in 1.32% and choroidal infilterate in 0.66% . Mansour A M in a study reported abnormalities in the form of ocular motor nerve palsies ,papilledema, optic neuritis, cortical blindness, conjugate gaze palsy, and altitudinal visual field defect in about 6% of the patients [172] which can be explained as they combined various findings together while we reported papilloedema seperately . Gharai S et al observed retinal detachment in 0.4% of cases in their study [157], while Biswas J et al [85] reported 8 % and Dinesh S K et al [7] reported 1 % respectively . Biswas J et al[164] in their study noted 4

cases of multifocal choroidal infilterates . The observations in our study were in accordance with most other published studies.

Ocular manifestations in relation to duration of disease :

Analysis of ocular manifestation of AIDS in relation to duration of disease, suggest that , manifestations increased with increase in duration of disease period from 1-5 years. 81% of patients with ocular manifestations developed them within 5 years of disease . Beyond 5 years of disease duration , ocular manifestations reduced considerably and was noted to be present in the remaining 18 % of affected patients only in our study. Chi square analysis showed a significant result with a p value of <0.0001.This was in contrast to the observations made by Shah S U et al [173] and Pathai S et al [161] , who reported that relation of eye involvement with duration of disease was statistically insignificant.

Correlation of Ocular manifestations and visual status in HIV patients :

Correlation of visual status in HIV patients and CD4 counts, showed that right eye is affected more than the left eye. Majority of patients(>50%) had good vision in both eyes . In 53.84% of patients with moderate to severe visual impairment in right eye had CD4 counts lower than 200cells/mm ^{3} and it was found to be statistically significant. Significant association was also noted among 54.6% of patients with left eye moderate to severe visual deterioration had a CD4 count less than 200cells/mm ^{3} . Highly significant p value of <0.0001 was noted in the study. Observations by Biswas J et al [85] and Aratee P et al [174] noted that 19% patients in right eye and 18% patients and 25% patients in left eye had moderate to severe visual impairment .However they did not compare it with CD4 counts. Though previous reported studies have established that visual acuity may get worsened in the disease process due to various ocular lesions

, we could not find any study comparing visual loss with CD4 count levels as in our study. Hence, it is important to note that , lower CD4 count can also be sufficiently taken as a probable indicator for chances of developing visual impairment in a HIV patient and these needs detailed evaluation to look for the cause and treat as suggested by our study.

Correlation of ocular manifestations and HAART in HIV patients :

It was also noted in the study that multiple papules over lid , SCC of lid and HZO and 6th nerve palsy was found most commonly in patients who were not on treatment with significant p values. Findings in the study suggested that most patients on HAART had posterior segment manifestations like CMV retinitis , Retinal detachment and anaemic fundus .This can be explained by observations by Mesaric et al [175] that CMV retinitis may have been present prior to initiating HAART . Zidovudine induced anaemia (< 8g/dl) was reported in 16.2% of patients by Agarwal D et al in 2010 [176], suggesting that anemic fundus observed in our study could be induced by HAART itself .We also noted that blepharitis, cataract , multiple pustules on lid, molluscum contagiosum and uveitis ,were more common in patients on HAART therapy. The findings of retinal detachment , cataract and uveitis can be explained by observations made by Thorne et al [177] , Accorinti et al [178] and Karavellas et al [179] who have also reported similar statistically significant cases of cataract , uveitis and retinal detachment among patients on HAART in the process of immune recovery. However statistically significant increase in blepharitis , multiple pustules on lid, molluscum contagiosum , Choroidal infilterate , and Papilloedema as noted in our study , were not reported previously .

Correlation of ocular manifestations with CD4 counts :

In the study 20 patients (54.1%) with ocular manifestations had a CD4 count less than 100cell/µl. 14 patients (51.9%) with ocular manifestations had a cell count in the range of 101-200 cell/mm^3 and 14 patients (60.9%)with ocular manifestations had 201-300 cells/mm^3.Among the remaining patients with manifestations ,CD4 count was between 300-700 cell/µl. Chi square analysis of the data revealed p value of 0.002 which is highly significant. The mean CD4 count was 500+273.86 and median CD4 count was 266.66 cell/mm^3.

Pathai S et al[161] showed in their study that the prevalence of ophthalmic manifestations associated with HIV was significantly higher in patients with CD4+ T cell counts between 0-100 cells/µl and that these patients were six times more likely to have an HIV related ocular manifestation [102]. They also noted that overall the prevalence of eye disease among patients with CD4 cell counts ≤ 200 cells/µL was 23.8%, compared to 9.2% among those with CD4 cell counts > 201cells/µL. Similar observations were noted by Shah SU et al in a study have found the prevalence of the ocular manifestations due to HIV/AIDS to be maximum in patients with CD4+T cell counts 0-100 cells/µl than 101-200 cells/µl and the difference was statistically significant [171].

Correlation of ocular manifestation and CD4 counts showed that presence of Blepharitis , SCC of lid , Corneal opacity , HZO and cataract were independent of the CD4 counts. Multiple pustules and papules over lids was more common among patients with CD4 counts between 101-300 cells/mm3 and molluscum contagiosum among CD4 counts between 501-600 cells/mm3 with a significant p value of <0.05. A case report by Biswas J et al [164] reported cases of blepharitis and Molluscum contagiosum but CD4 status was not evaluated in them. Another study by Alan B et al

[42] reported 22 cell/mm [3] in a case of molluscum contagiosum , in contrast to a higher value observed in our study probably because they had observed the patient with AIDS while our patients were viewed much earlier in the course of the disease. Uveitis was noted to be present among patients with CD4 counts between 0-300 cells/mm3 with significant p value <0.05. The neuroopthalmic manifestation of esotrophia and nystagmus was common among low CD4 counts of <100 cells/mm3 and 6th nerve palsy was noted to be present in patients with CD4 counts 301-400 cells/mm3 with a significant p value of <0.05. Studies by Wani M Ga et al [180] suggested that neuroophthalmic manifestations were common at CD4 counts <500 cells/mm [3] and <100 cells/mm [3] . We noted low CD4 count <100 cells/mm3 among patients with CMV retinitis with a significant p value<0.05. It was in accordance to observations reported by Kupperman et al [128] and various other studies , CD4 counts less than 50 cells /mm^3 , CMV retinitis was more common.

In our study we found a significant association between ocular manifestations and lower CD4+T cell count in accordance with other previous studies.

CONCLUSION :

The present study is a hospital based prospective study evaluating patients with HIV infection for ocular manifestations. The study noted that HIV/AIDS is a significant cause of ocular disease with 53 patients(34.86%) having HIV/AIDS related eye disease. Comprehensive ophthalmic examination of all HIV infected patients , at regular intervals, will help in identifying ocular morbidity early .

The ocular manifestation was found to be more common in the sexually reproductive age group with males being affected more commonly which is due to general higher incidence of HIV among this population. The commonest mode of transmission was the transsexual mode of spread. 10 patients (18.8%) had only ocular manifestations with no systemic manifestation of HIV. Tuberculosis was most common systemic manifestation among patients with ocular manifestations. Majority of patients who developed ocular manifestations developed it within 5 years of disease. We also observed that moderate to severe visual impairment were more common at CD4 counts lesser than 200 cells/mm ^{3}.

The anterior and posterior segment involvement rates were almost equal and commonest ocular lesions observed were HIV retinopathy in the posterior segment and Blepharitis in the anterior segment. The study shows that the spectrum of the ocular lesions associated with HIV infection in India is different from elsewhere in the world. The prevalence of CMV retinitis is lower and there have been no cases of Kaposi's sarcoma. There is still a great need for the definitive diagnosis of the ocular lesions in HIV positive patients . Patients on HAART had manifestations like CMV retinitis , Retinal detachment and anaemic fundus , cataract , uveitis . With the advent of HAART, there is an increase of atypical presentations of ocular diseases. The

recognition and treatment of the Immune Recovery Inflammatory Syndrome, due to immune reconstitution in patients on treatment, poses a new challenge.

Overall ocular manifestations were found to be more common among patients with lower CD4 counts. This suggests that HIV related ocular disease is related to the degree of immunosuppression in HIV infected patients. With HAART being made widely available to the Indian population by NACO, there is a changing trend noted in the ocular manifestations. Hence , constant monitoring and increased awareness among general public and ophthalmologists is essential to understand the spectrum of ocular lesions as well as to timely treat them.

SUMMARY:

In this patients with HIV were examined for ocular manifestations with an aim to evaluate the nature and incidence of various ocular manifestations in patients with HIV infection and to correlate with CD4 counts .

- The result showed that the majority of the patients with ocular manifestations belonged to the sexually active age group of 21-50 years with a male to female ratio of 1.21:1. The mean age was 23.75±9.708 years in males and 24±2.808 years in females.
- 93.42% had acquired HIV infection by Trans-sexual mode of contact.
- Systemic manifestations were present in 31 patients (58.49%) with ocular manifestation in our study and the most common systemic involvement was various manifestations of Tuberculosis seen in 22.64% of patients with ocular manifestaions.
- 43 patients developed one or other ocular manifestation of HIV within 5 years of disease .
- Majority of 56.58% in right eye and 58.55% in left eye had good visual acuity. Visual impairment was common in right eye and were present at lower CD4 counts in both eyes.
- Prevalence of ocular manifestation is 34.86 % .Among these 19.08% had anterior segment manifestations , 18.42% had posterior segment manifestation and 2.63% had both.
- 10 patients (18.8%) had only ocular manifestations with no systemic manifestation of HIV.
- Commonest anterior segment manifestation was Blepharitis present in 6.58% and commonest posterior segment manifestation was HIV retinopathy in 11.18%.

- Various other manifestations were cataract 3.95%, corneal opacity 2.63% , 1.32 % pustules over lid , Herpes zoster ophthalmicus and, uveitis . We also noted 0.66% molluscum contagiosum , multiple papules over lid, SCC of lid. Neuroophthalmic manifestations included 0.66% of 6^{th} nerve palsy, esotropia and nystagmus .Posterior segment manifestation were CMV retinitis and Anaemic fundus 3.29% each, papilloedema 2.63% ,Retinal detachment 1.32% and choroidal infilterate 0.66% .
- Correlation of ocular manifestations with HAART showed varied manifestations like Retinal detachment ,anaemic fundus ,cataract and uveitis among patients on HAART in the process of immune recovery .With HAART being made widely available to the Indian population by NACO, there is a changing trend noted in the ocular manifestations.
- Correlation of ocular manifestation and CD4 counts showed that presence of blepharitis , SCC of lid , Corneal opacity , HZO and cataract were independent of the CD4 counts.
- Presence of multiple pustules and papules over lids was more common among patients with CD4 counts -101-300 cells/mm3 , molluscum contagiosum -CD4 counts 501-600 cells/mm3, Uveitis - CD4 counts 0-300 cells/mm3.
- Neuroopthalmic manifestation, esotrophia and nystagmus - low CD4 counts of <100 cells/mm3 , 6th nerve palsy -CD4 counts 301-400 cells/mm3.
- Posterior segment manifestations , CMV retinitis-low CD4 count <100 cells/mm3. HIV retinopathy , choroidal infilterate, papilloedema, retinal detachment and anemic fundus showed a non specific correlation with CD4 counts.

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ANNEXURE I

Ethical Committee
BIJAPUR-586103
OUT WARD
No 27/2011
Date 21-10-11
Sh. B. M. PATIL Med. col

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 20-10-2011 *at* 10-30am *to scrutinize the Synopsis/Research projects of postgraduate/undergraduate student/Faculty members of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis/Research project has been accorded Ethical Clearance.*

Title "Ocular manifestations in patients with HIV infections and its correlation with CD4 counts"

Name of P.G./U.G. student/Faculty member Dr. Akshatha M. Dharmesh
Dept of Ophthalmology

Name of Guide/Co-investigator Dr. M. H. Patil Prof Ophthalmology

DR.M.S.BIRADAR,
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Chairman
Ethical Committee
BLDEA'S Shri. B.M. Patil
Medical College
Bijapur-586103

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE – II

SAMPLE INFORMED CONSENT FORM

TITLE OF THE PROJECT: OCULAR MANIFESTATIONS IN PATIENTS WITH HIV INFECTION AND ITS CORRELATION WITH CD4 COUNTS.

PRINCIPAL INVESTEGATOR: Dr. Akshatha M. Dharmesh

PG GUIDE: Dr. M.H.Patil M.S.

PURPOSE OF RESEARCH:

I have been informed that this study will evaluate the nature and incidence of ocular manifestations in a group of patients with Human immunodeficiency virus and to correlate it with CD4 counts.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I have been explained that based on the test report from VCTC, I/my ward will be subjected to detailed history and systemic and ocular examination. I/My ward will then be subjected to CD4 evaluation and management.

RISKS AND DISCOMFORTS:

I understand that I/my ward have to undergo a complete ocular and systemic examination as required. I/My ward may have blurring of vision for a few hours as a result of pharmacological pupil dilatation for detailed fundus evaluation. I /My ward may have to undergo the various tests required and to expect a time delay for all the various test reports to come.

BENEFITS:

I understand that my/my wards participation in this study will help to analyse the nature and incidence of ocular manifestations in patients with Human immunodeficiency virus and to correlate it with CD4 counts.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Akshatha M. Dharmesh is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. Akshatha M. Dharmesh will terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me I/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. M.H.Patil (Guide) Dr.Akshatha M. Dharmesh (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. Akshatha M. Dharmesh has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail, in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date :

_____ _____

(Witness to above signature) Date :

ANNEXURE III

CASE SHEET PROFORMA

Name: Date:

Age/Sex: O.P.No./I.P.NO

Occupation/Education/Marital status/Rural/Urban:

DOA: DOD:

Address:

Socio Economic Status:

History of presenting complaints :

General complaints : Fever
Weight loss
Diarrhoea
Cough
Weakness
Difficulty in swallowing

Ocular Symptomatology:

Past history : History of similar complaints
History of ocular diseases
History of Hypertension/Diabetes/STD's/PTB

Treatment history : History of treatment taken for ocular \ diseases or other diseases
History of allergic reactions to drugs.
History of blood transfusion.

Family history : Married/Unmarried
Number of family members
History of similar complaints
HIV status of wife/husband/children

Personal history	:	History of IV drug abuse.	
Sexual history	:	Extra marital relation	
General Examination	:	Built Pallor Icterus Lymphadenopathy	Weight Clubbing Cyanosis
Vital Data	:	Pulse BP	Temperature RR
Systemic Examination	:	CVS CNS	RS GIT

Ocular Examination :

Right Eye		Left Eye
	Eye Brow	
	Eye lids and Adnexa (Lacrimal sac)Skin, Lid margin, Eye lashes	
	Eye Balls Position, Visual axis, Size of the eye ball	
	Ocular movements	
	Conjunctiva	
	Sclera	
	Cornea	
	Anterior Chamber Iris	
	Pupil	
	Lens	
	Vision	

Fundus

Intra ocular tension

Corneal sensations

Corneal staining

Direct ophthalmoscopy

Indirect ophthalmoscopy

Anterior segment photograph

Fundus photograph

Investigations

Blood test	Hb	TC
	DC	
	ESR	Serum creatinine

Chest X Ray

HIV-1/HIV-2 CD 4 Count

Other investigations

Diagnosis :

ANNEXURE IV

KEY TO MASTER CHART

M	**–**	Male
F	**–**	Female
MR	**-**	Married
UM	-	Unmarried
TS	-	Transsexual
IVD	-	IV Drugs
UE	-	Uneducated
HW	-	House wife
CSW	-	Commercial Sex Worker
SW	-	Social Worker
ND	-	Newly Detected
d	-	Days
m	-	Montha
y	-	Years
COPD	-	Chronic Obstructive Pulmonary Disease
PRES	-	Progressive Reversible Encephalopathy Syndrome
PTB	-	Pulmonary Tuberculosis
ATB	-	Abdominal Tuberculosis
AGE	-	Acute Gastroenteritis
EPTB	-	Extra Pulmonay Tuberculosis
LRTI	-	Lower Respiratory Tract Infection
TBM	-	TB Meningitis
CLD	-	Chronic Liver disease
NF	-	Necrotizing Fascitis
LL	-	Lower Limb
RTA	-	Road Traffic Accident
OPP	-	Organophosphate Poisoning

HS - Hydradenitis Suppurativa

AB - Acute Bronchitis

DIMPR- Drug Induced Maculopapular Rash

AA - Acute appendicitis

- Fracture

HP - Hemiparesis

ALD - Alchoholic Liver disease

CA - Cold Abscess

M.Ret - Mentally Retarded

UTI - Urinary Tract Infection

PLA - Pyogenic liver abscess

Ana - Anaemia

EC - Esophageal Candidiasis

CVA - Cerebrovascular Accident

TEN - Toxic Epidermal Necrosis

OC - Oral Candidiasis

PV - Psoriasis Vulgaris

F/A - Fistula in Ano

AFI - Acute Febrile Illness

PA - Pleomorphic Adenoma

DM - Diabetes Mellitus

CH - Communicating Hydrocephalus

DOV - Diminution of Vision

CF mt - Counting Fingers in metre

HM - Hand Movements

PL - Perception of Light

IMC - Immature cataract

PC IOL- Posterior chamber Intraocular Lens

AAB - Acute anterior blepharitis

CO - Corneal Opacity

PNT - Progressive nasal pterygium

EP - Early Papilloedema

HIVR - HIV Retinopathy

CI - Choroidal infilterate

ANT - Atrophic nasal pterygium

PSC - Posterior subcapsular cataract

MC - Molluscum contagiosum

AAU - Acute anterior uveitis

PPE - Papilloedema

AF - Anaemic Fundus

RD - Retinal Detachment

NV - Not visualized

SHH - Subhyaloid Haemmorhage

EK - Exposure keratopathy

LMN FP- Lower motor nerve Facial palsy

DE - Dry Eye

CRA - Chorioretinal Atrophy

GS - Glaucoma Suspect

KP - Keratic precipitates

PS - Posterior synechiae

EPPE - Established Papilloedema

F.CMVR- Fulminant Cytomegalovirus Retinitis

ANNEXURE V

MASTER CHART

Sl.no	Name	Age	Sex	Marital Status	Source	Education	Residency	Occupation	Duration of HIV	Systemic Illness	ART	Visual complaints	Vision(UCVA)		Anterior Segment		Posterior Segment		CD4 Count
													R	L	R	L	R	L	
1	Sangu	42	M	MR	TS	B.Ed	Rural	Teacher	ND	NIL	No	Mass in RE	No PL	6/ 12p	SCC of lid	N	NV	N	34
2	Basavaraj	28	M	MR	TS	4th Std	Rural	Farmer	1m	PTB	No	NIL	6/6	6/6	N	N	N	N	263
3	Sharanappa	45	M	MR	TS	SSLC	Rural	Farmer	2m	UTI	No	DOV for near	6/18p	6/12	N	N	N	N	171
4	Jettappa	45	M	MR	TS	7th Std	Rural	Driver	ND	PTB, FIA	No	NIL	6/18P	6/9	N	N	N	N	530
5	Gourawwa	60	F	MR	TS	UE	Rural	HW	10 y	AGE	Yes	NIL	6/36	6/24	IMC	IMC	N	N	94
6	Suvarna	26	F	MR	TS	UE	Rural	Farmer	14 d	AFI	No	Headache	6/6	6/6	N	N	N	N	529
7	Janabai	48	F	MR	TS	UE	Rural	Farmer	ND	Left PA	No	DOV	6/6	6/6	N	N	N	N	186
8	Madiwalawwa	55	F	MR	TS	UE	Rural	HW	1y	NIL	Yes	NIL	6/36	6/6	AAU	N	N	N	212
9	Ravi	43	M	MR	TS	BA	Rural	Goldsmith	2y	DM,AGE	Yes	DOV for near	6/6	6/6	AAB, IMC	AAB,IMC	N	N	336
10	Shivagangamma	22	F	MR	TS	7th Std	Rural	HW	2 y	Anaemia	Yes	DOV	6/6p	6/6p	N	N	Resolving Papillodema		326
11	Jayashree	28	F	MR	TS	II PUC	Rural	Clerck	15 d	AGE	No	NIL	6/6	6/6	N	N	N	N	380
12	Lalabi	36	F	MR	TS	UE	Rural	HW	ND	Cellulitis of Left LL	No	NIL	6/6p	6/6p	N	N	N	N	360
13	Basavaraj	34	M	MR	TS	SSLC	Rural	Driver	5m	PTB	Yes	NIL	6/6	6/6	Mebominitis	Mebominitis	N	N	49
14	Ramesh	32	M	MR	TS	II PUC	Rural	Mechanic	4Y	Prostatic Abscess	Yes	NIL	6/36	6/12	Mebominitis	Mebominitis	HIVR	N	149
15	Janatabi	55	F	MR	TS	UE	Rural	HW	7y	PTB	Yes	DOV in LE	6/6	CF1mt	PCIOL	PNT	N	N	412
16	Somappa	40	M	MR	TS	B.Com	Urban	LIC Agent	4y	Meningitis	Yes	Headache	6/36	6/36	AAB	AAB	N	N	567
17	Pavadeppa	50	M	MR	TS	SSLC	Urban	Farmer	4y	NIL	Yes	NIL	6/6	6/6	N	N	N	N	25
18	Muttappa	32	M	MR	TS	B.Ed	Rural	Labourer	1m	TBM	No	Headache	6/6	6/6	N	N	N	N	370
19	Hanamanthray	38	M	MR	TS	6th Std	Rural	Carpenter	3y	TBM	No	NIL	6/6	6/6	N	N	HIVR	HIVR	96
20	Chandrashekar	45	M	MR	TS	UE	Rural	Painter	2m	TBM	Yes	NIL	6/6	6/6	N	N	HIVR	HIVR	135
21	Mallikarjun	40	M	MR	IVD	7th std	Rural	Farmer	10y	AFI	No	DOV	6/12	6/12	N	N	N	N	64
22	Channappa	35	M	MR	TS	SSLC	Rural	Driver	3y	PTB	Yes	NIL	6/6	6/6	N	N	N	N	612
23	Umesh	41	M	MR	TS	BA	Rural	Farmer	2y	LRTI	No	DOV	6/6P	6/6	N	N	N	N	90
24	Chandrakanth	34	M	MR	TS	SSLC	Rural	Tailor	ND	NIL	No	Lesions over RE	6/9	6/6	HZO	N	N	N	134
25	Mandakini	38	F	MR	TS	4th Std	Rural	HW	1y	AGE	No	Headache	6/12p	6/9p	IMC	IMC	N	N	226
26	Kasappa	60	M	MR	TS	UE	Rural	Farmer	1y	PTB	No	NIL	6/12p	6/12p	N	N	N	N	122
27	Pawadappa	48	M	MR	TS	SSLC	Rural	Farmer	6y	AGE	Yes	NIL	6/9	6/9	N	N	N	N	25
28	Kalavathi	40	F	MR	TS	SSLC	Rural	Farmer	2y	NIL	Yes	DOV	6/12	6/6	Nystagmus	Nystagmus	N	N	24
29	Nanasaheb	30	M	MR	TS	II PUC	Rural	Teacher	3y	AFI	Yes	NIL	6/6	6/6	N	N	N	N	300
30	Mallamma	40	F	MR	TS	UE	Rural	Farmer	6m	LRTI	Yes	Headache	6/6	6/6	N	N	N	N	380
31	Mahadevi	35	F	UM	TS	UE	Rural	CSW	ND	LRTI	No	NIL	6/6	6/6	N	N	N	N	672
32	Sadashiva	30	M	MR	TS	II PUC	Rural	Farmer	1y	NIL	Yes	NIL	6/6	6/6	N	N	N	N	280
33	Ramlal	65	M	MR	TS	UE	Urban	Driver	3y	NIL	Yes	NIL	6/6	6/6	AAB	AAB	N	N	112
34	Mahantayya	35	M	MR	TS	UE	Rural	Farmer	2y	PTB	Yes	NIL	6/6 p	6/6p	N	N	N	N	780
35	Gangamma	32	F	MR	TS	3rd Std	Rural	Tailor	2d	NIL	No	NIL	6/6p	6/6p	PNT	PNT	N	N	168

36	Vittal Kumbar	55	M	MR	TS	UE	Rural	Labourer	2y	AGE	No	NIL	6/6	6/6	CO, IMC	IMC	N	N	212
37	Shivayya	38	M	MR	TS	BA	Rural	Farmer	2Y	PTB	Yes	DOV in LE	6/6	CF 1mt	N	N	N	CRA	416
38	Hanamanta	56	M	MR	TS	SSLC	Urban	Constable	9y	NIL	Yes	DOV for near	6/6	6/6	N	N	N	N	202
39	Sharanawwa	55	F	MR	TS	UE	Rural	Farmer	ND	NIL	No	DOV for near	6/6	6/18	Mebominitis	Mebominitis	N	N	297
40	Parubai	35	F	MR	TS	UE	Rural	Labourer	1y	AFI	Yes	Headache	6/6	6/6	N	N	N	N	80
41	Ashok Huseni	40	M	MR	TS	SSLC	Rural	Soldier	2m	CH	Yes	NIL	6/6	6/6	N	N	N	N	350
42	Mahadevi Manur	53	F	UM	TS	SSLC	Rural	CSW	ND	PTB	No	NIL	6/36	6/36	N	N	N	N	14
43	Siddawwa	35	F	MR	TS	UE	Rural	HW	2y	Hemiparesis	Yes	NIL	6/6	6/6	IMC	IMC	GS	GS	215
44	Chandrashekar	30	M	MR	TS	II PUC	Urban	Labourer	15d	CLD, OC	No	NIL	CF 6mt	CF 6mt	N	N	N	N	58
45	Siddu	30	M	MR	TS	Diploma	Rural	Secretary	5y	LRTI	Yes	NIL	6/6	6/6	N	N	N	N	412
46	Sangappa	30	M	UM	TS	UE	Urban	Farmer	ND	PTB	No	NIL	6/6	6/6	N	N	N	N	564
47	Saroja	18	F	UM	TS	3rd Std	Rural	UE	ND	M.Ret	No	NIL	Could not be tested	Could not be tested	N	N	N	N	276
48	Basavaraj Kallappa	35	M	MR	TS	II PUC	Rural	Driver	8y	PTB	Yes	NIL	6/6	6/6	AAB	AAB	N	N	85
49	Hanamanthraya	42	M	MR	TS,IVD	4th Std	Rural	Farmer	5m	NIL	Yes	DOV for near	6/6	6/6	N	N	N	N	142
50	Neelamma	35	F	MR	TS	UE	Urban	HW	ND	AFI, DM	No	NIL	6/6	6/6	N	N	N	N	96
51	Basavaraj Halasagi	40	M	MR	TS	UE	Rural	Farmer	ND	NIL	No	Headache	6/6	6/6	N	N	N	HIVR	152
52	Babu Nagappa	60	M	MR	TS	UE	Rural	Farmer	ND	AP	No	NIL	6/9	6/9	N	N	HIVR	HIVR	280
53	Sanju	28	M	MR	TS	8th Std	Rural	Goldsmith	5y	LRTI	Yes	NIL	6/6	6/6	N	N	N	N	450
54	Subhas Jadhav	56	M	MR	TS	II PUC	Rural	Farmer	1y	NIL	Yes	NIL	6/12p	6/12p	N	N	N	N	357
55	Shivaputrappa	32	M	MR	TS	UE	Rural	Farmer	8y	PTB	Yes	DOV in RE	CF 1mt	6/6	N	N	RD/VH	N	138
56	Shobha	28	F	MR	TS	II PUC	Urban	Counsellor	7y	PTB	Yes	NIL	6/6	6/6	Bening Conjunctival nevus	N	N	N	244
57	Sharada	30	F	MR	TS	7th Std	Urban	Weaver	6y	LRTI	Yes	NIL	6/6	6/6	N	N	N	N	258
58	Shankaremma	29	F	MR	TS	UE	Rural	HW	5y	PTB	Yes	Pricking in RE	6/6	6/6	PNT	N	N	N	1420
59	Savita	32	F	MR	TS	II PUC	Rural	SW	4Y	NIL	Yes	NIL	6/6	6/6	N	N	N	N	46
60	Sulabai	28	F	MR	TS	UE	Rural	Farmer	3y	NIL	Yes	NIL	6/6	6/6	N	N	N	N	386
61	Sumangala	30	F	MR	TS	3rd Std	Rural	Labourer	5y	PTB	Yes	NIL	6/6	6/6	N	N	N	N	179
62	Neelamma Kadakol	65	F	MR	TS	UE	Rural	HW	ND	COPD	No	NIL	6/36	6/18	IMC	PC-IOL	N	N	386
63	Shankaremma	50	F	MR	TS	UE	Rural	HW	3y	Nasal abscess	Yes	NIL	6/6	6/6	AAB	N	N	N	149
64	Smitha Parasu	25	F	MR	TS	UE	Rural	Tailor	ND	PRES , Anaemia	No	NIL	NC	NS	N	N	N	N	130
65	Gowrawwa Irappa	40	F	MR	TS	UE	Rural	HW	18 y	Meningitis	Yes	Headache	6/6	6/6	Esotropia 30	N	N	N	54
66	Gaibusab Mulla	45	M	MR	TS	UE	Rural	Farmer	ND	NIL	No	Pain, burning in RE	HM	6/6	**HZO ,6CNP**	N	N	N	336
67	Vittal Chandrappa	42	M	MR	TS	8th Std	Rural	Bussiness	1 1/2y	PTB	Yes	NIL	6/6	6/6	N	N	N	N	342
68	Siddappa Bhimappa	55	M	MR	TS	SSLC	Rural	Manager	ND	L foot cellulitis	No	NIL	6/24	CF 6mt	CO, IMC	PNT,IMC	N	N	576
69	Dundawwa	35	F	MR	TS	UE	Rural	HW	ND	ATB,AGE,Anaemia	No	NIL	6/18	6/18	N	N	N	N	312
70	Sahebgouda	30	M	MR	TS	UE	Rural	Farmer	2y	EPTB	No	NIL	6/9	6/9	N	N	N	N	510
71	Suresh	40	M	MR	TS	II PUC	Urban	Bussiness	ND	Acute LRTI	No	DOV for near	6/6	6/6	N	N	N	N	530
72	Sangamesh	32	M	MR	TS	SSLC	Urban	Electrician	1y	LRTI	Yes	DOV	6/6	6/6	N	N	N	N	162
73	Yallappa	35	M	MR	TS	UE	Rural	Carpenter	1m	TBM	No	NIL	6/6	6/6	N	N	Est PPE , HIVR	N	183

74	Basavantraya	61	M	MR	TS	UE	Rural	Farmer	8y	Anaemia	Yes	DOV	CF1mt	CF2mt	N	N	Resolving CMVR	44
75	Siddanagouda	41	M	MR	TS	B.Ed	Urban	Teacher	6m	Hemiparesis	Yes	NIL	6/6	6/6	N	N	N	N	74
76	Shivalinga	30	M	MR	TS	SSLC	Rural	Farmer	3m	PTB	Yes	DOV	6/18P	6/18P	ANT	N	N	N	174
77	Gollalappa	32	M	MR	TS	UE	Rural	Labourer	2m	CLD	Yes	NIL	6/12	6/6	N	N	CI	N	14
78	Sharanamma	35	F	MR	TS	UE	Rural	HW	ND	AGE	No	Headache	6/6	6/6	N	N	N	N	223
79	Satish Harijan	28	M	MR	TS	II PUC	Urban	Painter	5Y	TBM	No	NIL	NC	NC	N	N	N	HIVR	39
80	Renuka Madar	30	F	MR	TS	7th Std	Rural	Labourer	2Y	NIL	Yes	NIL	6/36P	6/60	IMC	IMC	N	N	54
81	Rukamabai	35	F	MR	TS	UE	Rural	Bussiness	ND	AGE	No	Pain in BE	6/6	6/6	N	N	N	N	385
82	Laxmi Gaddeppa	26	F	MR	TS	5th Std	Urban	Farmer	10 d	PTB	No	NIL	6/6	6/6	N	N	N	N	462
83	Gurulingappa	50	M	MR	TS	BA	Urban	Journalist	10y	Meningitis	Yes	Headache	6/36	6/60	N	N	Myopic ,Med n fibres		586
84	Sangawwa	50	F	MR	TS	UE	Rural	Farmer	ND	NIL	No	NIL	6/6	6/36	N	PSC	N	N	456
85	Laleetabai	48	F	MR	TS	UE	Rural	Scavenger	ND	NIL	No	NIL	6/6	6/6	N	N	N	N	492
86	Rukamavva	69	F	MR	TS	UE	Urban	HW	ND	?Typhoid	No	NIL	6/18	6/12	N	N	N	N	512
87	Jakawwa	40	F	MR	TS	UE	Rural	Farmer	ND	PTB	No	NIL	6/6	6/6	N	N	N	N	572
88	Ahmad	33	M	MR	TS	UE	Rural	Welder	7m	AGE	Yes	NIL	6/6	6/6	N	Pustules over lid	N	N	217
89	Shantabai	23	F	MR	TS	SSLC	Rural	HW	1 1/2 m	SJS	Yes	NIL	6/6	6/6P	N	N	HIVR		221
90	Danamma	44	F	MR	TS	II PUC	Urban	Attender	3y	PTB	Yes	NIL	6/6p	6/6p	N	MC	N	N	570
91	Gangabai	55	F	M	TS	UE	Urban	Labourer	5m	PTB	Yes	NIL	6/6	6/6	Pustules over lid	N	N	N	283
92	Chandrakanth	35	M	M	TS	UE	Rural	Labourer	8y	ATB	No	NIL	6/6	6/6	N	N	N	N	65
93	Dyamawwa Walikar	40	F	M	TS	UE	Rural	Labourer	6y	Pneumonia	Yes	DOV for near	6/24	6/36	Early PSC	Early PSC	N	N	42
94	Babugouda	48	M	M	TS	BA, B.Ed	Rural	Teacher	ND	NF Right LL	No	DOV	6/60	6/36	N	N	N	N	486
95	Ashok	30	M	M	TS	7th Std	Rural	Driver	ND	RTA	No	NIL	6/6	6/6	N	N	N	N	415
96	Chidanand	39	M	M	TS	II PUC	Urban	Bussiness	ND	Malaria	No	NIL	6/6	6/6	N	N	HIVR	N	218
97	Basavantraya	60	M	M	TS	UE	Urban	Farmer	6y	NIL	Yes	DOV	CF1mt	HM	N	AAU	N	CMVR	40
98	Chinnamma	40	F	M	TS	UE	Urban	HW	ND	PTB	No	NIL	6/24	6/18	N	N	N	N	338
99	Shantabai	30	F	M	TS	UE	Rural	Scavenger	6m	NIL	Yes	Headache	6/6	6/60	N	N	Established PPE		84
100	Suvarna	35	F	M	TS	SSLC	Urban	HW	1y	OPP	Yes	NIL	NC	NC	N	N	N	N	33
101	Siddram	55	M	M	IVD	3rd Std	Urban	Farmer	ND	NIL	No	DOV for near	6/18	6/18	N	N	HIVR	N	592
102	Suresh	30	M	M	IVD	3rd Std	Rural	Farmer	3m	HS	Yes	NIL	6/6	6/6	N	N	N	N	288
103	Uma Metri	27	F	M	TS	UE	Rural	Bussiness	3y	LRTI	Yes	NIL	6/6	6/6	N	N	N	N	257
104	Kamalabai	43	F	M	TS	5th Std	Urban	Labourer	6y	Anaemia	No	Redness	6/6	6/6	ANT	N	N	N	187
105	Parvati	40	F	M	TS	UE	Rural	Scavenger	ND	Anaemia	No	Headache	6/6P	6/18	AAB	AAB	HIVR/ AF		282
106	Bhimanagouda	38	M	M	TS	SSLC	Rural	Electrician	9y	PTB	Yes	DOV	PL+	No PL	PS,IMC,Hypotony	Pthisis , CO	RD	NV	128
107	Kamalabai	50	F	M	TS	UE	Rural	Farmer	2d	Anaemia	No	NIL	6/6	6/6	N	N	N	N	505
108	Nirmala	30	F	M	TS	UE	Rural	HW	3m	PTB ,AGE	Yes	DOV for near	6/6	6/6	N	N	HIVR	N	220
109	Sadashiv	40	M	M	TS	UE	Rural	Driver	5y	Meningitis	Yes	NIL	6/6	6/6	N	N	N	N	436
110	Amoghi	39	M	M	TS	7th Std	Rural	Farmer	2y	NIL	Yes	NIL	6/9	6/9	N	N	N	N	110
111	Parasappa	48	M	M	TS	UE	Rural	Mason	2m	PTB	Yes	NIL	6/18	6/18	N	N	N	N	153
112	Gurubai	30	F	M	TS	UE	Rural	HW	8m	NIL	Yes	Headache	6/36	6/60	N	N	HIVR with Est PPE		667
113	Sangamma	30	F	M	TS	UE	Rural	HW	ND	Hepatitis	No	NIL	6/18P	6/18P	N	N	Hypermetropic disc		652
114	Sangeeta	30	F	M	TS	SSLC	Rural	Tailor	ND	NIL	No	Itching , DOV	6/6	6/6	Mebominitis	Mebominitis	N	N	43
115	Saroja	35	F	M	TS	UE	Rural	Farmer	10y	NIL	Yes	NIL	6/6	6/6	N	N	N	N	350
116	Siddaramappa	66	M	M	IVD	SSLC	Rural	Farmer	ND	NIL	No	DOV	6/24	6/36	N	N	N	N	320

117	Yallappa	38	M	M	TS	UE	Rural	Mechanic	8y	AB	Yes	NIL	6/6	6/6	N	N	N	N	658
118	Gollal Halli	50	M	M	TS	4th Std	Rural	Farmer	3y	DIMPR	Yes	NIL	6/36	6/36	PC-IOL	PC-IOL	N	N	514
119	Renuka	18	F	M	TS	7th Std	Rural	HW	1 1/2 m	AFI	Yes	NIL	6/6	6/6	N	N	N	N	632
120	Bharathi	30	F	M	TS	2nd Std	Rural	HW	4y	Anaemia	Yes	NIL	6/6	6/6	N	N	HIVr	N	176
121	Raju Chauhan	30	M	UM	TS	UE	Rural	Labourer	ND	AA	No	NIL	6/6P	6/6P	N	N	N	N	482
122	Jiwaji Namadev	45	M	M	IVD	PUC,TCH	Rural	Teacher	5yr	Left LL #	No	DOV	6/6	6/6	N	N	N	N	336
123	Meghu	28	M	UM	IVD	UE	Rural	Farmer	12y	Anaemia	Yes	NIL	CF 3mt	CF3mt	N	N	HIVR, anaemic fundus		71
124	Shivanand	55	M	M	TS	B.Ed	Urban	Teacher	8y	left HP	Yes	DOV	6/6	6/6	N	N	N	N	47
125	Mahantesh	42	M	M	TS	D.Pharma	Rural	Bussiness	8y	PTB , AGE	Yes	NIL	6/6p	6/6p	N	N	N	N	95
126	Jayashree	25	F	M	TS	UE	Rural	Farmer	ND	AGE	No	NIL	6/6	6/6	N	N	N	N	614
127	Tanuja	24	F	M	TS	UE	Rural	HW	2y	PTB	Yes	NIL	6/6	6/6	N	N	N	N	99
128	Sanjaya	44	M	M	IVD, TS	Diploma	Urban	Bussiness	10y	PTB	Yes	NIL	6/6	6/6	N	N	N	N	277
129	Gudeppa	60	M	M	TS	UE	Rural	Farmer	1y	NIL	Yes	NIL	6/24	6/36	N	N	N	N	154
130	Yallappa	54	M	M	TS	II PUC	Urban	Constable	1 1/2y	LRTI	Yes	Black spots	6/9	6/6	N	N	HIVR	HIVR	270
131	Siddaramappa	53	M	M	TS	II PUC	Urban	AsstOfficer	3y	ALD	Yes	DOV	6/6	6/6	N	N	N	N	454
132	Bhuvaneshwari	36	F	M	TS	UE	Rural	HW	7d	CA	No	NIL	6/6	6/6	N	N	N	N	453
133	Ravi	44	M	UM	IVD	UE	Urban	Labourer	10m	NIL	Yes	NIL	6/6	6/6	N	N	N	N	662
134	Sharada	38	F	M	TS	UE	Urban	Farmer	3y	PTB	Yes	DOV	6/6	6/6	N	N	N	N	374
135	Sanjeevappa	70	M	M	TS	UE	Urban	Farmer	ND	Malaria	No	DOV	6/60	6/60	IMC	IMC	N	N	602
136	Badesab	40	M	M	TS	UE	Rural	Labourer	ND	AGE	No	NIL	6/6	6/6	N	N	N	N	456
137	Dareppa	40	M	M	TS	7th Std	Rural	Driver	ND	NIL	No	NIL	6/6p	6/6p	N	N	Grade IHtn retinopathy		386
138	Ningamma	40	F	M	TS	UE	Urban	HW	ND	PTB	No	NIL	6/6	6/6	N	N	N	N	512
139	Gangabai	40	F	M	TS	UE	Rural	Farmer	3m	NIL	No	NIL	6/6	6/6	Multiple papule in lids	N	N	N	135
140	Radhabai	50	F	M	TS	UE	Rural	HW	4y	PTB	Yes	NIL	6/12	6/6	CO	N	N	N	92
141	Appu	45	M	M	TS	5th Std	Rural	Mechanic	2y	ATB , PTB	Yes	DOV	6/60	6/60	N	N	F. CMVR	Early CMVR	80
142	Girija	35	F	UM	TS	8th Std	Rural	CSW	5m	UTI	No	DOV	6/6	6/6	N	N	N	N	429
143	Sangappa	35	M	M	TS	7th Std	Urban	Labourer	10 d	PLA	No	NIL	6/6	6/6	N	N	N	N	48
144	Yallappa	65	M	M	TS	4th Std	Rural	Bussiness	5y	NIL	Yes	DOV	6/60	6/60	IMC	IMC	N	N	193
145	Annapurna	58	F	M	TS	7th Std	Urban	HW	3y	HTN,Ana	Yes	NIL	6/36	6/60	PCIOL	IMC	Anaemic fundus		193
146	Bhagawwa	25	F	M	TS	UE	Rural	Scavenger	5m	AGE	Yes	NIL	6/6	6/6	N	N	N	N	99
147	Siddappa	35	M	M	TS	UE	Rural	Driver	10y	Haed	Yes	DOV	6/6	6/6	N	N	N	N	153
148	Megu Pawar	35	M	UM	IVD	UE	Rural	Farmer	12y	AGE	Yes	DOV	6/36	CF4mt	N	N	CMVR with AF		82
149	Lakshmibai	35	F	M	TS	UE	Rural	HW	8y	Anaemia	Yes	NIL	6/6	6/6	N	N	HIVR, AF		330
150	Noorjan	60	F	M	TS	UE	Rural	Farmer	ND	NIL	No	NIL	6/24	6/36	N	N	N	N	562
151	Shankaragouda	50	M	M	TS	UE	Urban	Farmer	1y	UTI	No	NIL	6/6	6/6	N	N	N	N	660
152	Nirmala Pattar	45	F	M	TS	UE	Urban	HW	1y	LRTI	No	DOV in LE	6/18	CF3mt	N	N	N	CMVR	46

ANNEXURE VI

COLOUR PLATES

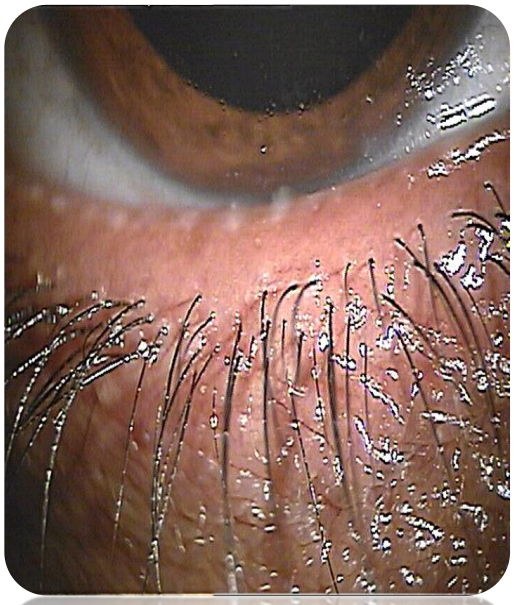

Fig.1.Mebominitis

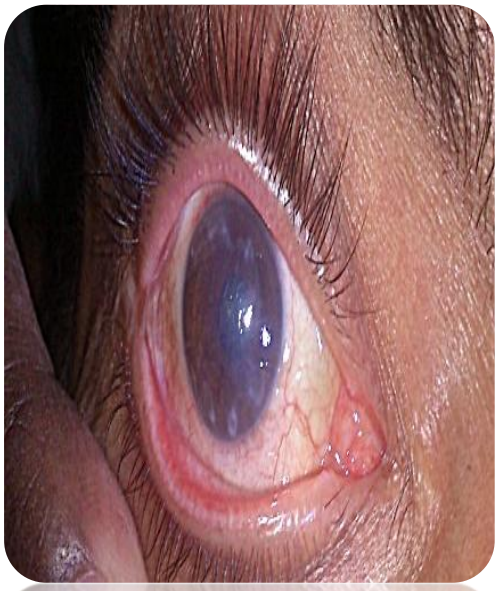

Figure 2.Right eye Corneal Opacity

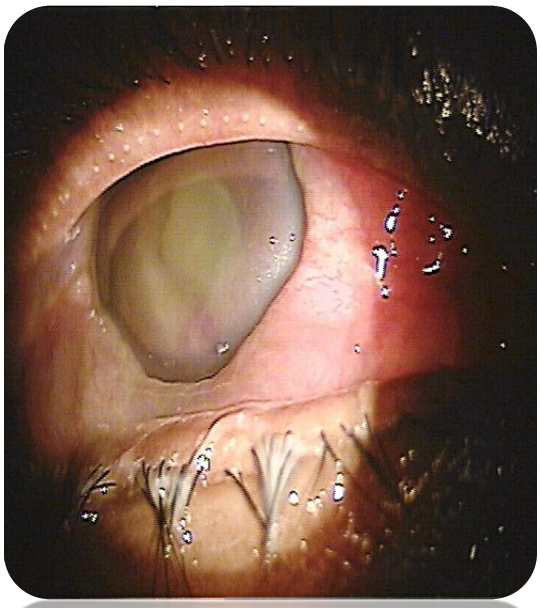

Fig 3.Right eye Acute anterior Uveitis

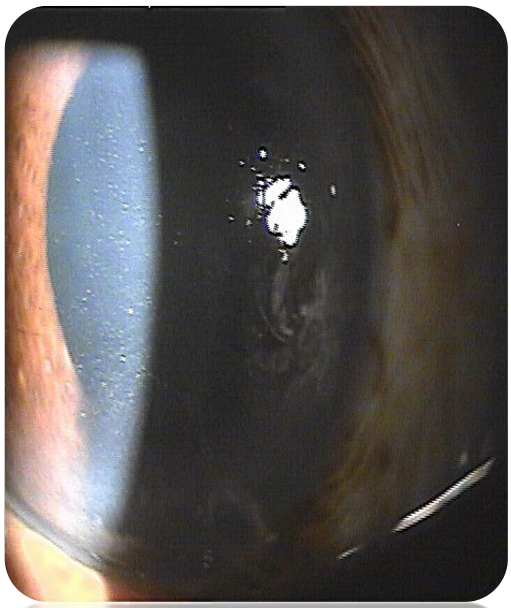

Fig 4.Slitlamp section showing keratic precipitates

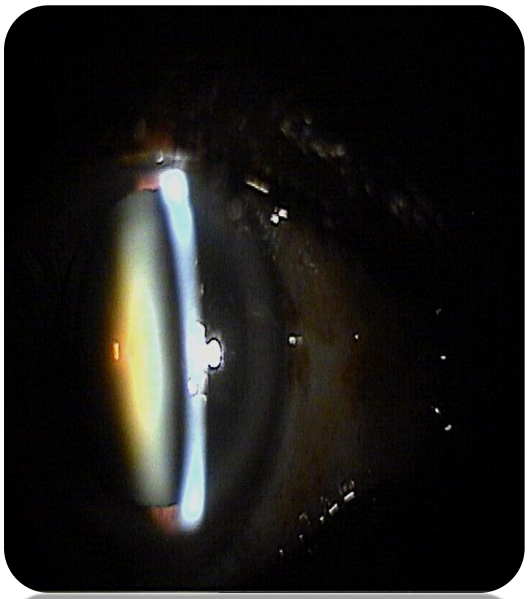

Fig 5. Slitlamp section showing immature cataract

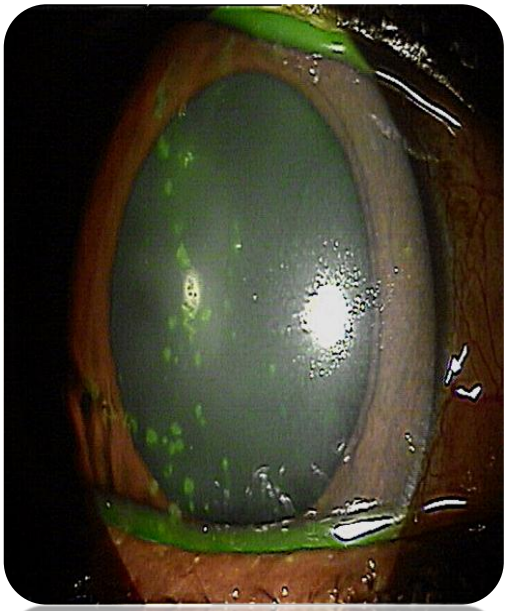

Fig 6. Punctate epithelial keratitis in a case of HZO

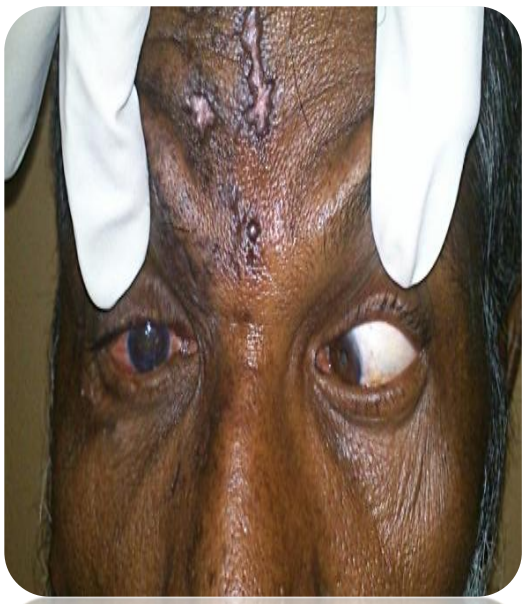

Fig 7.HZO with isolated 6th nerve palsy in Right Eye

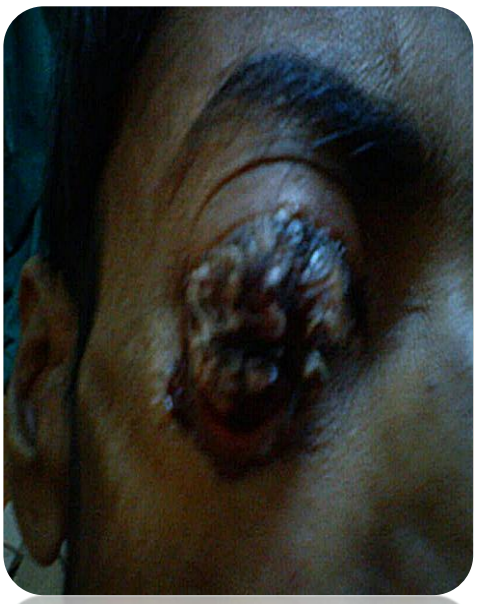

Fig 8.Squamous cell carcinoma of Right eye lid invading the orbit

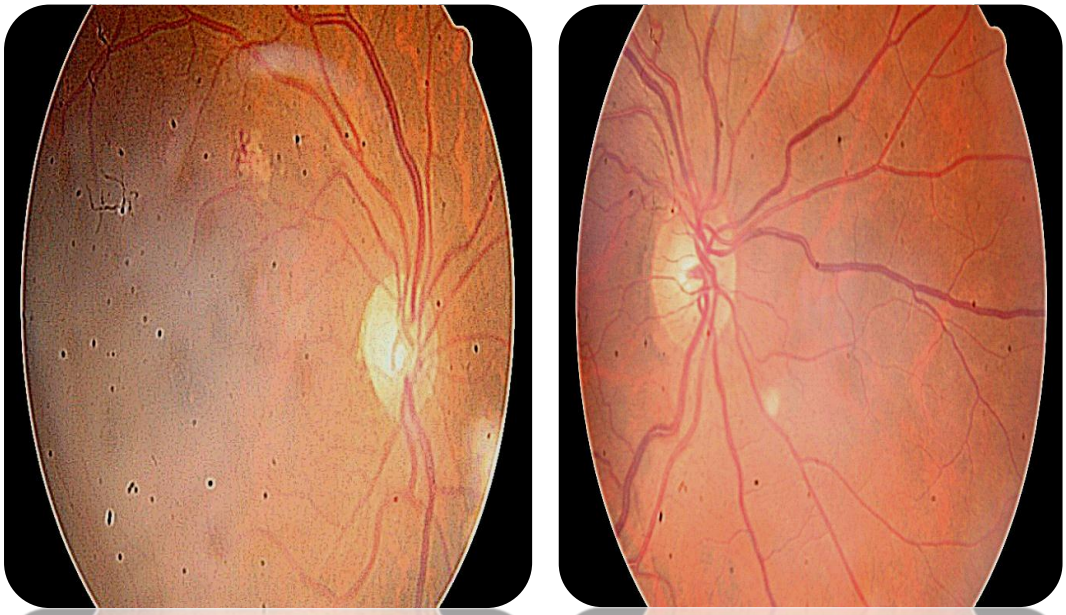

Fig 9 and 10. Fundus photograph showing HIV retinopathy

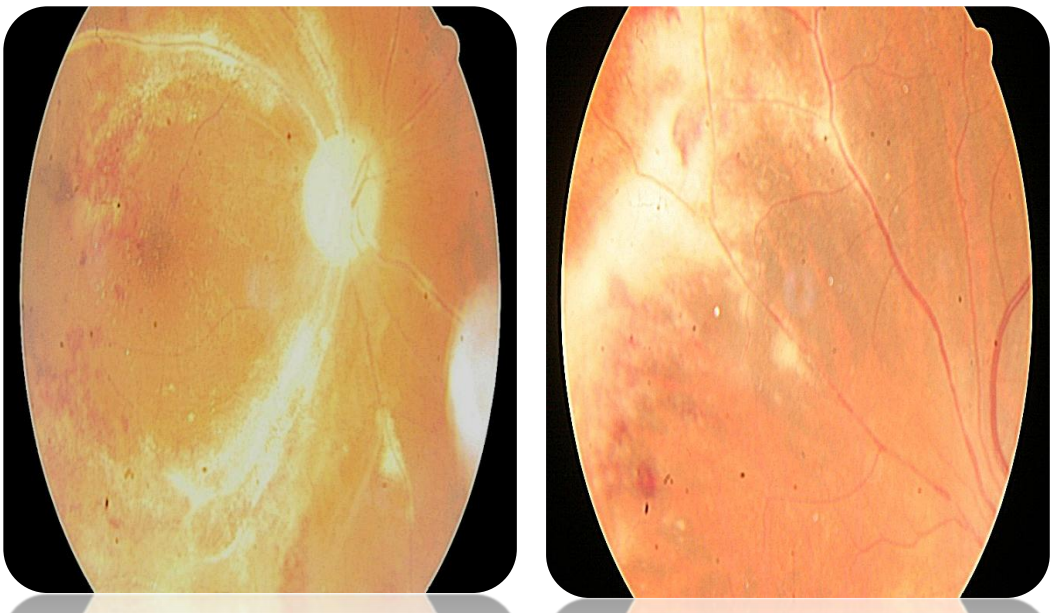

Fig 11 and 12.Fundus photograph showing CMV retinitis

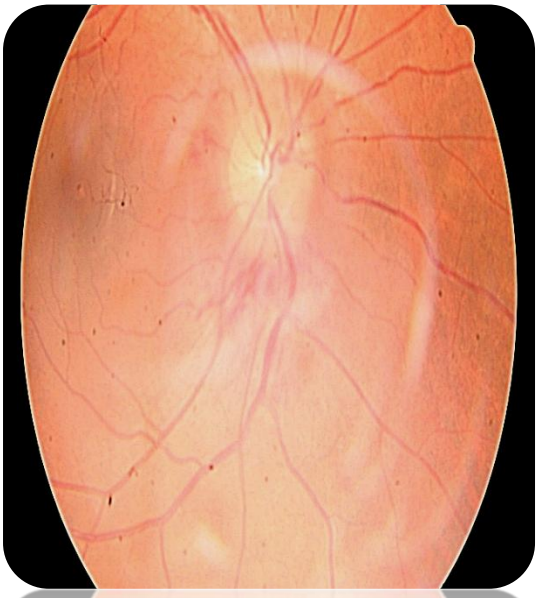

Fig 13.Fundus photograph showing established papilloedema

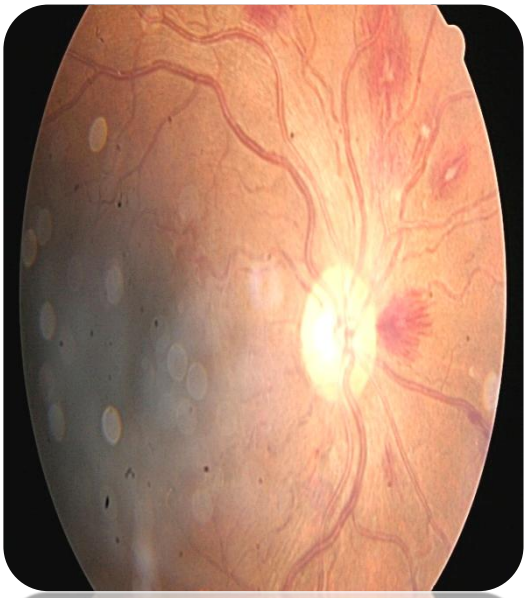

Fig 14.Fundus photograph showing Anaemic Retinopathy