



## A Review Study on Ocular Posterior Segments & Neuro-Ophthalmic Manifestations Associated with Human Immunodeficiency Virus (HIV) Infection and its Management Options

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**ABSTRACT:** To describe the various types of ocular posterior segment and neuro-ophthalmic manifestation associated with Human Immuno-deficiency virus (HIV) infection. And also describe the management or preventive measures associated with it. In all cases of ocular disease due to HIV, there is only one reason i.e. immune system.

A Descriptive study was done to review the articles available on PubMed, Google Scholar, Medline, Publon, Orcid, Healthstar, Science Open, Cochrane Library, Paperity and others related to the ocular complications associated with HIV infections. Peer-reviewed articles/ studies were referred to ascertain the available screening tests, preventive measures, hygiene, neuro-ophthalmic manifestation and management options for HIV patients. Some authors suggest that ocular posterior segment & neuro-ophthalmic manifestation due to HIV infection is not recovered, but few authors suggest that it can be recovered with the help of highly active antiretroviral therapy (HAART) in combination with some preventive measures and hygiene.

The Eye-care professional's responsibility is to spread awareness about the complications related to the eye and their management or preventive measures. Ocular complications are very diverse and relatively frequent in the case of HIV infection. Commonly it is associated with a concurrent diagnosis of depression, anxiety, panic, attack and psychiatric disorders, etc. There are various management or preventive measures like regular eye examinations, follow-up of the HIV patients, following the preventive measures strategies, taking therapy properly, preventing to spread of the infection, etc.

**KEYWORDS:** CMVR, HIV, Neuro-ophthalmic manifestation, Posterior segment, Visual impairment.

### INTRODUCTION

AIDS, or acquired immune deficiency syndrome, was initially identified in the US in 1981. Human immunodeficiency virus (HIV) was discovered in 1983, and by 1984 it had been conclusively proven to be the cause [1, 2]. The problem posed by HIV-AIDS is significant [3, 4]. All body organs are affected by the disease AIDS, which has a wide range of clinical symptoms. [5] HIV-AIDS also affects the eyes. In underdeveloped nations, 5–25% of all HIV-positive people may become blind at some point during their illness. [6] Patients with AIDS should be cautiously watched for symptoms of opportunistic ocular disease, which may initially be asymptomatic. Seventy percent of HIV-AIDS patients [7] have eye problems.

Numerous microorganisms, including viruses, bacteria, and fungus, which can cause eye disorders, can infect HIV-infected individuals. [8] Opportunistic infections arise as a result of a decline in the person's immune function, which can be assessed using CD4 cell counts. [9]

Pre-highly active antiretroviral treatment (HAART) period descriptions of ocular involvement were widespread, and many of them were categorized as AIDS-defining conditions. With the introduction of HAART, ocular lesions brought on by opportunistic infections (OI) are decreasing. Due to emerging symptoms including those caused by systemic medications, the pattern of occurrence of ocular lesions in people with HIV has changed as a result. [10-12]

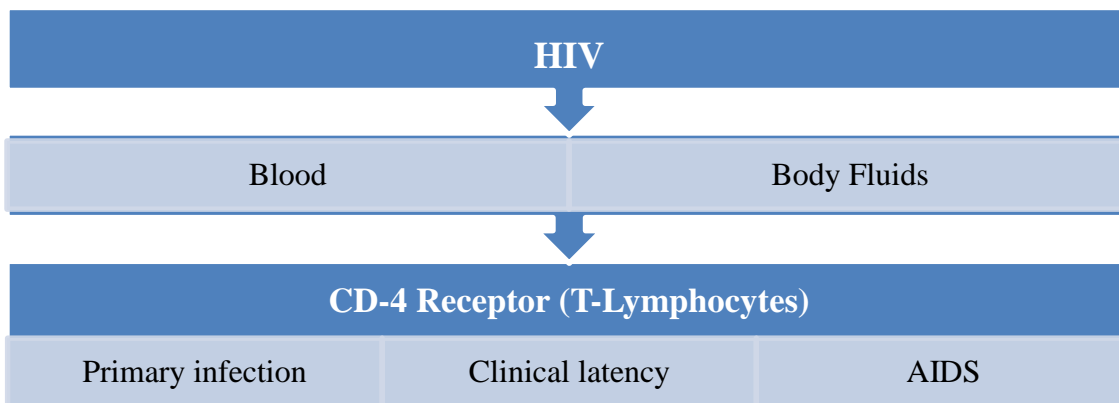


Fig 1: Etiology of HIV infection [13]

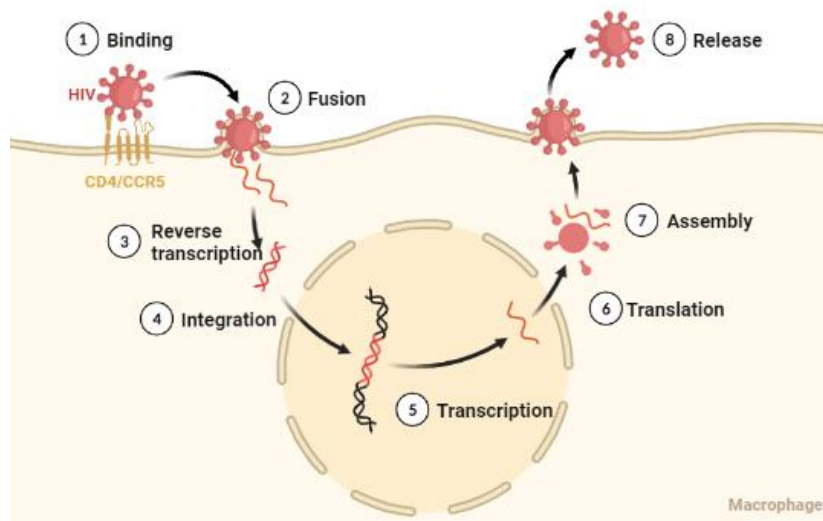


Fig 2: HIV Mechanism of Infection (Courtesy from web page)

**A. POSTERIOR SEGMENT MANIFESTATIONS**

**1. Cytomegalovirus Retinitis (CMVR)**

Even in the era of HAART, CMV retinitis (CMVR) continues to be the most frequent HIV/AIDS infection despite a marked drop in incidence. [14-16] Prior to HAART, it was responsible for 15% to 40% of ocular lesions in HIV. [15],[17] It was discovered to be the most frequently observed in 24.8 percent of 1000 patients from India in a large study. [17] Low CD4 levels are the main risk factor for CMVR in AIDS. Even with moderate CD4 numbers, there have only been a few instances of CMVR; nevertheless, CMVR is not prevalent if CD4 counts are greater than 100 cells/mm<sup>3</sup>. Specific interleukin 10 receptor (IL 10R1) haplotypes and chemokine receptor 5 haplotypes are examples of genetic risk factors (CCR5). [18-20]

The mainstay of treatment is to restore the patient's immunological status using HAART, which should always be utilised because it lowers the risk of vision loss, retinal detachment, involvement of the second eye, and mortality. [20-25]

The traditional suggested regimen [Table 1] provides for 2-3 weeks of intravenous ganciclovir induction therapy, followed by a maintenance dosage. Since oral Valganciclovir, a prodrug with strong oral bioavailability, is equally efficacious, it has replaced hospitalisation and the hazards associated with indwelling catheters as the preferred first line of treatment.

Primary vitrectomy with higher viscosity silicone oil tamponade is the preferred course of treatment (5000 cs). [22],[26-27] One of the key reasons why silicone oil is typically preferred over gas tamponade in most situations is the inability to seal the numerous



posteriorly situated holes. IRU can occasionally lead to proliferative vitreoretinopathy (PVR), which has excessive inflammation and greater chances of recurrent RD, despite the clear benefits of immunological recovery. [27]

## 2. Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN)

Both VZV and HSV are responsible for this severe, sight-threatening, rapidly progressing necrotizing retinitis. The clinical diagnosis is made. ARN typically manifests as circumferentially spreading peripheral confluent lesions. [28] When progressive outer retinal necrosis (PORN) first manifests, the outer retina appears to be whitening (cracked mud appearance). [29]

While it typically either doesn't exist or is only very minimally present in progressive outer retinal necrosis, vitritis is typically severe in ARN. The latter frequently happens in patients with immunosuppressed states and low CD4 levels. Necrotizing herpetic retinopathies with recognisable well-defined, multifocal, consolidating, deep or full thickness regions of primarily posterior retinal necrosis are among the most frequent appearances. [30]

Macula-threatening lesions necessitate vigorous systemic acyclovir or valacyclovir therapy along with additional intravitreal antivirals.

It has been demonstrated that oral valacyclovir achieves a bioavailability of between 50% and 65% at the prescribed dose, which is comparable to intravenous acyclovir.

[28] Higher doses to boost bioavailability should be avoided since they carry a risk of systemic adverse effects. Systemic steroids at low doses should be used with caution to treat vitritis and prevent retinal detachment from inflammation.

## 3. Ocular toxoplasmosis (OT)

Ocular toxoplasmosis in people with HIV is typically of the acquired variety, and reactivation occurs more frequently than not. [31-32] According to an Indian study, 2.8 percent of patients had ocular toxoplasmosis, the second most frequent ocular infection. [17] HIV-positive people who have atypical toxoplasmosis may experience localised, multifocal, or diffuse necrotizing retinitis with ill-defined borders and haemorrhages or without them. Additionally, they might exhibit active retinochoroiditis close to a retino-choroidal scar.

It is more likely that a toxoplasmic infection caused the nearby retinal vasculitis (Kyrieleis' arteriolitis) and varied degrees of vitreal inflammation (mild to extensive) in the presence of low CD4+ T cell numbers. Toxoplasmic chorioretinitis has the potential to become fulminant and can mimic CMVR as well as other ocular OIs including syphilis. In most cases, early diagnosis and treatment gives satisfactory results.

The most commonly used treatment plan combines clindamycin with/without pyrimethamine and sulfadiazine. Another medication is azithromycin. Oral corticosteroids, which should only be taken in conjunction with antiprotozoal medications, can reduce inflammation, but their usage should be cautious due to the clear systemic hazards of further lowering host immunity, which exceed their advantages. [33] In addition to systemic therapy, intravitreal clindamycin is beneficial and shows promise, particularly in aggressive OT. [34-36]

## 4. Ocular Tuberculosis

In India, Asia, and Latin America, tuberculosis (TB) is still endemic. According to studies from India, [37] OTB, which manifests as choroidal trabeculae, sub retinal abscess, conjunctival tuberculosis, and panophthalmitis, was observed in 3.8% of HIV patients in the pre-HAART era. [38]

Ocular TB could be a sign of a miliary disease or be considered a component of a widespread systemic illness. Typically, they are discovered during a regular ocular examination as asymptomatic choroidal tubercles. The ocular course does not usually match the course of the systemic disease, and they can happen in all CD4 count levels. [17],[37]

Along with HAART, systemic antitubercular therapy (ATT) is the preferred course of treatment. [39-40] MDR TB is potentially 10 times more common in HIV positive patients than HIV negative people. [41] Patients with HIV infection require more sophisticated management of MDR TB. [42-44]

## 5. Ocular syphilis

It has experienced a revival, particularly in cases of HIV co-infection among people at high risk for it, such as sex workers and men who have sex with males (MSM). [45-46] It is known as "the great imitator" since it can imitate any uveitic organism. Anterior



uveitis, severe vitritis, diffuse retinitis, placoid chorioretinitis, panuveitis, and optic neuropathy are examples of clinical characteristics.

A strong index of suspicion is required to identify the illness because of its numerous and unpredictable presentations. After ruling out other known ocular opportunistic infections, the diagnosis is made based on the presence of suspicious clinical symptoms and a positive serology. Treponemal and serum non-treponemal (VDRL, RPR) tests are the mainstays of diagnostic procedures (FTA ABS, TPHA). [47] Due to varying sensitivity and specificity, PCR of ocular fluids for diagnosis of ocular syphilis has limited utility.[47-48] In penicillin allergy, ceftriaxone or doxycycline can be used as an alternative treatment.[31]

## B. NEURO-OPHTHALMIC MANIFESTATIONS

Only 6% of AIDS patients experience neuro-ophthalmologic abnormalities, which typically indicate infection or cancer of the brain or meninges. Perineuritis, papilledema, papillitis, retrobulbar neuritis, and optic atrophy are examples of clinically evident anomalies of the optic nerve in an AIDS patient. [49]

Patients may complain of headaches, double vision, hazy or lost eyesight, or difficulties reading. According to an Indian study, disc edema (21.97%) and optic neuritis (14.28%) were the most prevalent conditions, followed by cranial nerve palsies (9.89%) and retrobulbar neuritis (49.45%). (2.19 percent). [17]

Cryptococcosis, toxoplasmosis, CMV, syphilis, herpes, and tuberculosis are the most typical concomitant illnesses. [50] Clinical evaluation may indicate retinal alterations, cranial nerve palsies, papilledema or optic atrophy, pupillary abnormalities such as anisocoria and light near dissociation, and visual field defects. [50] The most frequent cause of papilledema in HIV-positive people is meningitis, which is caused by *Cryptococcus*. Disseminated illness may manifest as multifocal choroiditis. [50] There have been a few isolated reports of zidovudine-induced anaemia leading to papilledema from idiopathic intracranial hypertension (IIH). [51-52]

In immunocompetent people, cat scratch disease (CSD), which is brought on by *Bartonella hensela*, manifests as a neural retinitis-like symptom. Patients who are HIV positive display different symptoms, such as vascular abnormalities and aberrant vascular network formations, among others. [53] Systemic doxycycline for 3–4 weeks leads to complete resolution.

### 1. Retinal toxicity and optic neuropathy

Didanosine, which has been discontinued from HAART regimens in the majority of nations, has been linked to reports of retinal toxicity[54]. There have also been reports of maculopathy linked to ritonavir and efavirenz. [55-56] Ethambutol, linezolid, and the relatively new medication combination of elvitegravir/cobicistat have all been linked to reports of optic neuropathy. [57]

### 2. Choroiditis

#### 2.1 Pneumocystis

*P. carinii* can cause conjunctivitis, orbital masses, optic neuropathy, and choroiditis in the eyes. [58] It is typically observed as bilateral and multifocal, well-defined yellow choroidal lesions in the posterior pole that are not connected to vitritis, iritis, or vasculitis. [59] Induction and subsequent maintenance therapy with systemic pentamidine, trimethoprim and sulfamethoxazole, or dapsone are effective in treating ocular lesions in the majority of cases.

#### 2.2 Cryptococcus

The most frequent cause of AIDS-related neuro-ophthalmologic lesions is *cryptococcus meningitis*. In addition to being linked with eyelid nodules, conjunctival masses, granulomatous iritis, iris masses, vitritis, necrotizing retinitis, endophthalmitis, and optic neuritis, cryptococcal choroiditis can also be multifocal, solitary, or confluent. [60] Even in the era of HAART, 200 mg/day of fluconazole maintenance medication is currently advised for all patients.

### 3. Meningitis

HIV-associated meningitis can develop as a result of viral infections, but it can also manifest as papilledema, neuritis, or direct involvement of the optic nerve with neuropathy or increased intracranial pressure. [61-65] *Cryptococcus* and tuberculosis were shown to be the causes of infectious meningitis in sub-Saharan Africa in 19–68% and 1-36% of cases, respectively. [66] Initial diagnoses of bacterial meningitis were made in 1.6 percent of cases, but subsequent molecular and microbiological analyses indicated tuberculosis in 2.5 percent of cases, neurosyphilis in 2.6 percent, toxoplasma in less than 1 percent, and viral aetiology in a small number of other cases.



In people with HIV, Cryptococcus is the most frequent cause of meningitis, and it can cause optic neuropathy either directly or indirectly. [65],[67-69] Up to 75% of patients with cryptococcal meningitis have intracranial hypertension, which can subsequently result in optic disc oedema.

Due to the fact that both the infection and the intracranial pressure need to be treated, the initial course of treatment frequently entails antifungal therapy coupled with pressure-lowering techniques utilising transient lumbar drains or shunts.

Common ophthalmic symptoms were nystagmus or impaired smooth pursuit in 26% and 22% of patients, respectively, as well as optic disc edema in almost 30% of cases and cranial nerve palsy in 17% of patients. Both pain during eye movement and acute vision loss only occasionally happened. [70-71]

#### 4. Retinal Microangiopathy and Neuroretinal Disorder

For individuals with a differential diagnosis of visual loss due to optic nerve or retinal involvement, neuro-ophthalmic examination is often advised. Patients at risk for infectious diseases that damage the retina and choroid include those that are less prevalent, such as cryptococcosis, tuberculosis, pneumocystis, and syphilis, as well as cytomegalovirus (CMV), herpesvirus, and toxoplasmosis. [72]

These infectious choroiditis/retinitis patients frequently have spectacular physical findings and are evaluated by retinal and uveitis experts rather than being referred for neuro-ophthalmic research. HIV infection, however, also causes microvascular abnormalities that damage the retina, optic disc, and cornea, as well as a neuroretinal condition where the layer of retinal nerve fibres is thinned. [73-78]

Indirect HIV infection of the neuroretinal tissue, chronic immunological activation, microvascular ischemia, accelerated ageing brought on by HIV infection, and chronic immune activation are all possible secondary causes of neuroretinal disease. [79-80] The neuroretinal condition is more likely to develop in HIV individuals who have more severe or advanced disease.

Lower CD4 + T cell numbers also have some association. These patients' eyesight loss will be minimal to moderate, and their contrast sensitivity will be diminished. [81] The multifocal electroretinogram (mERG) and the pattern electroretinogram (pERG) both show abnormalities. [82]

#### 5. Eye Movement Abnormality

With HIV, abnormal eye movements are known to happen. [83-85] The most frequent abnormalities found to happen even in persons without additional clinical signs of HIV infection are abnormal smooth pursuits and saccades. [86]

HIV infection has also been linked to cranial nerve palsies, though the prevalence varies depending on the community.

[83] The sixth and third cranial nerves have the highest frequency of palsies. The third nerve and sixth nerve were damaged alone or in combination, and the patients frequently reported headache, diplopia, and impaired vision. [87]

#### 6. Pupil Involvement

Lesions infiltrating the brainstem may be the source of pupillary abnormalities in HIV infection. Anisocoria and light near dissociation are examples of these. Researchers have also discovered that patients with HIV had irregular pupil cycle times, which may indicate subclinical ocular autonomic dysfunction. [88]

Anywhere along the sympathetic chain may have lesions, which can cause Horner's syndrome. The Argyll Robertson pupil, a classic example of neurosyphilis, is characterised by uneven, small-sized pupils and light-near dissociation. Despite the fact that dorsal midbrain syndrome can present with light-near dissociation, this observation is extremely specific for syphilis.

#### HIV PREVENTION

Since proper use of condoms should entirely prevent HIV transmission as well as transmission of many other sexually transmitted infections, condom use has been a cornerstone of HIV prevention in men. However, the efficiency of condoms has been estimated to be about 80% against heterosexual HIV transmission and 70% against male-to-male sexual transmission [18-19]. These lower than anticipated effectiveness estimates are likely caused by over-reporting of condom use; however incorrect use and condom failure also have an impact. [20] While syringe exchange programmes have not completely stopped HIV transmission in drug users, supplying clean injection equipment can significantly lower HIV transmission in injectable drug users [21]. To supplement these fundamental preventative techniques, more tools are required.

1. Prevention of mother-to-child transmission.



2. Medical circumcision.
3. Treatment as prevention.
4. Pre-exposure prophylaxis
5. Post-exposure prophylaxis
6. HIV vaccine.
7. Combination prevention.

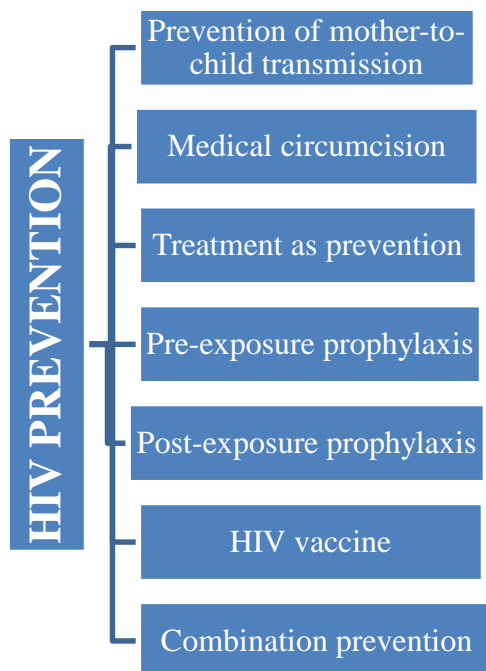


Fig 3: HIV Prevention

Table 1: Recommended treatment guidelines for major opportunistic infections

Opportunistic infection	Recommended treatment regime	Alternate regime	Adverse effects/Remarks
CMVR [24]	Induction Intravenous Ganciclovir: 5 mg/kg twice daily for 14-21 days; Or Oral Valganciclovir – 900 mg twice daily Maintenance IV Ganciclovir – 5 mg/kg/day to continue or Oral Valganciclovir – 900 mg once daily to continue Intravitreal Ganciclovir Induction - 2 mg/0.1 mL – twice weekly Maintenance - 2 mg/0.1 mL weekly	Induction Foscarnet (IV): -90 mg/kg twice daily for 14 days Cidofovir (IV): -5 mg/kg weekly for 3 weeks Maintenance Focarnet - 120 mg/kg/day; Cidofovir - 5 mg/kg every 2 weeks Intravitreal Induction Foscarnet: 1.2-2.4 mg 1-2 times weekly Cidofovir: 20 µg 1-8 times as needed to halt retinitis Maintenance Foscarnet - 1.2 mg Weekly OR Cidofovir 20 µg every 5-6 weeks	Ganciclovir/Valganciclovir Myelosuppression Foscarnet- Nephrotoxicity Electrolyte disturbance Nausea and vomiting Cidofovir-nephrotoxicity (Probenecid coadministration for prevention) Intravitreal cidofovir- anterior uveitis and hypotony CMV mutations in UL54 or UL97 genes cause ganciclovir resistance
ARN/PORN [24], [28]	Induction Intravenous Acyclovir: -500 mg 8th hourly for 2 to 3 weeks; Maintenance Oral Acyclovir- 800 mg 5 times daily (15 mg/kg in three divided doses) for 6 weeks		Nephrotoxicity



	to 3 months. OR Oral Valacyclovir: 1 gram three times daily		
Ocular toxoplasmosis [33]	1) Pyrimethamine- 200 mg on the first day, followed by 75-100 mg daily 2) Sulfadiazine- 1-1.5 g four times daily, and 3) Folinic acid-10-50 mg daily With/or (in sulpha allergy) Oral Clindamycin-300 mg 4 times a day for 6 weeks	Atovaquone, Azithromycin	Myelosuppression Leucopenia, Pseudomembranous colitis
Ocular TB [37-38]	New: (never had treatment or less than 1 month of ATT) - New* - 2H7 R7 Z7 E7 . + 4H7 R7 E7 Previously Treated: (one month or more of ATT) - 2 H7 R7 Z7 E7 S7 +1 H7 R7 Z7 E7 +5 H7 R7 E7	MDR TB: Aminoglycosides (Kanamycin, Amikacin), Fluoroquinolones (Ofloxacin, Levofloxacin), Linezolid, Bedaquiline	Hepatotoxicity Peripheral neuropathy Optic neuropathy
Ocular Syphilis [31]	Aqueous crystalline penicillin G: 18-24 million units/day, administered as 3-4 million units IV every 4 hours or continuous infusion for 10-14 days	Procaine penicillin G: 2.4 million units IM/day PLUS probenecid 500 mg orally four times a day, both for 10-14 day Penicillin allergy: Ceftriaxone two grams daily either intramuscularly or intravenously for 10 to 14 days OR Doxycycline 100 mg orally twice daily for 14 days	Jarisch-Herxheimer reaction in ocular syphilis with worsening of signs with treatment

[CMVR=Cytomegalovirus retinitis, CMV=Cytomegalovirus, ARN=Acute retinal necrosis, PORN=Progressive outer retinal necrosis, IV=Intravenous, IM=Intramuscular, TB=Tuberculosis, ATT=Anti-tubercular treatment, H=Isoniazid, R=Rifampicin, Z=Pyrazinamide, E=Ethambutol, S=Streptomycin, MDR=TB multidrug resistant tuberculosis, \*Never had treatment or less than 1 month of ATT ]

**MANAGEMENT/TREATMENT OF OCULAR COMPLICATIONS**

The management of ocular AIDS complications is challenging. Since the majority of ocular opportunistic infections cannot be completely eliminated, lifelong suppressive medication is required for their care. Patients who have had their endogenous immunity restored as a result of HARRT are an exception. [22]

Depending on the patient's immunological status and the site of the active retinitis, CMV retinitis is treated on an individual basis. The FDA has authorized 7 medications to treat CMV retinitis. Oral and injectable treatments for the system include ganciclovir sodium, foscarnet sodium, and cidofovir (ganciclovir and valganciclovir). [22-23]

**Systemic Therapy - Highly Active Anti-Retroviral Therapy (HAART)**

In India, NACO offers free HAART to everyone living with HIV. HAART guarantees that those who are ill will live longer and have higher quality of life. [33] With HAART, HIV patients can now live a life that is more similar to that of people with chronic conditions like diabetes or high blood pressure. Table 2 summarizes major anti-retroviral medication types and their mechanisms of action.



**Table 2: Highly active anti-retroviral drugs and treatment schedule as per NACO guidelines [33]**

NRTI	NNRTI	FI	PI	INI (new)
Zidovudine (AZT/ZDV)*	Nevirapine* (NVP)	Enfuvirtide (T-20)	Saquinavir* (SQV)	Elvitegravir
Stavudine (d4T)*	Efavirenz*(EFV)		Ritonavir* (RTV)	Raltegravir CCR5
Lamivudine (3TC)*	Delavirdine (DLV)		Nelfinavir* (NFV)	Entry Inhibitor (new)
Didanosine (ddl)*			Amprenavir (APV)	
Zalcitabine (ddC)*			Indinavir* (INV)	
Abacavir (ABC)*			Lopinavir/Ritonavir (LPV)*	
Emtricitabine (FTC)			Fosamprenavir (FPV)	
(NtRTI) Tenofovir (TDF)*			Atazanavir (ATV)*	
Current National program - Fixed drug combinations			Tipranavir (TPV)	
(i) Stavudine (30 mg) + lamivudine (150 mg)				
(ii) Zidovudine (300 mg) + lamivudine (150 mg)				
(iii) Stavudine (30 mg) + lamivudine (150 mg) + nevirapine (200 mg) (iv)				
Zidovudine (300 mg) + lamivudine (150 mg) + nevirapine (200 mg) (v)				
Efavirenz (600 mg) (vi) Nevirapine (200 mg)				
<ul style="list-style-type: none"> <li>▪ First choice: AZT + 3TC + NVP (for patients with Hb &gt;8 g/dL)<sup>1</sup></li> <li>▪ Second choice: d4T + 3TC + NVP</li> </ul>				

[NRTI: Nucleoside reverse transcriptase inhibitors, NNRTI: Non-nucleoside reverse transcriptase inhibitors, FI: Fusion inhibitors, PI: Protease inhibitors, INI: Integrase Inhibitors, \*Available in India. <sup>1</sup>Substitute NVP with EFV, for patients with TB or toxicity to NVP]

**CONCLUSION**

Ocular manifestations associated with HIV infection range greatly in kind and are very common. One of the essential treatments for HIV-positive people is routine follow up for ocular examination. Its main goal is to stop the progression of visual loss. Additionally, it permits indirect monitoring of the effectiveness of therapy, any relevant development of resistance, and patient compliance as well as long-term compensation of the immunological status of HIV-positive patients.

Ocular problems may be the first clinical sign of HIV infection in some people, indicating HIV positivity. The prevalence of sight-threatening CMV retinitis, which, despite aggressive treatment, remains the most common cause of blindness in HIV positive people, has significantly decreased as a result of the prevention of opportunistic infections and the development of highly efficient ART.

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