Abstract

Cytomegalovirus (CMV) retinitis is a condition of full-thickness retinal necrosis and edema that results in thin atrophic retinal scar tissue. The condition results from a reactivation of CMV, a member of the herpetic virus family, when an individual is immunocompromised, for example, due to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). CMV retinitis is the most common serious ocular complication of AIDS. Early and appropriate diagnosis and effective management are crucial. This teaching case report highlights the role of the primary care optometrist in the diagnosis and management of a patient with CMV retinitis. This case specifically examines the challenges involved in the diagnosis and management of CMV retinitis during the antiretroviral therapy (ART) era, managing and educating patients with HIV in a community health center setting, handling socially difficult questions and conversations with patients, and the critical-thinking skills needed for appropriate patient management.

Key Words: cytomegalovirus, retinitis, HIV/AIDS, ART, primary care, optometrist

Background

This case involves a 37-year-old Hispanic male who was diagnosed with cytomegalovirus (CMV) retinitis because of poorly controlled human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). CMV retinitis is a full-thickness retinal necrosis resulting from reactivation of CMV, which is a common virus in humans and a member of the herpetic virus family. The virus manifests itself in the retina when a patient is immunocompromised from a disease such as HIV/AIDS. CMV retinitis is usually a unilateral disease but when left untreated can involve the fellow eye.

This teaching case report highlights the role of the primary care optometrist in the diagnosis and management of a patient with CMV retinitis while focusing on the importance of critical-thinking skills for accurate diagnosis and effective patient education. The current medical landscape for managing and treating HIV/AIDS is much different compared with 30 years ago because of the prevalence and use of antiretroviral medications. When antiretroviral medications are used in combination with one another, it is referred to as antiretroviral therapy (ART). ART has led to lower incidence rates of CMV, but timely diagnosis and management are still important for the primary care optometrist.

This case is appropriate for use with students who have a moderate level of patient care experience and knowledge in ocular disease. At most colleges, it would be appropriate for fourth-year optometry students and resident candidates.

Case Description

Patient HR, a 37-year-old Hispanic male, presented to a community health center eye clinic for a red-eye problem. He had been discharged recently after a 3-week hospital stay with instructions to establish eye care at the health center. HR reported redness and blurry vision in both eyes as his chief complaint. He stated that he drives a car for work and was having difficulty seeing while driving. HR stated that while in the hospital he was examined by an on-call eye doctor who told him that he had an infection inside his eye and needed to take medication for the infection. HR also said he had noticed floaters in both eyes but had not noticed flashes or a shadow over his side vision. HR was new to the eye clinic and denied any history of spectacle lens wear. He denied any previous ocular conditions and did not know when his eyes were last examined.

HR’s medical history and systemic health were positive for several conditions. Hospital notes were acquired and indicated the patient was being treated for pneumonia with presumed tuberculosis. A 2-week course of rifampin, isoniazid, pyrazinamide and ethambutol had been initiated and completed while he was in the hospital. HR tested positive for HIV. Laboratory results showed a CD4 count of 1 cell/µL and a viral load of 584,000 copies/mL. These markers confirmed that HIV had led to AIDS and confirmed the presence of an opportunistic infection from CMV. HR was started on valganciclovir 900 mg orally every 12 hours to treat the CMV infection. ART for the HIV had not been initiated because of the opportunistic infection. The patient was also taking glipizide 10 mg and lisinopril 5 mg daily to control diabetes mellitus type II and hypertension, respectively.

Uncorrected distance visual acuity measured 20/40 in each eye, and uncorrected near visual acuity measured 20/25 in
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Each eye. Pupils and extraocular muscles were normal. Finger-counting confrontation fields were full in the right eye but restricted in the nasal quadrant of the left eye. Intraocular pressure was 16 mmHg in each eye. See Table 1 for slit lamp findings and Figure 1 for fundus photographs.

HR was diagnosed with CMV retinitis in both eyes with active retinitis and retinal necrosis, left eye worse than right eye. He was shown his fundus photographs and educated about the seriousness of his conditions, which were life- and sight-threatening. HR was taken by ambulance to the ophthalmology department at a local eye hospital for immediate consultation.

Figure 1. Fundus photographs of the right eye and left eye at the initial visit. Click to enlarge

Visit 2: same-day ophthalmology consult

At this visit, the diagnosis of CMV retinitis, left eye worse than right eye, was confirmed. HR received a 2-mg intravitreal injection of ganciclovir in the left eye based on the extent of the retinitis and proximity to the optic nerve. No injection was given in the right eye based on the extent and location of the retinitis. Topical prednisolone acetate was prescribed to be used four times per day in each eye. The patient was advised to accept admittance to the hospital for intravenous treatment and close monitoring, but he refused. Oral valganciclovir 900 mg twice a day was to be continued and he was to return in 3 days for further consultation.

Visit 3: 2-day follow-up

HR returned a day sooner than expected for follow-up because of concern with changes in his vision. At this time, he agreed to be admitted to the hospital and was started on 5 mg/kg of intravenous ganciclovir twice a day. He continued to receive prednisolone acetate eye drops twice a day in both eyes.

Visits 4-11

HR was examined eight more times over the course of 23 days. At visit five, the retinitis continued to regress in both eyes, and ART was initiated. Treatment for the opportunistic infection was continued. Following the initiation of ART, the level of ocular inflammation increased because of immune system recovery, a condition known as immune recovery uveitis (IRU). At subsequent visits the retinitis and opportunistic infection continued to regress (Figure 2).
Figure 2. Fundus photographs of the right eye and left eye following treatment, 9 months after the initial visit.

Educator’s Guide

The Educator’s Guide includes the necessary information for teaching and discussing the case. The key concepts, learning objectives and discussion questions should guide the teaching of the information.

Key concepts

1. Managing patients diagnosed with HIV in the optometry office — lab markers, medications
2. Hallmark symptoms and signs of HIV retinopathy and CMV retinitis
3. Clinical course of HIV retinopathy and CMV retinitis
4. Critical thinking in diagnosis, using the optometry toolbox when extra testing is warranted
5. The role of communication from beginning to end of the exam; developing patient rapport and trust, thorough case history and patient education and reassurance
6. Understanding the HIV landscape, historical context and current public health status in the United States and globally

Learning objectives

At the conclusion of this case discussion, participants should be able to:

1. State how to elicit a comprehensive history for a patient with HIV in an optometry setting (i.e., lab values, current medications)
2. Describe the retinal findings seen in fundus photos
3. Describe the ocular signs and symptoms of CMV retinitis
4. Apply critical-thinking skills to correlate symptoms with clinical findings
5. Identify differential diagnoses that can present with similar findings to HIV retinopathy and CMV retinitis
6. Understand the critical role of communication, from being able to elicit patient’s concerns through a thorough case history to patient education
7. Describe additional testing that can be performed to confirm the diagnosis of CMV retinitis

Discussion questions

A. Knowledge, concepts, facts and information required for critical review of the case

1. Describe the classic signs and symptoms of CMV retinitis
2. Describe signs and symptoms of retinitis and how they differ from CMV retinitis
3. Determine the differential diagnosis in this case based on analysis of case history, risk factors and demographics
4. Describe the etiology and demographics of CMV retinitis
5. Discuss the general risk factors for CMV retinitis and compare them with the patient’s individual risk factors
6. Describe the testing performed to determine the diagnosis
7. Discuss the impact of CMV retinitis diagnosis on a patient’s life
8. Discuss management and expected prognosis
9. Discuss community health aspects as they impact care for patients with HIV
10. Discuss how barriers to care (patient education, access to care, cultural competencies) can impact progression or management of HIV and CMV retinitis

B. Differential diagnosis
1. What clinical findings were used in this case to diagnose CMV retinitis?
2. What were the differential diagnoses for the patient’s symptoms and how were the other hypotheses ruled out?
3. How were the clinical findings and information analyzed to rule out or support the potential differential diagnoses in this case?
4. What evidence or information is needed to diagnose CMV retinitis?
5. After analysis of the information, what is the best possible diagnosis at this time?
6. Is the diagnosis logical?
7. At this time, are there other diagnoses one should consider?

C. Patient management and the role of the primary care optometrist
1. What are appropriate management options?
2. What is an appropriate follow-up schedule?
3. What is the prognosis for a patient with CMV retinitis?
4. How does a patient’s mental or financial health influence the recommendations for follow-up?
5. What happens when symptoms worsen or do not improve?
6. What education should be given to patients diagnosed with CMV retinitis?
7. Discuss this patient’s reaction to diagnosis and how it affects the education provided and communication with the patient throughout the examination

D. Communication and doctor/patient relationship
1. Discuss the ethical and legal responsibilities of a provider in disclosing examination findings to a patient even if that information may increase patient stress
2. What are some strategies for reassuring patients at risk for irreversible vision loss as an outcome?
3. Use role-playing to simulate the delivery of the diagnosis and management
4. Identify the interactions where patient/doctor trust was established and lost
5. Discuss the interprofessional communication that facilitated or hindered care of this patient
6. Discuss the impact on family members or significant others given the diagnosis

E. Critical-thinking concepts
1. What inferences are made in the determination of the differential diagnoses?
2. What are the potential implications involving the management of this patient?
3. How might decision-making have changed if vision was not reduced?
4. How would management have been different if ophthalmology was not as easily accessible to the patient?
5. What is the role of empathy in this case?
6. What are some effective strategies when reassuring patients?
7. What impact do current breakthroughs in medical advances play for an optometrist?

Literature Review
HIV has extensive impact on the health and function of the eye. The impact of the virus on eye health is variable and gradient. The greater the immune system is compromised from increasing virus replication, the more significant the impact of the virus on the eye. Ocular involvement with HIV is most commonly due to opportunistic infection and neoplasms, but HIV microvasculopathy, which is called HIV retinopathy, also occurs. As the patient’s immune system tries to attack the virus, it causes damage to the vascular system in the body including the vascular system of the eye. The
immune response causes immune complex deposition, increased plasma viscosity or invasion of vascular endothelium causing microvasculopathy and contributing to signs of retinopathy in the eye. Forty to sixty percent of HIV-positive patients demonstrate HIV retinopathy, which can include cotton-wool spots, intraretinal hemorrhages and microvascular changes such as microaneurysms and telangiectasia, during eye examinations.

Virus replication contributes to further immune cell death, which shifts the balance between viral load and CD4 count in the body. Viral load, determined by a laboratory test, is the extent of virus present in the patient’s blood. The higher the viral load, the more the virus has replicated inside the patient. CD4 cells are part of the immune system and are targeted by HIV. As the viral load increases, the CD4 cell count decreases. If the CD4 count of a patient drops below 200 cells/µL, AIDS is diagnosed. As CD4 cells lower in a patient, other viruses that lie dormant and suppressed by the immune system can become active. A common opportunistic infection seen in HIV patients that has complications for the eye is CMV. CMV is a DNA herpes-class virus that is ubiquitous in humans.

Within the United States, seroprevalence is estimated to be approximately 60% overall, and it rises with age, ranging from 36.3% in children ages 6-11 years to 90.8% in adults 80 years or older. Transmission requires contact with body fluids of individuals who are shedding the virus. Like other members of the herpesvirus family, CMV establishes latent infection after the resolution of acute (or primary) infection. Recurrence from latency occurs in patients who are immunocompromised. CMV infects the retina, central nervous system, reticuloendothelial system, kidneys, adrenal glands, lungs and gastrointestinal system.

CMV retinitis occurs only in severely immunosuppressed patients, such as organ transplant recipients, patients who have malignancies or are receiving chemotherapy, and persons with HIV/AIDS. In patients with AIDS, CMV retinitis is the most common opportunistic ocular infection. CMV retinitis was first reported as a complication of AIDS in 1982. Prior to the availability of potent ART, CMV retinitis occurred in 21-44% percent of patients with AIDS, primarily in those with a CD4 T lymphocyte count below 50 cells/µL. In early case series, patients who survived beyond 6 months without CMV-specific treatment became severely visually impaired or blind. The median time to progression of disease into previously uninvolved areas of the retina while on CMV-specific antiviral therapy was 47-104 days, mean survival after diagnosis was 6-10 months, and indefinite maintenance therapy was essential. Following the introduction of ART in 1996, the incidence of CMV retinitis declined sharply among patients with HIV/AIDS. Visual morbidity has also declined, with the rate of bilateral blindness (vision loss to 20/200 or worse) from CMV retinitis decreasing from 14.8/100 person-years in the pre-ART era to 0.4/100 person-years in the modern era.

ART is the use of at least three antiretroviral drugs to suppress HIV and stop progression of the disease. At least 25 antiretroviral medications in six different classes are available. The different classes are related to the life cycle of HIV. The HIV life cycle can be broken down into six steps: 1) entry (binding and fusion), 2) reverse transcription, 3) integration, 4) replication (transcription and translation), 5) assembly, and 6) budding and maturation. The identification and understanding of these processes have provided the basis for antiretroviral drug discovery. For most individuals, the ART regimen consists of a dual nucleoside combination plus a third agent from another class.

The exact pathogenesis of CMV retinitis is unknown, but many studies support the hypothesis that it results from the spread of CMV to the eye. Studies in transplant recipients and patients with AIDS indicate that CD4-dependent cytotoxic T lymphocyte activity of CMV antigen-specific CD8 T cells is critical for preventing CMV replication and end-organ disease. Impaired CD4 cell function or volume is the key immune deficit that allows uncontrolled CMV replication.

Clinical features

- Symptoms: Patients may complain of blurring or loss of central vision, scotoma, floaters or flashes of light. A complaint of floaters or photopsia is the single most powerful symptomatic predictor of CMV retinitis in an AIDS patient. Acute loss of vision can occur if retinitis leads to retinal detachment.
- Retinal lesions: CMV retinitis appears as areas of full-thickness retinal necrosis and edema. Yellow-white, fluffy or granular retinal lesions are often located close to retinal vessels and associated with retinal hemorrhages. There are several recognized patterns of CMV retinitis: wedge-shaped areas of whitening with associated hemorrhage (“brush fire”), variable small dot-like lesions (granular type), or, rarely, retinal vasculitis with perivascular sheathing. Lesions can be described as “fulminant and edematous” vs. “indolent and granular” based on several factors, including the degree of retinal whitening, retinal hemorrhage, and lesion shape and location.
Other: CMV retinitis typically begins in the peripheral retina and progresses centrifugally toward the posterior pole.

**Diagnosis and testing**

CMV retinitis is generally diagnosed on the basis of characteristic retinal changes. These retinal changes include the degree of retinal opacification, degree of retinal hemorrhages and location. CMV viremia detected by polymerase chain reaction (PCR), antigen assays or blood culture are not used to make a diagnosis of CMV retinitis because these tests have poor sensitivity and specificity for end-organ disease. Careful case history, clinical appearance, appropriate lab testing and auxiliary testing will help differentiate among other forms of retinal disease.

- Smoldering retinitis and subtle reactivation may be difficult to recognize without examining serial fundus photographs. Several studies have shown that wide-angle fundus photographs are a more sensitive indicator of retinitis progression than clinical examination.
- Humphrey visual field testing may reveal scotomas in the areas of retinal necrosis. Scotomas are potentially noticeable on confrontation fields, as in this case.
- Optical coherence tomography does not provide any additional information in patients with HIV/AIDS and CMV retinitis. It can be helpful in patients with IRU to detect macular edema and epiretinal membranes.
- Fluorescein angiography is not useful in diagnosing patients with HIV/AIDS and CMV retinitis. For patients who develop IRU, it can be helpful for detecting macular edema and neovascularization.

**Differential diagnosis**

- HIV retinopathy: In certain cases, CMV retinitis may be subtle or less developed at the time of eye examination and could render a diagnosis of HIV retinopathy and not CMV retinitis. In rare cases of HIV retinopathy, retinal involvement could be extensive, demonstrating retinal hemorrhages and cotton-wool spots, and appear severe enough to mimic CMV retinitis. In cases of HIV retinopathy, the patient is not immunocompromised; therefore, careful history and laboratory testing can help with correct diagnosis.
- Toxoplasmosis: Ocular findings related to toxoplasmosis most often have a typical appearance of chorioretinal scar. During active toxoplasmosis, a vitritis might be present and an active infiltrative lesion in the retina can be present near the border of an older retinal lesion. This retinal activity can resemble that of CMV retinitis. Providers must pay close attention to history and acquire laboratory testing as needed. The presence of a chorioretinal scar should help to differentiate toxoplasmal from CMV retinitis.
- Syphilis: Syphilis can have variable retinal and ocular appearances. Certain cases may present with significant retinal hemorrhages or inflammation that could resemble CMV retinitis. Blood testing can help in differentiating syphilis retinopathy and ocular involvement from that of CMV retinitis. Although, it must be remembered that patients with CD4 counts below 200 cells/µL may be seronegative to all studies available for syphilis.
- Acute retinal necrosis (ARN) syndrome: This retinal condition can occur in either immunocompetent or immunosuppressed patients. This disease, however, is a result of the herpes simplex virus (HSV) or herpes zoster virus (HZV). ARN typically involves peripheral retina before progressing toward the posterior pole and tends to have a more pronounced vitritis compared with CMV retinitis. ARN also progresses more rapidly than CMV retinitis. Testing of serum and vitreous antiherpes antibody levels, as well as PCR for CMV, HSV and HZV in aqueous and vitreous samples, can be performed.
- Progressive outer retinal necrosis (PORN): PORN is a herpetic retinitis that occurs in patients with AIDS and CD4 cell counts less than 200 cells/µL. PORN begins as a smooth, granular, multifocal retinal opacification. Progression is much faster than with CMV retinitis, and there is typically little or no intraocular inflammation. Vasculitis and
hemorrhage do not usually occur. The markedly atypical case could, however, resemble CMV retinitis.

Management and treatment

For patients who develop HIV/AIDS-related CMV retinitis, treatment consists of CMV antiviral therapy and ART for the HIV. In clinical settings where follow-up care and patient reliability is trusted, it is best to initiate CMV treatment without ART for 2 weeks to help prevent any complications from an immune response. However, if compliance is in question, both treatment options can be started at the same time. Antiviral treatment options for CMV retinitis include systemic and/or intravitreal therapy. For patients with newly diagnosed infection, assessing the location of the lesions is the first step in determining treatment options. If the location of the lesions is central and immediately sight-threatening (lesions < 1,500 microns from the fovea or adjacent to the optic nerve head), intravitreal injections in conjunction with systemic therapy should be started. For patients without sight-threatening disease, systemic therapy alone can be initiated. An initial induction therapy is typically administered until retinitis has become inactive. This can be in the time frame of 2-3 weeks. After initial induction therapy, a lower-dose maintenance therapy is put into place.

Teaching methodology, critical-thinking concepts and assessment

Often in health care, difficult conversations surrounding sensitive topics have to occur because of the impact on systemic or ocular health. These conversations can be about topics such as substance abuse, partner or child violence, or sexually transmitted disease. HIV/AIDS can be a difficult topic for interns and providers to talk about with patients in the eyecare examination setting because of complexity and social stigmas. Studies have demonstrated that communication techniques can increase reliability and validity of patient self-reporting in the context of sensitive topics. One study identified three factors that affect reliability and validity of patient self-reporting for sensitive topics: 1) the intern or provider’s own anxiety to talk about certain topics, 2) the patient’s anxiety to talk about certain topics, and 3) the “how” of asking questions.

Five communication techniques can help doctors to discuss sensitive topics with patients and improve patient self-reporting:

1. Normalizing – Use universality statements to normalize the problem (if appropriate) and/or the anxiety. For example, “Many people find it difficult to talk about their sexual concerns, activities, practices, etc.” Or, “Many people with chronic illness notice they have problems with sexual function. Have you?”
2. Using transparency – Explain why you are asking; be open about your reasons. For example, “I need to ask you some very specific questions about your sexual history in order to better understand your current problem.”
3. Asking permission – For example, “Would it be alright with you if I asked you some questions about your sexual history?”
4. Giving the option of not answering a question – Patients can be informed that they do have the option of not answering a question if it makes them feel uncomfortable.
5. Addressing confidentiality concerns – Patients have a right to be informed that a healthcare provider cannot promise them 100% confidentiality regarding their condition. Healthcare providers in many jurisdictions are required by law to report cases of sexually transmitted diseases to a public health agency.

An example of normalizing, transparency and permission all together: “I ask all my patients about their sexual activity as part of gaining their medical history (normalizing) because it can have an important impact on their overall health (transparency). Would it be OK if I asked you some questions about your sexual activities (permission)?

Doctor/patient communication has been evaluated and written about in many different ways. It is important that providers and interns learn the principles of good provider/patient communication regardless of the topic but especially when handling sensitive topics.

This case lends itself to several options for assessment. Factual information may be assessed with a multiple-choice test. Analytical information including decision-making may lend itself to a short-answer or essay-type format. Alternatively, a dedicated person may evaluate the quality of the oral discussion using a rubric. The rubric should include important critical-thinking concepts such as assumptions, inferences, implication of alternative treatment, point of view, etc.
ability to access and evaluate information independently (digital literacy) could be utilized as a separate homework assignment.

Discussion

The purpose of this case report is to help eyecare providers review the clinical features and course of CMV retinitis, as well as develop strategies for talking to patients about sensitive topics during a clinical encounter. Optometry students can be guided through a discussion in a classroom or clinical setting. They should be presented with case details in a stepwise fashion (i.e., case history, dilated fundus examination and fundus photography) in order to critically think through the clinical presentation, devise differentials and arrive at a diagnosis. The key aspects of patient education can be discussed, including delivery of the diagnosis, management options and ocular prognosis. Further discussion can include the historical context of CMV retinitis compared with present time based on the role of antiretroviral medications.

The patient in this teaching case report presented with bilateral red eyes and blurry vision from an urgent care referral. The patient had also been discharged from the hospital recently and was advised to establish care. Ocular assessment revealed constricted confrontation fields and anterior chamber reaction. Dilated examination revealed bilateral retinitis with the left eye worse than the right eye. The key to diagnosis in this case was obtaining a thorough case history including systemic history, recent laboratory findings and review of systems, as well as using critical-thinking skills to incorporate and interpret the patient’s fundus photography. It is important that a CMV retinitis diagnosis be accurate. A clinician should know the clinical spectrum of HIV retinopathy prognosis and that management can vary. In some cases, patients may require invasive treatment. In other cases, it is reasonable that they be monitored without intervention. The primary eyecare physician should ensure that the patient has the opportunity to ask questions and understands his/her condition. Referrals should be made urgently when appropriate.

A clinician should be aware that HIV/AIDS can have a serious impact on ocular function and lead to irreversible vision loss if left untreated. The patient in this teaching case report was negligent to his diagnosis of HIV/AIDS, which is currently uncommon. Prior to the initiation of ART, the rate of CMV retinitis in HIV/AIDS patients was 30%. Since 1996 and the introduction of ART, the rate has dropped 80-90%. The current incidence of CMV retinitis for individuals living with HIV/AIDS for 4 years is 1.2%, and the rate for 10 years is 4.9%. Though the rates of associated vision loss have decreased approximately eight-fold in the ART era, CMV retinitis remains an important predictor of incident vision loss. With ART in present time, HIV is typically well-controlled, resulting in high CD4 counts and undetectable viral loads. This type of control for the virus typically reduces any ocular involvement. However, certain barriers can be present for patients who may not understand the condition or have access to medication and care. Despite incredible advances in medication, primary eyecare providers have to be aware of the impact HIV/AIDS can have on the eye, especially when the patient is immunosuppressed and at risk for opportunistic infections such as CMV leading to CMV retinitis.

A clinic pearl for students to remember is how to correlate laboratory findings for a systemic condition and the risk for ocular findings. In this particular case, the patient had a CD4 count of 1 cell/µL. This CD4 count indicates a severely immunocompromised patient at high risk for opportunistic infections and ocular complications who should be evaluated urgently and carefully. The patient also had an anterior chamber reaction in both eyes. A key clinical pearl is to always dilate patients who demonstrate an anterior chamber reaction because the cells and flare in the anterior chamber can be a sign of further inflammation in the posterior segment. The cells and flare in the anterior chamber of this patient signified “smoke” to the “fire” that was occurring in the posterior segment.

Conclusion

This case serves as a reminder that HIV retinopathy and CMV retinitis are not extinct conditions. Despite incredible control of CD4 counts and viral loads in the ART era, immunocompromised patients with sight-threatening ocular manifestations can still present and require immediate attention and competent management. In a community health center optometric practice, barriers to care can exist. Patient education, access to medication, cultural barriers and barriers to compliance can exist. Primary eyecare providers need to be aware of the important history and laboratory findings (and what those values represent) to discuss with patients who have HIV. Providers should always remember the importance of dilated fundus examination and to be aware of the signs and symptoms of CMV retinitis, as it is still the leading cause of irreversible vision loss in the HIV population in the ART era.

References


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