

Skin in HIV

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Oral, Ocular, Nail and Hair Changes in HIV

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INTRODUCTION

With the increasing prevalence of HIV worldwide, the need to understand varied spectrum of manifestations has been increasing beyond the conventional disease defining sign and symptoms. Skin signs give an indication of the degree of immunodeficiency and prognosis of the patient and also form an integral component of the WHO staging system.

In this chapter, alongside oral and ocular manifestations, changes in nail and hair have also been enumerated.

ORAL MANIFESTATIONS OF HIV

HIV-related oral disorders affect around 30% to 80% of HIV-infected individuals, and they are often misdiagnosed or inadequately treated. Oral lesions are features of HIV infection and are well described in the literature in adults and oral lesions are diagnostic of HIV infection, they are also useful in monitoring HIV disease progression [1-3]. Oral lesions in paediatric HIV infection are characteristic of the disease process and though, similar to adults, certain lesions are typical in the paediatric population [4].

The common manifestations of HIV-related oral conditions include xerostomia, candidiasis, oral hairy leukoplakia, periodontal diseases like linear gingival erythema and necrotizing ulcerative periodontitis, Kaposi's sarcoma, human papilloma virus infections, and Herpes Simplex Virus ulcers, recurrent aphthous ulcers, and neutropenic ulcers [5].

HIV SALIVARY GLAND DISEASE

Human immunodeficiency virus-associated salivary gland disease (HIV-SGD) is defined as the presence of xerostomia and/or swelling of the major salivary glands. It is common among children but uncommon among adults. Lymphoepithelial lesions and cysts involving the salivary glands and/or intraglandular lymph nodes, and Sjögren's syndrome-like conditions, diffuse interstitial lymphocytosis syndrome, are the various manifestations seen [6].

Incidence

Xerostomia occurs commonly (2-10%) in HIV-infected individuals. Enlargement of the major salivary glands occurs frequently (19%) among HIV-infected children, but rarely among adults (0.8%) [7].

Etiopathogenesis

Although the exact pathophysiology remains uncertain, theories concerning the origin of SGD include lymphoepithelial lesions, cysts involving the salivary parenchyma, interglandular lymph nodes, and an inflammatory infiltrate similar to that seen in Sjögren's syndrome. Multicystic lymphoepithelial lesions may also occur, but cystic change can also arise from intraglandular ductal obstruction by hyperplastic lymphoid tissue [8].

Viral infections are often associated with salivary gland pathology. Studies have detected BK viral shedding [9] in the saliva of HIV-SGD patients consistent with viral infection and replication, which suggests oral transmission.

A study has also shown strong immunohistochemical reaction for LMP-EBV [10] and p-24 proteins in ductal cells in all cases of HIV- SGD implicating its role in the pathogenesis. CMV virus is also implicated in its pathogenesis [11].

Xerostomia independent of HIV-SGD may arise in HIV infection as a consequence of some nucleoside analog HIV reverse transcriptase inhibitors or protease inhibitors, by an unknown mechanism. Didanosine induces xerostomia [12].

Clinical Features

Salivary gland disease (SGD-HIV) commonly arises in late HIV infection, but it can rarely be the first manifestation. The parotids are most frequently affected, often presenting with significant enlargement of glands bilaterally. Another manifestations of HIV -SGD is diffuse infiltrative lymphocytosis syndrome (DILS). It is characterized by lymphocytosis and lymphocytic infiltration involving the salivary glands and lungs.

The diagnostic criteria for DILS includes

- HIV seropositivity documented by enzyme linked immunoassay (ELISA) and Western Blot
- Bilateral salivary gland enlargement, or xerostomia persistent for more than six months,
- Histologic confirmation of salivary or lacrimal granulomatous or neoplastic involvement.

Patients with DILS have a four-fold risk of developing non-Hodgkin's lymphoma (Figure 10.1a,b,c).

Xerostomia is a major contributing factor in dental decay in HIV-infected individuals. Approximately 30% to 40% of HIVinfected individuals experience moderate to severe xerostomia in association with the effects of medications (eg, didanosine) or the proliferation of CD8+ cells in the major salivary glands. Changes in the quantity and quality of saliva, with diminished antimicrobial properties, can lead to rapidly advancing dental decay and periodontal disease.



Figure 10.1a: Non Hodgkins lymphoma involving oral cavity.



Figure 10.1b: Non Hodgkins lymphoma involving oral cavity.

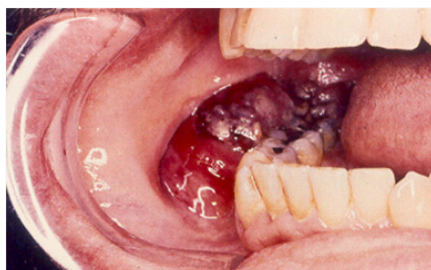


Figure 10.1c: Non Hodgkins lymphoma involving oral cavity.

(Photo courtesy: Dr Mubeen, Department of oral medicine,, Government Dental college and Research Institute, Bangalore)

Table 10.1: Effects of long-standing xerostomia [8].

- Salivary gland enlargement
- Oral mucosal soreness
- Dry, sore cracked lips
- Oral candidiasis
- Increased frequency of cervical caries
- Gingival and periodontal diseases
- Depapillation of tongue (burning tongue)
- Trouble eating, swallowing and speaking
- Dysgeusia (bad taste)

Histopathology

The diffuse infiltrative lymphocytosis syndrome (DILS) in HIV patients is characterized by the persistence of CD8-circulating lymphocytes and lymphocytic infiltration, predominantly in salivary glands [11].

Labial salivary gland (LSG) biopsy specimens from patients contained lymphocytic infiltrates in focal and other patterns, whereas specimens from three HIV-infected patients without salivary gland symptoms did not. The inflammatory infiltrates in LSG specimens showed a preponderance of T8-positive cells and a tissue T4/T8 average ratio of 0.66 [13].

Differential Diagnosis

The clinical picture of HIV-SGD mimics that of Sjögren's syndrome; however, there are distinct histopathologic and serologic differences between the two disorders.

Patients with HIV-SGD generally do not have anti-Ro or anti-La antibodies. The minor salivary gland histopathology of HIV-SGD is generally similar to that of Sjögren's syndrome, with perivascular, periaccinar, and periductal lymphocytic (majority of CD8 Tcells) infiltrates.

Treatment

General measures

To relieve the symptoms of xerostomia- lubricating agents in the form of gels, mouthwashes, lozenges, and toothpastes can be used but with varied improvement. Commercial artificial saliva can also be used to relieve discomfort. Sugar-free gum or sugar-free candies may help to increase salivary output, but they may be inconvenient and affect patients' compliance.

Therapeutic management

Pilocarpine a parasympathetic agonist, Cevimeline, a quinuclidine analog of acetylcholine are the few of the treatment options.

PERIODONTAL DISEASES IN HIV

Severe forms of periodontal disease are frequent in patients with acquired immunodeficiency

syndrome (AIDS). The periodontal conditions most closely associated with HIV infection include linear gingival erythema and necrotizing gingival and periodontal diseases. These conditions are declining, in part because of antiretroviral therapy, dental and healthcare practitioners will need to diagnose and treat these periodontal diseases in HIV-infected people [14].

HIV-associated periodontal lesions can also be classified as unusual forms of gingivitis, necrotizing periodontal diseases (**Figure 10.2 a & b**) and exacerbated periodontitis [15].

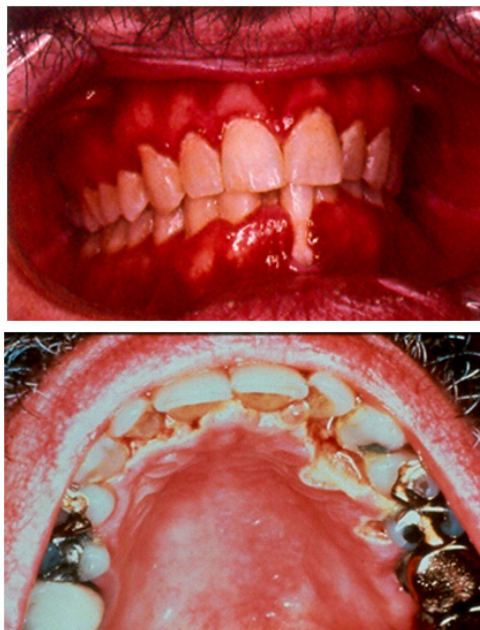


Figure 10.2a and 10.2 b: Necrotising ulcerative periodontitis

(Photo courtesy: Dr Mubeen, Department of oral medicine,, Government Dental college and Research Institute, Bangalore)

LINEAR GINGIVAL ERYTHEMA

Linear gingival erythema (LGE) is a progressive disease described in HIV-positive patients and is considered to be an early stage of necrotizing periodontitis [16]. It is defined as an erythematous band of at least 2 mm extending between adjacent papilla [17]. The presence of LGE in pediatric patients with AIDS may indicate its feature as a predictive marker in progression of HIV-infection in children [18].

Incidence

Linear gingival erythema is the most common form of HIV-associated periodontal disease in HIV-affected children, prevalence from 0-48% [19,20].

Etiology

Although linear gingival erythema has no specific etiology, probably due to erythematous candidiasis [21,22].

Clinical Features

Linear gingival erythema also called as red band gingivitis presents with red band along the gingival margin (Figure 10.3) and sometimes it can be accompanied by occasional bleeding and discomfort. It involves anterior teeth more frequently but can extend to posterior teeth. It can also present as petechial like patches [5].



Figure10.3: Linear gingival erythema.

(Photo courtesy: Dr Mubeen, Department of oral medicine, Government Dental college and Research Institute, Bangalore)

Histopathology

Immunohistochemical study has shown, that progressive periodontal disease is characterized by increased tissue inflammation with changes in the proportion of specific inflammatory cells. There is decreased proportions of T-lymphocytes, macrophages and high percentage of neutrophils and IgG bearing plasma cells in LGE. Many neutrophils cells in LGE were found inside oral gingival epithelium. The high number of neutrophils along the gingival epithelium is probably associated with the severe gingival necrosis reported in AIDS patients [16].

Treatment

The erythema often persists following simple dental prophylaxis. Periodontal debridement, chlorhexidine mouth rinses (twice a day for two weeks), and improved home oral hygiene; antifungal regimens also may be considered [19,20].

NEUTROPENIC ULCERS

Neutropenia is an absolute decrease in the number of circulating neutrophils in the blood which results in susceptibility to severe pyogenic infections. Periodontitis, alveolar bone loss and ulceration with other oral findings may be seen in neutropenic patients [23]. Nonspecific oral ulcers in HIV-seropositive subjects with neutropenia should be regarded as neutropenic ulcers.

Nonspecific ulcers have nonspecific histopathological features in patients without neutropenia or a nutritional deficiency like iron, folic acid, and vitamin B [24].

Etiology

Neutropenic ulcerations are associated with absolute granulocyte counts of less than 800/ μ L.

Clinical Features

They present as very painful ulcerations that can involve both keratinized and non-keratinized tissues. Large, unusual looking, or fulminant ulcers in the oral cavity that cannot otherwise be identified or explained should prompt suspicion of this condition.

Treatment

Includes standard periodontal treatment and administration of granulocyte colony-stimulating factor (G-CSF) [24].

ORAL CANDIDIASIS

Oral candidiasis is one of the disease defining condition in HIV. Thrush may be the first sign of human immunodeficiency virus (HIV) infection; its appearance in advanced HIV indicates poor prognosis.

History

French pediatrician Francois Valleix was the first to describe in 1838.

Pathogenesis

Candida albicans is the most frequently isolated species from HIV patients but recently non-albicans species have emerged. The frequent use of fluconazole to treat HIV patients with candidiasis has resulted in a change in the prevalence of candida species and the emergence of azole resistance with refractory and recurrent infections [25].

Other species: *Candida tropicalis* (29-26.6%), *C. guilliermondii* (13-11.9%), *C. parapsilosis* (10-9.2%), *C. lusitaniae* (6-5.5%), *C. krusei* (5-4.6%), *C. dublinensis* (2-1.8%) and *C. glabrata* (2-1.8%).

C. albicans causes thrush when normal host immunity or normal host flora is disrupted. Increased growth of yeast on the oral mucosa leads to desquamation of epithelial cells and bacteria, keratin, and necrotic tissue accumulation. They form a pseudomembrane, which may closely adhere to the mucosa. This membrane which is not large but may rarely involve extensive areas of edema, ulceration, and necrosis of the underlying mucosa.

Incidence

National AIDS Control Organization reports candidiasis as the second most common opportunistic infection in HIV patients. Oral candidiasis is the commonest manifestation observed

in HIV reactive patients reflecting a declining immune system and a prognostic indicator for the development of AIDS. It affects one-third of HIV positive and more than 90% of patients with AIDS at some point during their progression to full-blown AIDS.

Clinical Features

Lesions often start as tiny focal areas that enlarge to white patches on oral mucosa (Figure 10.4 a & b).

When scraped, lesions are difficult to remove and leave behind an inflamed base that may be painful and may bleed.



Figure 10.4 a & b: Oral candidiasis

(Photo courtesy: Dr Mubeen, Department of oral medicine, Government Dental college and Research Institute, Bangalore)

Pseudomembranous and erythematous forms, are predictive of the development of AIDS, irrespective of CD4 counts [26].

Angular cheilitis

It presents as erythema, fissuring at the corners of the mouth. It can occur alone or along with erythematous or pseudomembranous candidiasis, and can persist for long period of time if left untreated.

Erythematous candidiasis

It is one of the underdiagnosed and misdiagnosed oral manifestations of HIV disease.

Patients complain of burning sensation while eating salty or spicy foods or drinking acidic beverages. Examination reveals erythematous, flat, lesion involving either on the dorsal surface of the tongue or on the hard or soft palates. It sometimes present as a kissing lesion involving the opposing surfaces of tongue and palate.

Medical history, clinical examination, demonstration of fungal hyphae help in diagnosis.

Pseudomembranous candidiasis (Thrush)

It appears as creamy, white, curd like plaques on the oral mucosal surfaces which can be wiped away, leaving an underlying bleeding surface.

Investigations

To confirm the diagnosis of thrush, tongue blade is used to scrape the plaques to reveal an inflamed and/or bleeding base.

Plaques can be cultured, although cultures are rarely indicated. Gram stain demonstrates large, ovoid, gram-positive yeast.

Treatment

Topical and oral antifungals especially azoles remain the mainstay of treatment. The available drugs, dosage and treatment regimen are given in the table 1 and 2. The primary lesson to be learnt in the treatment of any candidiasis—whether it be with a topical agent for mild to moderate disease or a systemic agent for more severe disease—is that treatment must be continued for at least 2 weeks in order to reduce organism colony-forming units to levels low enough to prevent recurrence [5].

Table 10.2: Treatment guidelines for different types of oral candidiasis.

Type	Treatment
Angular Cheilitis	Topical antifungal cream to be applied directly to the affected areas 4 times a day for the 2-weeks.
Erythematous candidiasis	For mild to moderate cases- Topical treatments with clotrimazole troches, nystatin oral suspension, and nystatin pastilles. For moderate to severe disease- Systemic agents like fluconazole,(the most widely used drug) itraconazole are used. For fluconazole resistant cases- voriconazole
Pseudomembranous candidiasis	For mild to moderate cases- clotrimazole troches, nystatin oral suspension, and nystatin pastilles. For moderate to severe disease- Systemic agents like fluconazole,(the most widely used drug) itraconazole are used. For fluconazole resistant cases- voriconazole.

Table 10.3: Treatment regimens with various antifungals.

Drug	Strength	Dosage
Topical agents		
Clotrimazole troches	10 mg	dissolve 1 troche in mouth 5 times a day for 14 days.
Nystatin oral suspension	500,000 units	Swish 5 mL in mouth as long as possible then, swallow (optional), 4 times a day for 14 days.
Nystatin pastilles	100,000 units	Dissolve 1 in mouth 4 times a day for 14 days.
Systemic agents		
Fluconazole	100 mg	2 tablets on day 1, followed by 1 tablet a day for 14-days.
Itraconazole oral suspension	10 mg/10 mL	Swish and swallow 10 mL per day for 7 to 14 days. *empty stomach.
Voriconazole	200 mg	1 tablet twice daily for 2 weeks.
Drug interactions- Possible with rifampin, rifabutin, ritonavir, and efavirenz (all are potent CYP 450 inducers). Interactions are most significant with voriconazole and with itraconazole oral suspension.		

Azole Resistance

Azole resistance is one of the significant problem arising in the management of HIV associated oral candidiasis. Factors associated with azole-resistant disease include prior exposure to azoles, low CD4+ cell count, and presence of non-*albicans* species [5].

ORAL HAIRY LEUKOPLAKIA

Oral hairy leukoplakia (OHL) is one of the many new disease entities brought to light by the epidemic of HIV infection. Although innocuous, it is an early clinical marker of HIV infection and is associated with poor prognosis and increased severity of HIV disease. OHL can be seen in HIV infection and also in other immunosuppressive conditions [27].

Pathogenesis

The Epstein-Barr virus (EBV), like all herpes viruses, establishes a life-long, persistent infection of its host. The pathogenesis of hairy leukoplakia is complex. These factors include EBV co-infection, replication, genetic evolution, expression of specific “latent” genes, and immune escape, facilitated by host immunodeficiency.

EBV initially infects basal epithelial cells in the pharynx, where it undergoes replication repetitively leading to production and release of infectious virus into the saliva throughout the life of the infected person. In the pharynx, the virus persists indefinitely in latent state in B cells. Cytotoxic T lymphocytes are essential in maintaining the latent state of the infection.

In addition, biopsy tissues of hairy leukoplakia also showed marked decrease or an absence of Langerhans cell. Langerhans cells are required for an immune system response to the viral infection and their deficiency may permit EBV to persistent replication and escape immune recognition.

Clinical Features

Hairy leukoplakia is often asymptomatic. Patients with oral hairy leukoplakia may report a nonpainful white plaque along the lateral tongue borders. Some patients have mild pain, dysesthesia and altered taste.

Typically, OHL manifests as unilateral or bilateral, adherent, white or gray patches on the lingual lateral margins and, to a lesser extent, the dorsum or ventrum of the tongue. The surface of the patches is usually irregular, forming prominent folds or projections (sometimes so marked as to resemble “hair” but more commonly giving rise to a corrugated or shaggy appearance, hence its name [28]. Occasionally, the lesion can be flat, particularly at the ventral surface of the tongue [29]. Rarely it can involve other areas of buccal mucosa like floor of the mouth, soft palate, and oropharynx [30-32]. Lesions are adherent, and only the most superficial layers can be removed by scraping.

Lesions may be either continuous or discontinuous along both borders of the tongue, and they are often not bilaterally symmetric. Hairy leukoplakia may also involve dorsal and ventral tongue surfaces, the buccal mucosa, or the gingiva, lacking the characteristic “hairy” appearance.

Diagnosis

In most cases, the diagnosis is established on clinical basis, histopathological appearance and the demonstration of EBV within the epithelial cells of the lesion. Tissue biopsy is indicated only if the lesions are unusual in appearance or ulcerated and suggest cancer.

Histopathology

The histopathology of hairy leukoplakia is characterized by following histologic features [30].

- There is a hyperkeratosis of the upper epithelial layer, which is largely responsible for the characteristic shaggy or “hairy” gross appearance of the lesion.
- There is a parakeratosis of the superficial epithelial layer.
- There is an acanthosis of the stratum spinosum in the epithelial mid-layer. This abnormal expansion of cells occurs with foci or layers of ballooning “koilocyte”-like cells. The cell nuclei have a homogenous “ground-glass” appearance and may contain Cowdry type A intranuclear inclusions.
- There is minimal or absent inflammation in the epithelial and subepithelial tissues.
- The basal epithelial layer is histologically normal.

Differential Diagnosis

Other oral lesions with a similar appearance to hairy leukoplakia include the following (Table 10.4):

Table 10.4: Differentials for oral thrush

Condition	Differentiating points
Candidiasis or thrush	• Flat lesion • Removed by scraping, revealing an erythematous base. • Demonstration of fungal elements. • Resolution with antifungals.
Frictional keratosis	• History of tongue biting by the molar teeth or some other abrasive irritant. • Resolves after removal of the provoking stimulus.
Tobacco-induced leukoplakia	• History of smoking or tobacco chew. • Lesions are not shaggy. • Occurs anywhere in the oral cavity.
Lichen planus	• In HIV-infected patients, lichen planus often occurs on the buccal mucosa. • Shows reticulated pattern. • May also be associated with cutaneous lesions.

Treatment

1. Systemic antiviral therapy (Table 10.5) usually achieves resolution of the lesion within 1-2 weeks of therapy [33-36]. They inhibit productive EBV replication but do not completely eliminate the latent state of infection. Chances of recurrence of hairy leukoplakia are common several weeks after the cessation of antiviral therapy.

Table 10.5: Table enumerating treatment regimens for oral thrush.

Antiviral drug	Dosage
Acyclovir	800mg five times per day
Valacyclovir	1000mg three times a day
Famciclovir	500mg three times a day

2. Topical therapy with podophyllin resin 25% solution usually achieves resolution after 1-2 treatment applications [37-40]. The exact the mechanism of action in resolving hairy leukoplakia is not known but Podophyllin has cellular cytotoxic effects. Hairy leukoplakia often recurs several weeks after cessation of therapy.

3. Topical therapy with retinoic acid (tretinoin) has been reported to resolve hairy leukoplakia [41,42]. Retinoic acids inhibit EBV replication *in vitro* and induce epithelial cell differentiation.

4. Cryotherapy has been reported as successful but is not widely used [43].

5. Surgical excision may be useful in cases where histologic examination of the lesion might be diagnostically important [33].

ORAL HERPES INFECTION

Oral herpes is caused by a specific type of the herpes simplex virus.

Etiopathogenesis

There are two types of HSV, termed HSV-1 and HSV-2. Herpes simplex virus 1 (HSV1) is the common cause of cold sores (oral herpes) around the mouth. HSV2 causes genital herpes. Through

certain sexual practices, HSV1 can cause infections in the genital area, and HSV2 can infect the mouth area. However, HSV-1 causes about 80% of all oral lesions and only about 20% of genital lesions while HSV-2 causes the reverse (about 80% genital and 20% oral).

The hallmarks of HSV infection are periodic reactivation and asymptomatic viral shedding. Infection with HSV virus becomes permanently latent in the nerve root ganglia corresponding to the site of inoculation (the trigeminal ganglia for orolabial infection and the sacral ganglia for genital infection). HSV induces antibody and cell-mediated immune responses that modulate the severity of recurrent disease, but do not eradicate infection. In HIV-1 infection, impaired immunity leads to recurrent symptomatic and asymptomatic HSV infection [44].

After HSV-1 infects a person, it has a rather unique ability to proceed through three stages as given in the Figure 10.5.

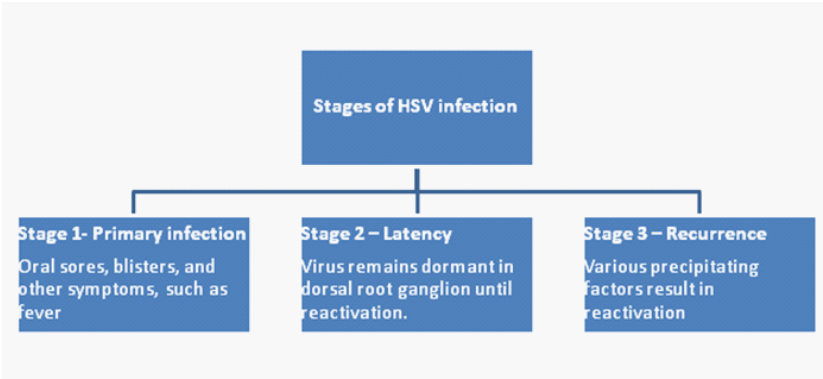


Figure 10.5: Different stages of HSV infections.

Precipitating factors for HSV reactivation is shown in table 10.6.

Table 10.6: Precipitating factors for HSV reactivation.

• Emotional or physical stresses • Ultraviolet light (including sunshine), • Fever • Fatigue • Hormonal changes • Immune depression • Trauma
--

Clinical Features

Pain, burning, tingling, or itching occurs at the infection site before the vesicles appear. Vesicles appear in groups, which rupture soon leaving behind tiny, shallow gray ulcers on a red base. A few days later, they become crusted or scabbed and appear drier and more yellow (Figure 10.6 a &b).

Primary oral lesions can cause intense pain at the onset and can make oral intake difficult. Vesicles can occur on the lips, gums, throat, tongue, mucosa of the cheeks, and palate. Regional lymph nodes can become enlarged.



Figure 10.6a & 10.6b: Extensive erosions and crusting in Herpes Labialis.

(Photo courtesy: Dr Mubeen, Department of oral medicine,, Government Dental college and Research Institute, Bangalore)

Among HIV-1 infected persons, the clinical presentation of symptomatic HSV infection varies considerably. As it does in HIV-1-uninfected persons, HSV reactivation among the HIV-1-infected typically presents with vesicular and ulcerative lesions of the oral and anogenital areas. HIV-1-infected persons, however, also can have frequent or persistent HSV lesions, often with extensive or deep ulcerations, particularly among those with low CD4 counts. Frequent and severe recurrent oral or genital herpes can be a source of significant pain and morbidity among some HIV-1-infected persons [44].

Most HSV infected individuals, regardless of HIV-1 serostatus, shed HSV in oral or genital secretions, and most shedding is asymptomatic. Prospective studies have shown that oral and genital shedding of HSV (both HSV-1 and HSV-2) occurs more frequently among those who are also infected with HIV-1 than among HSV-infected/HIV-1-uninfected persons [45-47].

Diagnosis

Among HIV-1-infected persons, the potential for atypical presentations of HSV may increase the chance of inaccurate diagnosis and result in a delay in the initiation of appropriate care. Polymerase chain reaction (PCR) testing of samples taken from mucocutaneous lesions yields consistently higher rates of HSV detection than does viral culture analysis and should be considered the gold standard for diagnosis of HSV infection in persons presenting with ulcerative disease [48].

For asymptomatic individuals, type-specific serologic testing based on glycoprotein G can accurately distinguish HSV-1 and HSV-2 infections with high sensitivity and specificity [49].

Treatment

The nucleoside analogues acyclovir, valacyclovir, and famciclovir inhibit HSV-1 and HSV-2 replication through specific inhibition of a virally encoded thymidine kinase. All have good oral

bioavailability; topical therapy offers little clinical benefit and is not recommended. Studies among HIV-1-infected individuals have shown that these medications are well tolerated in this population and, importantly, demonstrate no interaction with antiretroviral medications used in the treatment of HIV-1. Antiviral chemotherapy provides clinical benefits both as episodic treatment of symptomatic patients and as suppressive therapy for prevention of recurrent disease [44] (Table 10.7).

Table 10.7: Treatment regimens in HSV.

	Dosage	
Drug	Episodic Therapy	Suppressive Therapy
Acyclovir	400 mg orally 3 times per day for 5-10 days	400-800 mg orally 2-3 times per day
Famciclovir	500 mg orally 2 times per day for 5-10 days	500 mg orally 2 times per day
Valacyclovir	1,000 mg orally 2 times per day for 5-10 days	500 mg orally 2 times per day
Source: Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. Morb Mortal Wkly Rep 2006; 55: 1-94.		

Antiviral Resistance

Although acyclovir resistance was first documented more than 20 years ago, isolation of drug-resistant HSV remains rare (<1% of isolates).Among HIV-1-infected persons, rates of acyclovir resistance are also generally low (<5%), but drug-resistant disease can be a significant problem for severely immunocompromised patients, in whom a poor response to escalating doses of HSV antivirals may indicate acyclovir resistance. Notably, in vitro evidence of acyclovir resistance alone does not ensure poor clinical response to standard therapy, and thus routine acyclovir sensitivity testing is not indicated. Resistance to acyclovir implies resistance to valacyclovir, and most strains are also resistant to famciclovir. Intravenous foscarnet is the drug of choice for treatment of severe resistant disease. Topical cidofovir and foscarnet also have been used successfully [50].

APHTHOUS ULCERATIONS

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disorder found in men and women of all ages, races, and geographic regions. Recurrent aphthous ulcers in patients with HIV infection can cause significant morbidity [51].

Clinical Features

There are three forms of the lesions (minor, major, and herpetiform), with major aphthous ulcers (Figure 10.7) causing significant pain and potential for scarring. In HIV-infected individuals, these ulcers occur more frequently, last longer, and produce more painful symptoms. Similar ulcerations can involve the esophagus, rectum, anus, and genitals. The diagnosis of HIV-induced RAS requires a careful history of the condition, and a thorough extra- and intra-oral examination.



Figure 10.7: Recurrent aphthous ulceration.

(Photo courtesy: Dr Mubeen, Department of oral medicine,, Government Dental college and Research Institute, Bangalore)

Oral mucosal biopsies are required for non-healing ulcers in order to exclude the possibility of deep fungal , viral infections, and neoplasms. Local diseases, genetic, immunologic, and infectious factors all probably play a role in the causation. Treatments are aimed at promoting ulcer healing, reducing ulcer duration and pain while maintaining good nutrition, and preventing the frequency of recurrence. Initial therapy for infrequent RAS recurrences includes over-the-counter topical protective and analgesic products. Initial therapy for frequent RAS outbreaks requires topical anesthetics, and corticosteroids. Major RAS and non-healing minor or herpetiform RAS may require intralesional corticosteroids and systemic prednisone. Second-line immunomodulators for frequent and non-healing ulcers includes thalidomide and other immunomodulators [52].

Recurrent aphthous stomatitis (RAS), commonly known as canker sores, has been reported as recurrent oral ulcers, recurrent aphthous ulcers, or simple or complex aphthosis. RAS is the most common inflammatory ulcerative condition of the oral mucosa in North American patients. One of its variants is the most painful condition of the oral mucosa. Clinical evaluation of the patient requires correct diagnosis of RAS and classification of the disease based on morphology (MiAU, MjAU, HU) and severity (simple versus complex).

The lesions of RAS are caused by trauma, smoking, stress, hormonal state, family history, food hypersensitivity and infectious or immunologic factors. The treating clinician must identify or exclude associated systemic disorders or “correctable causes.” Behçet’s disease and complex aphthosis variants, such as ulcer vulvae acutum, mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, fever, aphthosis, pharyngitis, and adenitis (FAPA) syndrome, and cyclic neutropenia, should be considered. The association of lesions of RAS with hematinic deficiencies and gastrointestinal diseases can be treated with appropriate corrections [53].

KAPOSI'S SARCOMA OF ORAL CAVITY

Kaposi's sarcoma (KS) is an angioproliferative disorder caused by human herpes virus 8. KS of the oral cavity is often associated with KS at other sites and sometimes, may be the first manifestation of AIDS. It has a marked predilection for homosexual or bisexual males. The palate is the most common oral site of KS. Multiple lesions are not uncommon and often they are in different stages of development. Early lesions appear as red or blue colored plaques (Figure 10.8). The epithelium becomes stretched over the surface of the expanding lesions and may ulcerate.

A biopsy clinches the diagnosis. In early lesions, the lamina propria shows a focal perivascular chronic inflammatory infiltrate and proliferation of irregular thin walled vascular channels. Late lesions show proliferating randomly arranged spindle cells, erythrocytes (both inside and outside the vascular spaces) and deposits of hemosiderin.

Antiretroviral therapy promotes regression of KS. Oral Kaposi's sarcoma treated with radiotherapy has shown good results.

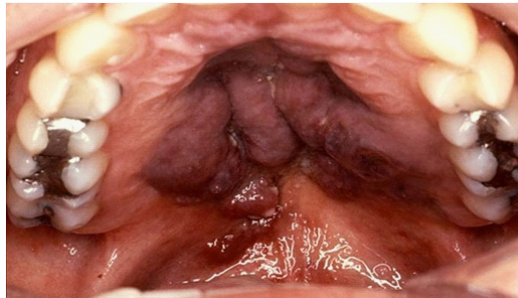


Figure 10.8: Kaposi sarcoma involving the hard palate.

(Photo courtesy: Dr Mubeen, Department of oral medicine,, Government Dental college and Research Institute, Bangalore)

OCULAR MANIFESTATIONS OF HIV

Introduction

The introduction of highly active antiretroviral therapy (HAART) has greatly changed the pattern and natural history of ocular diseases of HIV-infected patients, resulting from the immune recovery and reduction of opportunistic infections. However, ophthalmic complication continues to be concern in AIDS even in the HAART era, especially in developing areas, where absolute majority of HIV-positive patients live [54].

Risk Predictors of Ophthalmic Involvement in HIV

There are various factors that can be considered as predictors of eye involvement in HIV individuals. These include

1. CD4 count: CD4 T lymphocytes counts has been proved a reliable and important predictor of the risk for developing and indicator for managing ocular complications of HIV infection. Different ocular complications may develop at different CD4 threshold [55].
2. WHO clinical stage of HIV/AIDS. Stage 4 patients suffer the great chance to be affected. The prevalence of ocular manifestations in patients with stage 3 is greater than those with stages 1 and 2 [55].
3. Sexual practice. Studies have shown increased incidence of ocular complications in homosexuals [56].

Ophthalmic Manifestations

For descriptive purpose diseases of eye can be discussed under following headings (Table 10.8).

Table 10.8: Ocular manifestations in HIV.

Anterior Segment	• Herpes Zoster Ophthalmicus • Kaposi's Sarcoma of the Lids and/or Conjunctiva • Microsporidia • Molluscum contagiosum • Anterior uveitis
Neuro-Ophthalmic	• Orbital infection with Aspergillus • Progressive multifocal leukoencephalopathy (PML) • CNS toxoplasmosis • Cryptococcal meningitis
Retinal And Choroidal	• HIV-Related Retinal Microangiopathy • Infectious Retinitis and Choroiditis

HERPES ZOSTER OPHTHALMICUS

Herpes zoster is a common infection caused by the human herpes virus 3, the same virus that causes chickenpox.

Etiopathogenesis

It is a member of herpes viridae, the same family as the herpes simplex virus, cytomegalovirus and Epstein-Barr virus. Herpes zoster ophthalmicus occurs when a latent varicella zoster virus in the trigeminal ganglia involving the ophthalmic division of the nerve is reactivated. Of the three divisions of the fifth cranial nerve, the ophthalmic is involved 20 times more frequently than the other divisions [57].

Incidence

HIV positive patients have a 15–25 times greater prevalence of zoster compared to the general population [58].

Clinical Features

It can be grouped under the following headings.

- Prodromal phase
- Eruptive or vesicular phase
- Post herpetic neuralgia

Prodromal stage

Fever, flu like symptoms, malaise, fatigue, Hyperaesthesia, can occur during this stage and may persist for upto one week followed by vesicular phase.

Rash

Initially, erythematous macules appear, then progress into papules and vesicles, and later pustules, which rupture and crust, taking several weeks to heal. HIV positive patients may have a generalized vesicular rash and become very ill one to two weeks after the onset of the disease, resulting in very severe visual impairment. In the immuno-compromised patient, the dermatitis and ocular inflammatory disease are more prolonged and it is more difficult to prevent complications. Herpes zoster ophthalmicus may be the initial clinical manifestation of HIV infection [57].

Ocular manifestations of herpes zoster ophthalmicus

The skin manifestations of herpes zoster ophthalmicus strictly ‘observes’ the midline with involvement of one or more branches of the ophthalmic division of the trigeminal nerve, namely the supraorbital, lacrimal, and nasociliary branches. Because the nasociliary branch innervates the globe, the most serious ocular involvement develops if this branch is affected [57]. Classically, involvement of the tip of the nose (Hutchinson’s sign) has been thought to be a clinical predictor of ocular involvement [59]. It is important to note that patients with a positive Hutchinson’s sign have twice the incidence of ocular involvement, but one third of patients without the sign develop ocular manifestations [60].

Eyelid

The eyelids are commonly involved in herpes zoster ophthalmicus. They present with vesicular lesions on the eyelids that resolve with minimal scarring. Sometimes other complications like blepharitis, secondary bacterial infection, eyelid scarring, marginal notching, loss of eyelashes, trichiasis and cicatricial entropion, scarring and occlusion of the lacrimal puncta or canaliculi, ptosis, secondary to oedema and inflammation may also occur [57].

Conjunctiva

Conjunctivitis is one of the most common complications of herpes zoster ophthalmicus. The conjunctiva is often injected and oedematous, which may last for only one week [57]. Secondary bacterial infection with *Staphylococcus aureus* may complicate the situation.

Sclera

Nodular or diffuse Episcleritis or scleritis associated with herpes zoster may persist for months.

Cornea

Corneal complications occur in approximately 65% of cases with herpes zoster ophthalmicus [58]. Corneal involvement can result in significant visual loss. It presents with pain, photosensitivity and poor vision.

Epithelial keratitis: The earliest manifestation of corneal involvement is punctate epithelial keratitis. These punctuate lesions harbour live virus and may either resolve or progress into dendrites. The dendrites appear as elevated plaques and consist of swollen epithelial cells. They form branching or 'medusa-like' patterns and have tapered ends.

Stromal keratitis: This is an immune reaction to viral glycoprotein antigens deposited during the acute attack and possibly during late sub-clinical migration of the virus from the ganglion. Chronic stromal keratitis can lead to vascularization, corneal opacification, keratopathy, corneal thinning and astigmatism [57].

Uveal tract

Anterior uveitis occurs frequently with herpes zoster ophthalmicus. The inflammation is generally mild and transient, frequently causing a mild elevation of intraocular pressure [60]. Without timely and appropriate treatment the course of the disease may be prolonged and can lead to glaucoma and cataract [57].

Retina

The retinitis of herpes zoster ophthalmicus is often associated with anterior uveitis. It presents as necrotizing retinitis with haemorrhages and exudates, posterior vascular occlusions and optic neuritis. These lesions begin from the retinal periphery. The vision deteriorates rapidly as the disease progresses [57].

Post herpetic neuralgia and post herpetic itch

Pain and itching, late in the disease, are both acute and more common in HZO than in any other form of zoster. PHN is described as constant boring pain, sudden transient sharp pain, or pain elicited by usually non-painful stimuli [57,60].

Complications

1. Corneal neovascularization and scarring resulting in poor vision.
2. Neurotrophic ulcer with perforation.
3. Secondary bacterial or fungal infection.

4. Secondary glaucoma from uveitis or steroid treatment.
5. Necrotizing interstitial keratitis.
6. Vision loss from optic neuritis or chorioretinitis.

Treatment

Table 10.9: Treatment regimens in Herpes zoster ophthalmicus.

Site of involvement	Therapy
For herpes zoster skin lesions	Acyclovir 800mg orally five times daily for 7 to 10 days. Saline compresses-for crusted lesions.
Conjunctivitis	Topical lubrication and antibiotic drops.
Keratitis	Debridement or none for epithelial keratitis. Topical steroid drops for stromal keratitis. Topical lubrication and antibiotics for neurotrophic keratitis along with tissue adhesives and protective contact lenses to prevent perforation.
Uveitis	Topical steroids along with oral steroids and oral acyclovir. Topical NSAIDs and steroids for scleritis/episcleritis.
Acute retinal necrosis/ Progressive outer retinal necrosis	IV acyclovir-1,500 mg per day in three divided doses for 10 days followed by oral acyclovir 800mg 5 times daily for 14 weeks.

KAPOSI'S SARCOMA

Ocular involvement can occur in AIDS related Kaposi sarcoma common area being conjunctivae or eyelids.

Incidence

Eye involvement occurs in 20-24% of patients with AIDS-related Kaposi sarcoma.

Etiology

Human herpesvirus-8 (HHV-8) DNA or Kaposi sarcoma-associated herpesvirus (KSHV) has been implicated with patients who are HIV-negative or HIV-positive [61].

Clinical Features

Depending on the site of involvement patients can present with varied manifestations. They can present with pain, photophobia, recurrent red or bloody eyes, irritation and foreign body sensation, epiphora, dry eyes, mucopurulent discharge, heavy or swollen eyelids, cosmetic disfigurement of the eyelids, inability to close the eyes, visual obstruction, blurred vision. Conjunctival involvement may present with subconjunctival hemorrhage, injection, and chemosis.

Examination shows macular/ plaque like/ nodular purplish-red to bright-red lesions which are highly vascular along with surrounding telangiectatic vessels. Lesions can involve the eyelids, conjunctiva, caruncle, lacrimal sac and rarely are found inside the orbit with choroidal involvement [62].

Differential Diagnosis

It has to be differentiated from eyelid basal cell carcinoma, blepharitis, orbital cellulitis,

cavernous hemangioma, hordeolum, subconjunctival hemorrhage.

Diagnosis

Cutaneous or conjunctival biopsy of the lesion may be necessary for a definitive diagnosis.

Treatment

The goal of therapy is to relieve ocular irritation, mass effect, and disfigurement.

For AIDS-related Kaposi sarcoma, consider immune reconstitution with triple antiviral medication [63].

Various treatment regimens are available. They are as shown in Table 10.10.

Table 10.10: Treatment regimens for Kaposi’s sarcoma.

	Drugs	Dose and duration
Combination therapy (ABV)	Adriamycin	40 mg/m ² every 4 weeks or 20 mg/m ² every 2-3 weeks. 10 U/m ² every 2 weeks. 1.4 mg/m ² with 2 mg maximum dose every 2 weeks.
	Bleomycin sulphate	
	vinblastine sulfate	
Single-agent therapies	Liposomal daunorubicin Pegylated liposomal doxorubicin	40 mg/m ² intravenously (IV) every 2 weeks until complete response. 20 mg/m ² every 3 weeks.
Alternative therapies	Paclitaxel	Paclitaxel (Taxol) is administered at 135 mg/m ² IV over 3 hours every 3 weeks or a total dose of 100 mg/m ² given IV over 3 hours. every 2 weeks.*
Intralesional chemotherapy [64]	Interferon alfa-2a	0.5 mL of 3 million IU in a subconjunctival injection adjacent to the tumor [65,66].
**Recommendation to prevent hypersensitivity reactions: 1. Premedication with Dexamethasone 10 mg orally (PO) 12 hours before treatment. 2. Diphenhydramine 50 mg IV 30 minutes prior to treatment. 3. Cimetidine or ranitidine IV 30 minutes before treatment.		

MICROSPORIDIAL INFECTIONS

Microsporidial keratoconjunctivitis is a rare ocular complication of HIV/AIDS.

Etiology

Microsporidia are obligate intracellular spore-forming eukaryotic protozoan parasites, some of which are pathogenic in humans [67,68]. The pathogenic genera which affect humans are *Encephalitozoon*, *Nosema*, *Enterocytozoon*, *Trachipleistophora*, and *Pleistophora* [69]. The spores are resistant to degradation and have the capacity to survive in the environment for up to 4 months in its infective form. Mode of infection in humans is through ingestion, inhalation, or sexual transmission of spores [68,70].

But how exactly microsporidia enter into the cornea is not clear the possible mode could be traumatic inoculation or contact with contaminated water or food [70].

Clinical Features

Clinically it is present in 2 forms.

1. In immunocompetent individual it presents as necrotizing stromal keratitis
2. In HIV-infected individuals it presents as an epithelial keratoconjunctivitis

The common presenting symptoms are foreign body sensation, dryness, redness, reduced visual acuity, and photophobia [68].

Bilateral punctate epithelial involvement of the cornea with white intraepithelial infiltrates that stain irregularly with fluorescein is the typical pattern of ocular microsporidiosis described in immunocompromised individuals [71].

Investigations

Following investigations can be done

- Scrapings or biopsy of the conjunctiva or cornea.
- Transmission electron microscopy (gold standard)
- Molecular methods (polymerase chain reaction)

Treatment

Microsporidial infections in HIV-infected individuals responds to combination of antibiotics and antiparasitic agents, including topical propamidine isothionate, topical fumagillin, topical fluoroquinolones, oral albendazole, and/or oral itraconazole. However, treatment often has been followed by recrudescence of infection [68,70,72-74].

ANTERIOR UVEITIS

Uveitis is an intraocular inflammatory condition involving the uveal tract and adjacent structures, and due to a large group of various diseases [75-77] among which HIV infection is one of the cause.

Etiology

The various associated conditions resulting in uveitis are given in the Table 10.11

Table 10.11: Conditions causing Uveitis.

• Herpes zoster ophthalmicus [78]. • Tuberculosis [79]. • CMV retinitis [79]. • Cryptococcal retinochoroiditis [80]. • P. Carinii [81].

CMV RETINITIS

Cytomegalovirus (CMV) retinitis is the most common cause of vision loss in patients with acquired immunodeficiency syndrome (AIDS).

Incidence

CMV retinitis afflicted 25% to 42% of AIDS patients in the pre-highly active antiretroviral therapy (HAART) era, with most vision loss due to macula-involving retinitis or retinal detachment. The introduction of HAART significantly decreased the incidence and severity of CMV retinitis [82].

Etiopathogenesis

Cytomegalovirus (CMV), a ubiquitous organism, is the largest of the herpes viruses [83].

Healthy individuals infected with CMV frequently remain asymptomatic, although some develop an influenza-like syndrome characterized by fever, chills, malaise, myalgias, and arthralgias [82]. People with normal immune systems rarely develop long-term sequelae. Similar to other herpes viruses, CMV then enters a latent state, continually suppressed by cell-mediated immunity [82]. CMV remains latent unless the patient suffers from a significant local (regional corticosteroid therapy) or systemic immunodeficiency, acquired immunodeficiency syndrome (AIDS), pharmacologic immunosuppression to prevent allograft organ transplant rejection, local and systemic corticosteroid therapy, or an autoimmune condition such as Wegener's granulomatosis. Recurrent CMV infections may cause colitis, encephalitis, or retinitis (which account for 75% to 85% of CMV end-organ disease) [82,84].

Clinical Features

Presenting symptoms vary depending on the location of retinal involvement. Posterior lesions present with diminished visual acuity. More peripheral lesions initially can be asymptomatic. Floaters often are noted if significant vitreitis is present. The eye usually is white and quiet. CMV retinitis is a slowly progressive disease, requiring weeks to months to involve the entire retina [85,86]. Vision is lost with involvement of the posterior pole (macula or optic nerve) or retinal detachment [87].

Investigations

Eye examination include the following

- External examination of the lids and adnexa
- Visual acuity as a baseline.
- To check field of vision
- Ocular motility

- Slit lamp examination
- A dilated fundus examination with indirect ophthalmoscopy

Ocular Findings

- Stellate keratitic precipitates (KP) on the corneal endothelium [88-90].
- Posterior Lesions- appear along retinal vessels as large areas of thick white infiltrate accompanied by retinal hemorrhage described as “pizza pie” or “cheese pizza” in appearance (Figure 10.9).
- The peripheral type of lesion demonstrates a more granular appearance with satellite lesions and less hemorrhage. Behind the advancing border is necrotic retina with mottled pigmentation from hyperplasia of the retinal pigment epithelium (RPE).
- Retinitis produces wide areas of necrosis, scarring, and atrophy.
- Retinal vascular occlusion/nonperfusion can be seen on fluorescein angiogram [91].
- Peripheral holes and tears can be seen
- Optic neuritis can develop without apparent retinitis [92].



Figure 10.9: CMV Retinitis

(Photocourtesy: Minto ophthalmic Research Institute, Bangalore)

Treatment

Table 10.12: Treatment regimens for CMV retinitis.

Drug	Mode of Action	Dosage	Side effects
Intravenous therapy			
Ganciclovir	Triphosphate form interrupts viral DNA synthesis by competing with deoxyguanosine triphosphate.	*Induction- twice daily at a dose of 5 mg/kg. Maintenance- For weeks to months	Hematologic abnormalities (neutropenia, anemia, and thrombocytopenia) Birth control measures to be adopted in reproductive age group females.
Foscarnet	It interferes with the binding of the diphosphate to the viral DNA polymerase	Induction -180 mg/kg (usually given as 90 mg/kg twice daily) followed by maintenance therapy of 90 mg/kg once daily for weeks to months.	Nephrotoxicity.
Cidofovir	Targets the viral DNA polymerase by acting as a chain terminator.	Induction dose- 5 mg/kg once weekly for two weeks, followed by 5 mg/kg every other week during maintenance.	Renal toxicity and ocular hypotony.
Oral therapy			
Valganciclovir	Prodrug of ganciclovir.	*Induction therapy, typically 900 mg once daily for 2–3 weeks, Maintenance therapy is usually 450 mg once daily.	Hematologic (neutropenia, anemia), and gastrointestinal (diarrhea, nausea, and vomiting).
Intravitreal therapy			
Ganciclovir	As above	Doses ranging from 200 µg/0.1 mL to 2000 µg/0.1 mL. Twice-weekly injections are given during the induction phase, followed by weekly injections during maintenance.	Vitreous hemorrhages (3%), retinal detachments (8%), and endophthalmitis.
Foscarnet injections	As above	Induction therapy six injections of 2400 µg given at 72-hour intervals followed by weekly maintenance injections.	Vitreous hemorrhages (3%), retinal detachments (8%), and endophthalmitis.
Fomiversin	It hybridizes with and blocks expression of CMV mRNA.	Two intravitreal injections every other week were followed by monthly maintenance injections.	Vitreous hemorrhages (3%), Retinal detachments (8%), and endophthalmitis.
Cidofovir	As above	20 µg every 5–6 weeks	Vitreous hemorrhages (3%), retinal detachments (8%), and endophthalmitis.

OCULAR TOXOPLASMOSIS

It is an infective condition caused by *Toxoplasma gondii*.

Incidence

Only 1-2% of patients with the human immunodeficiency virus (HIV) are affected with ocular toxoplasmosis.

Etiopathogenesis

Toxoplasmosis is the infection caused by *Toxoplasma gondii* an obligate intracellular protozoan parasite. It belongs to the phylum Apicomplexa.

It persists in 3 major forms

- **Oocysts:** These are shed in the feces.
- **Tachyzoites:** These are rapidly multiplying organisms present in the tissues.

- **Bradyzoites:** These are slowly multiplying organisms present in the tissues.

Its life cycle and pathogenesis is given in Figure 10.10.

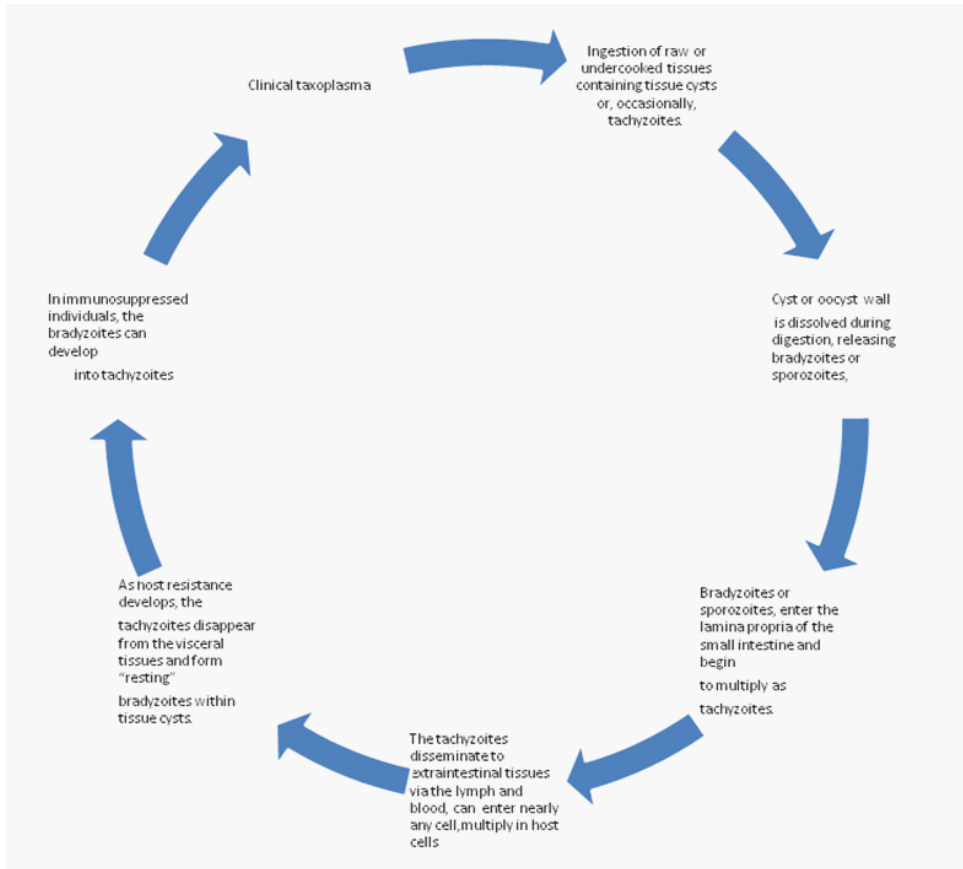


Figure 10.10: Life cycle and pathogenesis of toxoplasma.

Clinical Features

The hallmark of ocular toxoplasmosis is a necrotizing retinochoroiditis, which may be primary or recurrent. In primary ocular toxoplasmosis, a unilateral focus of necrotizing retinitis is present at the posterior pole in more than 50% of cases. The area of necrosis usually involves the inner layers of the retina and is described as a whitish, fluffy lesion surrounded by retinal edema. The retina is the primary site for the multiplying parasites, while the choroid and the sclera may be the sites of contiguous inflammation.

When the disease involves the optic nerve, the typical manifestation is optic neuritis or papillitis associated with edema, often called Jensen disease.

Treatment

In the case of ocular toxoplasmosis, several therapeutic regimens have been recommended as shown in table 10.13.

Table 10.13: Treatment regimens in Ocular toxoplasmosis.

Regimens	Drugs prescribed
Triple drug therapy	• Pyrimethamine (Loading dose of 75-100 mg during the first day, followed by 25-50 mg on subsequent days.) • Sulfadiazine (Loading dose of 2-4 g during the first 24 h followed by 1 g qid). • Prednisone (1 mg/kg of weight).
Quadruple therapy	• Pyrimethamine. • Sulfadiazine. • Clindamycin. • Prednisone.
To prevent recurrent toxoplasmic retinochoroiditis	• A combination of 60 mg of trimethoprim and 160 mg of sulfamethoxazole given every 3 days.
During pregnancy	• 1st trimester- Spiramycin and sulfadiazine. • 2nd trimester- spiramycin, sulfadiazine, pyrimethamine, and folinic acid. • 3rd trimester- Spiramycin, pyrimethamine, and folinic acid.
• Topical corticosteroids and topical cycloplegic agents are used depending on the anterior chamber reaction.	

NAIL MANIFESTATIONS IN HIV

Nail abnormalities can be a revealing sign of underlying disease, and because the nails are readily examined, a convenient diagnostic tool, as well [93]. Nail changes are classified according to whether they occur in the morphology (shape) or color of the nail. Fingernails usually provide more accurate information than toenails because clinical signs on toenails are often modified by trauma [94]. Diseases of the nail may be observed in up to 32% of patients [95]. Some of these nail changes, such as proximal white subungual onychomycosis, are well-defined clinical entities, which appear to be related to the effects of HIV infection on the immune system. Severe herpetic infection of the distal fingers, which may result in loss of the growing nail on that finger, has been reported. The spectrum of psoriasis, psoriatic arthropathy, and Reiter's syndrome may have typical nail changes: pitting, subungual hyperkeratosis, and lateral and distal onycholysis. The existence of the yellow nail syndrome in patients with AIDS is still controversial. Episodes of severe illness in AIDS patients may result in Beau's lines.

Proximal White Subungual Onychomycosis

The incidence of onychomycosis (Figure 10.11, Figure 10.12 a & b) caused by dermatophytes has diminished since the introduction of the highly active antiretroviral therapy in the 1990s. Nonetheless, onychomycosis still is a common and recurrent finding, four times more common in HIV infected individuals than in the general population, which is reported to be up to 23% [96,97]. The main etiological agent continues to be *Trichophyton rubrum*.

Proximal subungual onychomycosis (PSO) is also known as proximal white subungual onychomycosis (PWSO), a relatively uncommon subtype, and occurs when organisms invade the nail unit via the proximal nail fold through the cuticle area, penetrate the newly formed nail plate, and migrate distally.

The clinical presentation includes subungual hyperkeratosis, leukonychia, proximal onycholysis, and destruction of the proximal nail plate [98]. The pattern of growth in PSO is from the proximal nail fold on the lunula area distally to involve all layers of the nail.

Although PSO is the most infrequently occurring form of onychomycosis in the general population, it is common in AIDS patients and is considered an early clinical marker of HIV infection [98].

Nail Sampling in PWSO

While collecting nail specimen, because the fungus invades under the cuticle before settling in the proximal nail bed while the overlying nail plate remains intact, the healthy nail plate should be gently pared away with a no. 15 scalpel blade. A sharp curette can then be used to remove material from the infected proximal nail bed as close to the lunula as possible.

Treatment

Two general categories of concern are important in the context of selection of appropriate therapy: disease-oriented and patient-oriented factors. Selection of an agent depends, first and foremost, on the accurate identification of the infecting organism [98]. However, of considerable importance, too, are patient-related factors that may influence decision-making [98]. Host-related factors such as a compromised immune system (typically seen in individuals infected with HIV), diabetes mellitus, or peripheral vascular disease may also impede success.

Topical treatments are limited because they cannot penetrate the nail deeply enough, so they are generally unable to cure onychomycosis. Topical medicines may be useful as additional therapy in combination with oral medicines. These topical agents should only be used if less than half the nail is involved or if the person with onychomycosis cannot take the oral medicines. Topical preparations include amorolfine, ciclopirox olamine, sodium pyrithione, bifonazole/urea, propylene glycol-urea-lactic acid, imidazoles, such as ketoconazole, and allylamines, such as terbinafine.

Newer oral medicines are available. These antifungal medicines are more effective because they go through the body to penetrate the nail plate within days of starting therapy. Common side effects include nausea and stomach pain.

Fluconazole is not approved by the Food and Drug Administration (FDA) for treatment of onychomycosis, but it may be used by some clinicians as an alternative to itraconazole and terbinafine.



Figure 10.11: Superficial onychomycosis.

(Photocourtesy: Victoria Hospital, Bangalore)



Figure 10.12a & b: Proximal subungual onychomycosis.

(Photocourtesy: Victoria Hospital, Bangalore)

Acute Paronychia

It is erythema, inflammation and pain occurring in proximal nail folds of several nails immediately after intake of the offending drug. This is because of the toxic effect of the antiretroviral drugs [99] on nail epithelia resulting sometimes in nail loss. Paronychia resolves with stopping of drug and is frequently followed by onychomadesis. Rechallenge is often positive. It can also occur secondary to methotrexate [100] and retinoids [101].

Pyogenic Granulomas PG

It is also known as granuloma telangiectaticum, granuloma pediculatum or lobular capillary hemangioma. PG is a benign vascular tumour, presenting as a rapidly evolving, solitary, sessile or polypoid vascular nodule, most commonly seen on the hands (especially fingers), the feet, lips, face, upper trunk and the mucosal surfaces of the mouth and perianal area.

In the nail unit, pyogenic granuloma (Figure 10.13) generally arises in the nail folds. Sometimes it may be subungual when arising from the nail matrix. In this location, it is generally associated with onycholysis. The lesion has a prominent collarette at the base and is often tender. Bleeding occurs with minor trauma and causes much patient morbidity. Pain is generally absent except when the lesion becomes infected.



Figure 10.13: Pyogenic granuloma.

(Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore)

The exact etiopathogenesis is unknown. It is believed to be a reactive hyperproliferative vascular response to a variety of stimuli, such as infective organisms, penetrating injury, hormonal factors and drugs. Granulation tissue with formation of painful bleeding nodules may arise from the proximal and lateral nail folds of several nails due to activation of angiogenic factors by the offending drugs. The occurrence of the same side effects with different drugs (eg, retinoids and indinavir), is probably due to the fact that the HIV-1 protease catalytic site and cellular retinoic acid-binding proteins have structural analogues. Ciclosporin [102], lamivudine, capecitabine and cetuximab can also cause pyogenic granuloma.

Diagnosis is generally clinically apparent; however differentiation from other benign and malignant tumours (especially cavernous angioma, pseudo-pyogenic granuloma, hemangiosarcoma, amelanotic melanoma, Spitz nevus or metastatic tumours) may become difficult at times.

Histological examination shows proliferation of blood capillaries with a radiating pattern set in a loose oedematous collagenous matrix [103]. The epidermis shows inward growth at the base of the lesion, producing an epidermal collarette and causing in some cases slight pedunculation of the lesion. A dermal mixed inflammatory infiltrate is a common finding.

Older pyogenic granulomas tend to organize and partly fibrose with fibrous septa intersecting the lesion and producing a lobular pattern. Recently, dermoscopy has been studied as a diagnostic tool for the diagnosis of this disorder. A reddish homogeneous area surrounded by a white collarette was seen most frequently. Importantly, there is absence of known dermoscopic signs of other tumours. Therapy should be as simple as possible to avoid disfiguring scars or nail deformity.

Treatment failure and local recurrence of the lesion is a problem with all treatment methods.

The lesion may be removed by excision at its base followed by electrodesiccation or application of Monsel's or aluminum chloride solution. The use of argon, CO₂, and 585-nm flash lamp pumped pulsed dye lasers has also been described [104].

Hyperpigmentation of Nails

Melanonychia

Nail matrix melanocytes are activated by several drugs to produce melanin leading to longitudinal or transverse bands of melanonychia varying from brown to black color pigmentation. When the band is isolated, it is important to distinguish a band of longitudinal melanonychia (Figure 10.14) due to drugs from a band of longitudinal melanonychia due to a nail matrix melanocytic neoplasm. In doubtful cases, a nail matrix biopsy is mandatory.

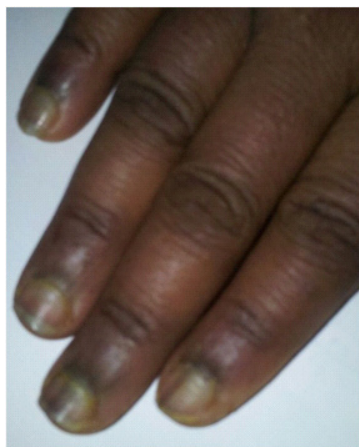


Figure 10.14: Longitudinal Melanonychia.

(Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore)

Drug-induced melanonychia most commonly appears 3 to 8 weeks after drug intake.

Pigmentation is usually reversible within 6 to 8 weeks, but may persist for months after drug interruption. Rechallenge is usually negative. The pathogenesis of nail melanocyte activation is unclear and is independent of melanocyte-stimulating hormone, corticotropin activity and ultraviolet light. Hyperpigmentations due to melanin incorporation are occasionally observed as mucosal hyperpigmentation also.

The longitudinal discoloration of the nails is diagnosed especially during therapy with azidothymidine (AZT), more rarely with lamivudine (3TC), with an increased incidence and intensity in the dark skin type. The hyperpigmentation may fade after switching medications (body of evidence: C III) [105].

Nail changes due to antiretroviral drugs

Table 10.14: Nail changes due to antiretroviral drugs.

Drugs		
<i>Nucleotide analogues reverse transcriptase inhibitors</i>	Lamivudine	Paronychia, Pseudo pyogenic granuloma, Longitudinal melanonychia.
	Zidovudine	Bluish to brown diffuse nail Discoloration, Transverse or longitudinal bands, Faint blue pigmentation of the Lunula, Slow nail growth Paronychia.
<i>Protease inhibitors</i>	Lopinavir Nelfinavir Indinavir	Paronychia. Pyogenic granuloma.

Yellow nail syndrome

The color is secondary to thickening, and a tinge of green may also occur in the presence of infection. Loss of cuticle, obscuring of lunula and increased curvature both longitudinally and horizontally are seen. The condition often seen in adults is accompanied with acquired lymphoedema and a nasal sinus or respiratory disease. All nails get affected and obvious is the slow nail growth. Evaluation for occult malignancies, hypothyroidism and AIDS needs to be done. Nail changes are often permanent [106].

HAIR CHANGES IN HIV

Seborrheic Dermatitis

Pityrosporum ovale causes pityrosporum folliculitis and plays a significant role in the pathogenesis of seborrheic dermatitis. Seborrheic dermatitis afflicts up to 80% of HIV-infected individuals and is often observed in patients in the early stage of HIV infection [107]. It is one of the earliest clinical markers of HIV infection. Although most persons tend to have a chronic course with seborrheic dermatitis, HIV-infected individuals generally have a more severe condition, especially those with advanced stages of HIV disease [108].

Clinically, seborrheic dermatitis appears as scaling and erythema in the hair-bearing areas such as eyebrows, nasolabial folds, beard, and moustache areas, retroauricular fold, scalp, chest, and pubic area. The density of *Pityrosporum ovale* on the involved skin correlates with the severity of the seborrheic dermatitis [109]. At times, the organism causes an infection of the hair follicle, pityrosporum folliculitis, which is characterized by numerous pruritic papules or pustules occurring on the upper trunk and proximal arms. Overgrowth of *Pityrosporum ovale* on the keratinized skin causes pityriasis versicolor, characterized by well-demarcated scaling plaques (hypo- or hyperpigmented), most commonly on the trunk. These lesions are very extensive in HIV- infected patients.

It differs histologically from typical seborrheic dermatitis by the presence of keratinocyte necrosis and inflammatory changes at the dermo-epidermal junction.

Seborrheic dermatitis responds to low potency corticosteroids or topical antifungals or a combination of both [110]. Pityrosporum folliculitis responds to topical antifungals or 10–14 days course of azole drugs. In severe cases of seborrheic dermatitis, systemic antimycotics are given: ketoconazole (200 mg/day), itraconazole (100 mg/day), or terbinafine (250 mg/day).

Follicular Pruritic Eruptions

Follicular pruritic eruptions can be caused by eosinophilic folliculitis, Demodex folliculitis, staphylococcal folliculitis, and pityrosporum folliculitis.

Staphylococcal Folliculitis

Staphylococcus aureus is the most common pathogen in cutaneous and systemic bacterial

infections occurring in HIV-infected individuals. A wide range of *S. aureus* cutaneous and soft tissue infections occurs in HIV-infected individuals, including impetigo, bullous ecthyma, papular and plaque like folliculitis, furuncles and carbuncles, cellulitis, botryomycosis, and pyomyositis. Their incidence increases with the degree of immunodeficiency [111].

The diagnosis of staphylococcal pyoderma is established by Gram stain and culture. The treatment of *S. aureus* infection in HIV-infected persons is identical to that for HIV seronegative persons. For recurrent infections, rifampicin 600 mg once daily for five to ten days may be added as a second oral antimicrobial agent to clear nasal carriage and enhance therapeutic response. Long-term application of mupirocin in the nares may prevent recurrent nasal colonization.

Demodicidosis

Demodex folliculorum is a vermiform mite that inhabits the pilosebaceous units of the nose, forehead, chin, and scalp [112,113]. It may be a normal commensal, rarely producing disease in some individuals with HIV. It causes a pruritic papular eruption mainly limited to the face and neck. Some rosacea-like lesions may also be caused by *Demodex*. Skin scrapings show numerous *Demodex* mites. Demodicidosis must be differentiated from staphylococcal folliculitis, pityrosporum folliculitis, pruritic papular dermatitis of HIV, and seborrheic dermatitis. Treatment of the eruptions in which *Demodex* has been implicated consists of applying 1% permethrin, 10% sulfur, 1% lindane, 10% benzyl benzoate, pilocarpine gel or 5% benzoyl peroxide. Oral ivermectin and metronidazole have also been used [113].

HIV-associated eosinophilic folliculitis

Eosinophilic folliculitis (EF), is typically seen in HIV-infected individuals with a CD4 count less than 100. It is a chronic, pruritic, culture-negative folliculitis that is unresponsive to systemic antibiotics and that occurs in HIV-infected patients. It has also been reported in HIV-seronegative individuals with immune dysregulation.

EF is a chronic, extremely pruritic dermatosis. EF is characterised clinically by multiple reddish, oedematous, follicular papules arising on the face, neck, upper trunk, and proximal upper extremities. Most lesions (90%) occur above the nipple line on the anterior trunk, and typically extend down the midline of the back to the lumbar spine. The disease waxes and wanes in severity and may spontaneously clear only to flare unpredictably. Occasionally pustules are seen. Excoriations and postinflammatory hyperpigmentation occur commonly secondary to chronic scratching. Photosensitivity may be present [114].

EF must be differentiated from staphylococcal folliculitis, Pityrosporum folliculitis, dermatophyte folliculitis, herpetic folliculitis, scabies, acne vulgaris, rosacea, papular urticaria and papular dermatitis [114].

Diagnosis is made by histopathology, which is characterized by eosinophilic and neutrophilic

infiltration of the hair follicle. The serum IgE and blood eosinophil count may be raised. The most effective therapy is prednisone.

Oral isotretinoin (0.5–1 mg/kg per day), itraconazole (200 mg twice a day), and topical tacrolimus or pimecrolimus may be effective. UVA and UVB phototherapy, potent topical corticosteroids, and nonsedating antihistamines ameliorate pruritus significantly and clear the eruptions. Sedating antihistamines such as doxepin are most effective for symptomatic control of nocturnal pruritus.

Straight Hair Sign

This phenomenon has been described both in symptomatic and asymptomatic individuals, often preceding the diagnosis of AIDS [115-117]. The “straight hair sign” is now considered a hallmark of HIV infection. The “straight hair sign” phenomenon has been attributed to a variety of factors, including caloric and protein malnutrition as well as deficiencies in minerals that affect hair growth, such as copper, zinc, and selenium [118]. Endocrine factors, such as decreased androgen levels and increased estradiol levels, are seen in patients with liver disease associated with alcoholism and late-stage HIV disease, and they are thought to play a role in abnormal hair development [115,119].

Other Manifestations

Severe tinea capitis (Figure 10.15) with significant hair loss has been reported in several adult patients with AIDS. Changes in hair length and consistency, hypertrichosis of eyelashes and very long eyelashes, alopecia areata, premature graying of the hair have been reported in association with HIV infection.



Figure 10.15: Tinea capitis.

(Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore)

CONCLUSION

Disease defining manifestation of HIV includes cutaneous and systemic manifestations. The oral manifestations of HIV act as a key signal in suspecting HIV, while severe ocular manifestation

leading to blindness as a sequelae of HIV associated conditions also need an eagle eye of supervision. The nail changes in HIV are more sort of secondary to antiretroviral drugs. The hair related changes are either secondary to deficiency of hair related vitamins and growth factors or due to hair follicle related infections and infestations.

Nonetheless, these groups of manifestations are characteristic and vital in understanding HIV.

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