Chapter

HIV Infection and Oral Manifestations: An Update

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Abstract

Human immunodeficiency virus (HIV) causes a complete depletion of the immune system; it has been a major health issue around the world since the 1980s, and due to the reduction of CD4+ T lymphocytes levels, it can trigger various opportunistic infections. Oral lesions are usually accurate indicators of immunosuppression because these oral manifestations may occur as a result of the compromised immune system caused by HIV infection; therefore, oral lesions might be initial and common clinical features in people living with HIV. So, it is necessary to evaluate and understand the mechanism, prevalence, and risk factors of oral lesions to avoid the increase morbidity among those with oral diseases.

Keywords: HIV, acquired immunodeficiency syndrome, immune deficiency disease, oral cavity, oral manifestations, periodontal disease

1. Introduction

Since the twentieth century, the human immunodeficiency virus (HIV) has been a global public health problem, and for about 40 years, the structural aspects,

pathogenic mechanisms, forms of transmission, and cycle of infection have continued to be studied in order to reach a detailed understanding of the infection of this virus in its carriers [1–3], especially in key populations such as men who have sex with men, transgender people, sex workers, people who inject drugs, indigenous people, and prisoners [4–11], in order to seek to develop solutions for immunosuppression caused by HIV, such as antiretroviral therapies and even effective vaccines [12–14].

HIV is a member of the order *Ortervirales*, family *Retroviridae*, subfamily *Orthoretrovirinae*, and genus *Lentivirus*, which are currently grouped into two types, HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2) and infections caused by HIV. Lentiviruses generally have a chronic aspect of development, with a long period of clinical latency and persistent viral replication, and cause progressive immunosuppression in their hosts [2, 15–17]. Both HIV-1 and HIV-2 will infect specific cells of the immune system, such as CD4+ T lymphocytes, macrophages, dendritic cells, and mucosal lining cells such as vaginal, anorectal, and oral, which will later spread to regional lymph nodes and, consequently, into the bloodstream, which will cause changes in the development and function of the immune response [18–23]. Although certain differences can be seen between the two types, such as HIV-2 greater predilection for central nervous system infections and a lower virulent potential than HIV-1 [24–28].

In practice, HIV transmission requires direct exposure to blood or fluids, or secretions contaminated with areas such as skin or mucous membranes with mechanical trauma or discontinuity of integrity, either by punctures with needles or cuts with cutting instruments or abrasions of mucosal tissues during sexual relations or the vertical route [29, 30]. Furthermore, it should be understood that HIV transmission is directly dependent on the viral load, its concentration in the infected body fluid, and the susceptibility of the host [31, 32]. It is necessary to emphasize this because HIV cannot survive outside the bloodstream or lymph tissue and is easily inactivated by exposure to common detergents and disinfectants, so understanding the means of transmission is essential to reduce the stigma around people living with HIV (PLWH), mainly among health professionals [33].

Between the initial contamination and severe cases of immunosuppression such as the acquired immunodeficiency syndrome (AIDS), basically, the pathogenesis of HIV infection and the progression between its phases are related between the properties of the virus, risk factors, and the host's immune response. Patient adherence to antiretroviral therapy, that is, the balance between these items, will determine the development of the symptomatic and asymptomatic phase, AIDS, and even the medium- and long-term experience of the host [2, 32–34]. Among the main properties of HIV is the viral replication cycle that can be in the following steps: (1) binding in the cell receptor; (2) cell surface fusion; (3) uncoating; (4) reverse transcription; (5) integration of proviruses; (6) translation; (7) assembly of viral proteins; (8) budding; and (9) release [2, 35, 36].

In summary, HIV replication occurs when the heterodimer proteins gp120 and gp41 of the viral envelope bind to proteins in the cell membrane of target cells; that is, gp120 binds to CD4 monomeric glycoprotein on the cell surface of T lymphocytes or precursor T cells of lymphatic tissues such as bone marrow and thymus, macrophages, eosinophils, dendritic cells, and microglial cells [2, 21, 37–39] and after that, viral RNA is released inside the cells and tissues that will follow its cycle replication from the early stages of infection can be intensely active, as well as allowing the establishment of a latent infection, particularly known as permanent viral reservoirs promoting a major obstacle in the complete eradication of HIV infection and effectiveness in antiretroviral treatment [40–44].

It is estimated that between 10 and 12 days after the initial infection, the levels of viral RNA viremia in the blood plasma will increase slightly providing the anti-HIV

antibody seroconversion phase that occurs in a variable period of 3–5 weeks, and this period of the infection is critical, as it indicates that the infected host is transmissible [45–48] and is also possible to detect viral RNA in blood plasma by amplification methods such as reverse transcription polymerase chain reaction (RT-PCR) [49–51]. However, prior to the seroconversion of anti-HIV antibodies, there is a period of time in which the infection is present, but the antibodies are still not detectable; this period is known as the serological window, which, according to the literature, varies from 3 months to a longer period [52–54].

In the acute phase, the CD4+ T cell count decreases dramatically, while the serum levels of viral particles rise proportionally, which is usually of short duration because the host begins to generate humoral and cellular immune responses that partially control viral replication [55, 56]. And as the specific immune response progresses, primarily mediated by cytotoxic CD8+ T cells that produce the initial control of viral replication at this stage of infection, viremia tends to decrease until it reaches stable or undetectable levels signaling the beginning of the chronic phase [57–59]. However, even with this immune response, it is possible to verify the qualitative functional impairment of the immune responses due to HIV, which can be described as a dysfunction of CD4+ T cells and other cells of the immune system, with the need to complement the host's defense lines with antiretroviral therapy [2].

Clinically, PLWH in most cases will present symptoms from a few days to weeks from exposure and contamination by HIV; usually, individuals have systemic symptoms similar to flu or mononucleosis, such as fever, weight loss, night sweats, constant diarrhea, malaise, lymphadenopathy, arthralgia, pharyngitis, and myalgia [60, 61]. These clinical characteristics mentioned above are heterogeneous and may vary between cases; however, something that is common and previously documented is that individuals who delay in starting antiretroviral therapy or maintain inconsistency in treatment and who present the above-mentioned symptoms for a longer duration, which may worsen the infection, leading to systemic and oral opportunistic infections, secondary malignancies, and neurologic manifestations [62, 63].

2. HIV and oral manifestations

2.1 HIV and oral cavity

Systemic and local opportunistic infections caused by HIV will directly impact the innate immune response, impact and trigger negative consequences on quality of life, and increase the morbidity of HIV infection; among the main local opportunistic infections, we cite oral lesions (OLs) [64, 65]. OLs are commonly among the first signs and symptoms of HIV infection, and certain lesions, such as necrotizing periodontitis (NP), Kaposi's sarcoma, or linear gingival erythema (LGE), as they are naturally found in PLWH, can serve as a means of diagnosis or indications for individuals with HIV infection status unknown [66–68].

In the past, when the individual was diagnosed with HIV or was undisciplined about antiviral treatment and oral hygiene, the occurrence of certain OLs could predict the progression of chronic infection to acute phases and even AIDS [68, 69]. The presence of OLs in PLWH using antiretroviral therapy (ART) can serve as a marker of viral resistance to medication and, consequently, reduce the effectiveness of ART, indicating the replacement of the current medication. According to Heron and Elahi [70], the prevalence of OL will vary with the use of ART, so specific lesions,

such as candidiasis, hairy leukoplakia, and Kaposi's sarcoma, clinically, have shown a lower prevalence in patients who are regular users; however, evidence has shown that lesions, such as oral warts (OWs) and salivary gland diseases, are more prevalent resulting from the use of ART [71].

Oral health care is a vital component for maintaining a satisfactory general state of health and quality of life for PLWH, so it is interesting for health professionals to recognize and reinforce this care of adequate oral hygiene [72, 73], because when there is no such care and due to the immunosuppression conditions and systemic proinflammatory state of HIV-infected individuals and when we associate these systemic conditions with PLWH sites, they are simultaneously more prone to develop moderate and severe OLs such as oral candidiasis (OC), oral hairy leukoplakia (OHL), oral warts, oral aphthous ulcers, and oral herpes even in the presence of ART, demonstrating that the lack of oral hygiene or inadequate hygiene will have a high direct negative impact on the health of this population [74–76].

2.2 HIV and risk of oral transmission

Since HIV discovery, the means of transmission of HIV has been routinely studied aspects of infection, and until the present day, they are reasons for fear and stigma by the general population and even health professionals such as dentists [33]. Among the most controversial means of transmission is the oral cavity, and the presence of OLs that can serve as facilitators for transmission and contagion has been widely discussed [43]. Although it is known that HIV has periodontal tissues as reservoirs for its latency period, some studies that tried to detect the presence of viral particles in the cells of the oral epithelium demonstrated the absence of HIV in their results, making the transmission through the oral cavity as a somewhat questionable [77].

In theory, HIV infection *via* oral route would occur through oral sex; however, the data indicate low rates of oral HIV transmission. According to the literature studies, when there are cases of serodiscordant partners, the risk of contracting HIV by oral sex is estimated at between 0.04 and 0.06%, which has been shown to be well below the rates of anal sex, which is estimated at around 1.4%, and through sharing sharp instruments, which is estimated at between 0.63 and 2.4% [78–81]. To understand this low prevalence of oral transmission, we first need to understand that the oral epithelium is part of the innate immune system acting as a physical barrier that protects the underlying tissues from infection by pathogenic microorganisms such as HIV; that is, for oral contagion to occur by HIV, there must be a discontinuity in this oral tissue and, beyond this line of defense, the oral cavity [79]. In addition, the oral cavity has saliva and crevicular fluid as a means of defense, due to its low hypotonicity, which can act as antimicrobial factors, as well as macrophages, natural killer cells, and neutrophils, which will play important roles in the immune response of the oral mucosa [43, 70].

Although clinical and statistical data show that the oral transmission of HIV in adults is uncommon, it is understood that OL or mechanical trauma to the tissues of the oral mucosa causing ruptures or damage to the oral epithelium may be risk factors for the oral transmission of HIV, and key populations such as crack users, sex workers, and men who have sex with men may be more likely to be infected due to risky behaviors. As seen above, transmission in adults is rare, but postnatal vertical transmission seems to be a risky means of transmission to neonates, since in cases of HIV-infected postpartum women and neonates who were not contaminated via the uterus, they may contract HIV at ingesting infected vaginal secretions or amniotic fluids during childbirth or even while breastfeeding [82, 83].

2.3 HIV infection and oral mucosal

As discussed above, oral mucosal infections are commonly seen in HIV-infected individuals, suggesting that HIV infection is a risk factor for pathologies such as periodontal disease (PD), oral candidiasis, oral ulcers (OUs), angular cheilitis, and verrucous lesions [84, 85]. In fact, the literature indicates that ART-naïve PLWH users are more likely to have at least one OL during their lifetime, around 70–90% more likely when compared with PLWH ART users. Interestingly, this relationship may be proportional, because in the case of ART use, the appearance of these oral manifestations is still commonplace, but at a lower incidence, which is due to the fact that OLs, such as periodontitis, have multifactorial etiologies such as the presence of dental biofilm, and in cases of inadequate oral hygiene or absence of it, there will still be risks of oral manifestations [86, 87].

Therefore, it should be understood that the etiology of infections in the oral mucosa of ART-naïve PLWH has an intriguing combination because of systemic immunodeficiency due to the depletion of CD4+ T cells; local factors such as dental biofilm, environmental factors such as smoking, and compromise of oral defense cells producing interleukin-17 (IL-17) may be associated with increased susceptibility to opportunistic oral lesions. However, when ART is present, this incidence rate of OL tends to decrease; studies show that after the prescription and continuous use of ART, oral manifestations such as candidiasis, oral warts, hairy leukoplakia, and angular cheilitis will resolve as the immunosuppression is resolved by increasing the CD4+ T cell count and decreasing the viral load; however, it should be noted that each lesion will take a certain time to resolve due to the different associated causal factors as mentioned above, mainly factors related to impaction in the oral microbiota that undergo changes in the oral bacterial ecosystem [88–90].

2.4 HIV infection and oral microbiome

In the oral cavity, the role of the oral microbiota is extremely relevant to determine the health or disease of individuals; that is, when there is a process of oral dysbiosis, the diversity and composition of the oral microbiome changes overmuch. In PLWH cases, oral infections are commonly associated with significant proportions of highly pathogenic species such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella denticola*, *Tannerella forsythia*, *Prevotella intermedia*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans*. In the oral cavity of PLWH, microbial diversity was lower in individuals of this group than in individuals free of HIV infection and patients using ART; that is, in this HIV-infected population, the presence of aggressive bacteria was greater, and moreover, the presence of more virulent fungal communities can be identified. Therefore, the literature suggests that oral dysbiosis in PLWH promote greater chances of OL appearances due to the presence of more aggressive bacterial and fungal communities, even with a lower diversity of strains in the region [91–93].

2.5 Oral lesions caused by HIV infection

Several studies in the literature show the great harmful impact of HIV infection on the quality of life and oral health of this population [69, 94–104]. According to the Joint United Nations Program on HIV/AIDS (UNAIDS) in 2020, globally, there are about 37.7 million people living with HIV, with 1.5 million newly cases in 2020 alone,

and according to studies, the prevalence of OL in PLWH has a range between 40 and 93%, and this variance will depend on geographic and socioeconomic issues, access to ART and health services, and factors influencing a good quality of life [105]. As seen, OLs are commonly among the first signs and symptoms of a possible HIV infection and can be used as a diagnostic method suggestive of HIV, and these lesions were classified as lesions strongly associated with HIV infection, lesions commonly associated with HIV infection, and lesions seen in HIV infection (**Table 1**) [106, 107]. As for the quality of life of PLWH, OL can be associated with acute pain, chewing and feeding difficulties, esthetic impairment, speech problems, and impaired social life; thus, the need for adequate care, management, and treatment, as well as the prevention of oral diseases, is the duty of health professionals [33].

2.6 Oral lesions and their relationship with CD4 count and viral load

In addition to their diagnostic importance, OLs are useful to base a prognosis on the stages of infection, as, according to the literature, they will serve as clinical parameters with CD4+ and CD8+ cell counts. Since the introduction of ART, there has been a vertiginous drop in the morbidity and mortality of PLWH, and the lower presence of OLs in HIV-infected patients is also associated with this. That is, the literature indicates that the amount and severity of OL is also directly associated with immunosuppression, so the tendency is to have a high prevalence of OL in patients with a low CD4+ cell count (<200 cells/mm^3) and high viral load (>55,000 copies/mL). In cases of ART-naïve or newly diagnosed individuals, the presence of moderate or severe OL and a CD4+ cell count below 200 cells/mm^3, it is necessary to start treatment with ART and dental treatment [75, 108–111].

3. Oral lesions clinical characteristics

3.1 Oral candidiasis

Oral candidiasis (OC) is among the most common opportunistic infections among PLWH, with an estimated prevalence of between 15% and 80% in adults living with HIV. The OC is a fungal infection caused by the proliferation of different strains such as *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dubliniensis* and is usually associated with low CD4+ cell counts and risk factors such as smoking, being an important marker for the individual's immunity status and among the clinical features of OC we cite [112–120]:

- White and pasty stains (removable during smear);
- Pain or burning during chewing and swallowing;
- Oral ulcers;
- Bleeding;
- Reddish lesions on the palate due to dental prostheses;
- Dysgeusia or ageusia;

A- Lesions strongly associated with HIV infection	1. Oral candidiasis
	• Erythematous candidiasis
	• Pseudomembranous candidiasis
	2. Oral hairy leukoplakia
	3. Kaposi's sarcoma
	4. Non-Hodgkin's lymphoma
	5. Periodontal disease
	• Linear gingival erythema
	• Necrotizing gingivitis
	• Necrotizing periodontitis
	• Necrotizing stomatitis
B- Lesions less commonly associated with HIV infection	6. Bacterial infections
	• *Mycobacterium avium—intracellulare*
	• *Mycobacterium tuberculosis*
	7. Viral infections
	• Herpes simplex virus
	• Human papillomavirus (wart-like lesions)
	• Condyloma acuminatum
	• Focal epithelial hyperplasia
	• Verruca vulgaris
	• Varicella zoster virus
	• Herpes zoster
	• Varicella
	8. Melanotic hyperpigmentation
	9. Salivary gland disease
	• Xerostomia (decreased salivary flow rate)
	• Unilateral or bilateral swelling of salivary glands
	10. Thrombocytopenic purpura
	11. Various types of ulceration
C- Lesions seen in HIV infection	12. Bacterial infections
	• *Actinomyces israelii*
	• *Escherichia coli*
	• *Klebsiella pneumoniae*
	13. Fungal infections (different from candidiasis)
	• *Cryptococcus neoformans*
	• *Histoplasma capsulatum*
	• *Geotrichum candidum*
	• *Mucoraceae mucormycosis*

• *Mucoraceae zygomycosis*
• *Aspergillus flavus*
14. Cat-scratch disease
15. Drug reactions
16. Epithelioid angiomatosis
17. Viral infections
• Cytomegalovirus
• *Molluscum contagiosum*
18. Neurologic disturbances
• Facial palsy
• Trigeminal neuralgia

Table 1.
EC-clearinghouse oral lesions associated with HIV infection classification.

- Edema.

Currently, three types of OC are observed: pseudomembranous candidiasis, erythematous candidiasis, and angular cheilitis [112–120].

3.1.1 Pseudomembraneous candidiasis

They appear as whitish plaques, pasty consistency, can be found on the buccal mucosa, lingual belly, periodontium, hard and soft palate, labial region, and oropharyngeal region. Such plaques are formed by a mixture of fungal hyphae, desquamated epithelium, and proinflammatory cells that, when removed, leave the underlying surface red or bleeding. As for the clinical diagnosis, it is made through clinical symptoms, and the histological diagnosis can be used through the direct smear [112–118].

3.1.2 Erythematous candidiasis

They appear as petechiae or reddish ecchymoses, commonly associated in the region of the hard palate (indiscriminate use of complete dentures), dorsum of the tongue (similar to areas of depapillation), and buccal mucosa. In most cases, these lesions present characteristic symptoms such as burning mouth and altered taste. As for the clinical diagnosis, it is made through clinical symptoms, and the histological diagnosis can be used through incisional biopsy [112–118].

3.1.3 Angular cheilitis

It presents as linear fissures or ulcers in the flaky labial commissures, which can be unilateral or bilateral, with a whitish color, sometimes blisters, and are usually associated with small white plaques. In cases of severe immunosuppression or AIDS, angular cheilitis may be related to erythematous candidiasis or pseudomembranous candidiasis. Clinically, the patient reports itching and burning in the labial commissure; the clinical diagnosis is made through clinical symptoms, and the histological diagnosis can be used through incisional biopsy [112–118].

3.1.4 Treatment

The treatment of OC can be topical and/or systemic, depending on the severity of candidiasis, immunosuppression, and risk factors.

- Topical therapy:
- Mouthwash:

a. Chlorhexidine digluconate (0.12%): use two to three times a day for 10–14 days, dosage: 3 mL of oral solution.

b. Amphotericin B (0.1 mg/mL): use three to five times a day for 14–42 days, dosage: 1.0–5.0 mg/kg/day of oral solution.

c. Cleaning or replacing dental prosthesis.

- Dermatological cream:

a. Clotrimazole (10 mg/g): use three times a day for up to 28 days.

- Systemic therapy:
- Oral suspension:

a. Nystatin (100,000 IU/ml): use four times a day for 14 days, dosage: 1 to 6 ml of oral suspension.

- Oral pill:

a. Fluconazole (150–200 mg): use once daily for 14 to 42 days.

b. Ketoconazole (200 mg): use once daily for up to 14 days.

c. Itraconazole (100 mg): use once daily for up to 7 days, dosage: 2 tablets (200 mg) daily.

3.2 Periodontal disease

Periodontal disease (PD) can be categorized simply as gingivitis and periodontitis; PD is an infectious inflammatory disease of multifactorial etiology [121, 122]. Its main etiology is the interaction among dental biofilm, host immune defense, and risk factors. Therefore, the association among pathological microorganisms, proinflammatory cytokines, oral dysbiosis, and cytotoxic factors causes an intense inflammatory response, which leads to the destruction of periodontal tissues and potentially resulting in tooth and bone loss [123–125].

Host habits, such as poor oral hygiene and smoking, and systemic diseases, such as AIDS, can predispose and worsen the progression of PD, as HIV infection alters the immune system, progressively impairing the immune response, favoring a more

intense PD, such as acute and necrotizing. Necrotizing periodontal disease is the most severe form of PD due to rapid onset, severe pain, severe bone loss, suppuration, ulcerations, and areas of tissue necrosis. Among the clinical features of gingivitis and necrotizing periodontitis, we have the following [126, 127]:

- Intense pain;
- Spontaneous or provoked bleeding;
- Spontaneous or provoked suppuration;
- Areas of tissue necrosis;
- Ulcers in the periodontium (secondary aspects of the lesion);
- Presence of metallic taste in the mouth;
- Edema and gingival swelling;
- Presence of interproximal black space (interproximal bone loss);
- Increase in the degree of tooth mobility;
- Clinical attachment level loss;
- Halitosis;
- Periodontal pockets or gingival recessions (depending on tissue phenotype);
- Tooth loss.

3.2.1 Linear gingival erythema

Linear gingival erythema (LGE) is characterized by an erythematous band located on the free marginal gingiva; it can be generalized or localized and usually does not show signs of inflammation due to bacterial plaque accumulation. In other words, LGE can be considered a chronic non-plaque-induced gingivitis, a precursor of necrotizing diseases (**Figure 1**).

LGE is among the main oral signs and symptoms of HIV infection and possibly occurs due to the dysbiosis of the gingival sulcus microbiota and systemic immunosuppression. As a form of differential diagnosis between a common chronic gingivitis and LGE, in addition to the low presence and biofilm, the negative response to scaling and root planning treatment can be fundamental for the diagnosis [112–114, 128].

3.2.2 Necrotizing gingivitis

Necrotizing gingivitis (NG), also known as Vincent's disease or trench mouth, is the most severe form of PD and tends to be present in individuals with severe immunosuppression; it is characterized by rapid onset, ulcerations, tissue necrosis,

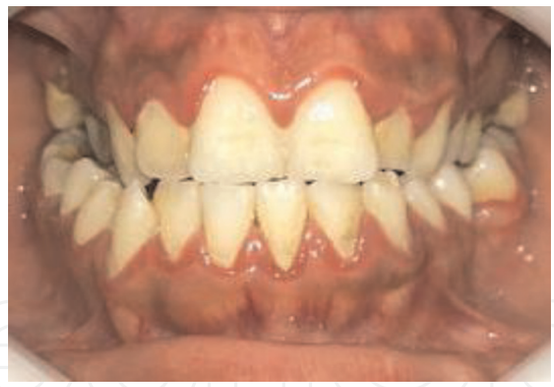

Figure 1.
Clinical linear gingival erythema.

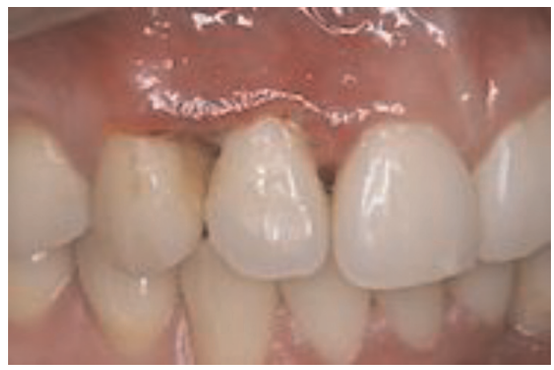

Figure 2.
Clinical necrotizing gingivitis.

suppuration, bleeding, foul odor, severe pain, and loss of interdental papillae (**Figure 2**) [127].

3.2.3 Necrotizing periodontitis

Necrotizing periodontitis (NP) is the natural evolution of NG; it is characterized by loss of soft tissue as a direct result of necrosis and acute ulceration arising from NG and presents a rapid bone destruction and extensive loss of the clinical level of bone attachment that can be generalized or located (**Figure 3**) [127].

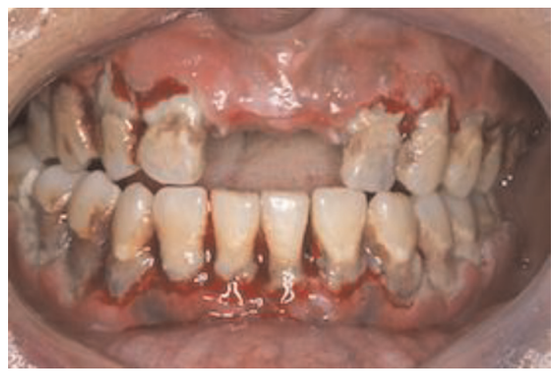

Figure 3.
Clinical necrotizing periodontitis.

3.2.4 Treatment

The treatment of periodontal diseases boils down to topical and systemic chemical-mechanical therapy [127].

- Topical therapy:
- Mouthwash:
    a. Chlorhexidine digluconate (0.12%: use two to three times a day for 10–14 days, dosage: 3 mL of oral solution.
- Scaling and root planing associated with tissue debridement.
- Oral hygiene instructions.
- Systemic therapy:
- Oral pill:
    a. Amoxicillin (500 mg): use three times a day for 7 days.
    b. Metronidazole (250 mg): use twice daily for up to 10 days.
    c. Amoxicillin and metronidazole can be combined to broaden the spectrum of action of antibiotic therapy.

3.3 Oral hairy leukoplakia: (OHL)

Oral hairy leukoplakia (OHL) is also among the most common oral signs and symptoms of HIV infection; it is usually caused by Epstein-Barr virus infections and is white asymptomatic plaques with a corrugated surface or a velvety hair-like appearance, which can be found on the lateral borders, unilaterally or bilaterally, of the tongue and in more severe cases also found on the dorsum or belly of the tongue, on the floor of the mouth, and on the buccal mucosa. If there is no removal of the plaque, the suggestive diagnosis is OHL, and if it comes out, it will be candidiasis. Among the histological features of OHL, we evidenced areas of hyperkeratosis, parakeratosis, acanthosis, papillomatosis, and the presence of layers of ballooned cells similar to koilocytes with nuclear alterations in the spinous layer, epithelial inflammatory infiltrate, and connective tissue [112–114, 129–132].

3.3.1 Treatment

The treatment of OHL is not just periodontal, and necrotizing diseases boils down to topical and systemic chemical-mechanical therapy [129–132].

- Topical therapy:
    - Podophyllin (25%): use three times a day for 7–14 days, use by applying the oral solution locally.

- Systemic therapy:
    - Prevention of smoking and alcoholism.
    - Acyclovir (800 mg): use five times daily for 7–14 days.
    - Desciclovir (250 mg): use three times daily for 7–14 days.
    - Valacyclovir (1000 mg): use three times daily for 7–14 days.
    - Surgical excision of the lesion with an electric scalpel or laser.

3.4 Kaposi's sarcoma

Kaposi's sarcoma is a neoplasm commonly associated with individuals with AIDS; its etiology is usually linked to the oncovirus human herpes virus-8 (HHV-8) and originates from endothelial cells as a direct response to HHV-8 infection and immunosuppression caused by HIV. Clinically, the lesions are found in the form of asymptomatic macules or nodules, fast growing, reddish, bluish, or purple, and in some cases, in addition to the OL, lesions in the gastrointestinal and pulmonary tracts can be found. They are usually located in the palate or alveolar process and can lead to bone destruction, tooth mobility, and invariably tooth loss. Histologically, this neoplasm presents fusiform tumor cells, similar to smooth muscle, fibroblasts, and myofibroblasts [108, 112–114].

3.4.1 Treatment

The treatment of Kaposi's sarcoma consists of excisional biopsy, radiation therapy, or chemotherapy [108, 112–114].

3.5 Non-Hodgkin's lymphoma (NHL)

Non-Hodgkin's lymphoma (NHL) is the most uncommon OL associated with HIV infection; however, apart from Kaposi's sarcoma, it is the second most common malignancy among PLWH, with an average prevalence of 4%. NHL is a type of malignant neoplasm of origin in the cells of the lymphatic system and with an unordered diffusion and clinically appears as lymphadenopathy of the head and neck, armpits, and/or groin; among the most common signs and symptoms, the individual has nocturnal sweating, pyrexia or hyperpyrexia, itching, weight loss, and rapidly growing oral nodules in the alveolar process and tongue [112–114, 133–135].

3.5.1 Treatment

The treatment of NHL is based on excisional biopsy or puncture and with confirmation the individual should start with immunotherapy, radiotherapy, or chemotherapy [112–114, 133–135].

3.6 Oral ulcers

Oral ulcers (OUs) are erosive lesions that occur in the oral epithelium, and when the epithelium sloughs, the nerve endings of the oral epithelium will be exposed and

trigger symptoms such as pain provoked and exudate, causing difficulty in swallowing and impaired speech and chewing. They can appear in all the areas of the oral mucosa, and among PLWH, it has a prevalence of about 50%; OUs can be classified into minor aphthous ulcers and major aphthous ulcers [112–114].

3.6.1 Minor aphthous ulcers

They are minor ulcerative lesions with about 2–5 mm in diameter and occur on nonkeratinized mucosa, have a predilection for areas of the buccal mucosa and lips, are clinically more superficial, covered by a whitish pseudomembrane, surrounded by an erythematous halo, and are extremely painful [112–114].

3.6.2 Major aphthous ulcers

They are larger ulcerative lesions measuring over 1 cm in diameter and can occur in both keratinized and nonkeratinized areas, generally affecting the lateral border of the tongue, soft palate, floor of the mouth, buccal mucosa, oropharynx, and alveolar process. Clinically, they have a crater-like appearance with raised edges and covered by a yellowish-white pseudomembrane and may be accompanied by regional lymphadenopathy [112–114].

3.6.3 Treatment

The treatment of OU is summarized in a topical therapy, in which the individual must maintain good oral hygiene, use 0.12% chlorhexidine digluconate mouthwash or dexamethasone mouthwash (0.5 mg/5 cc), rinse for 5 minutes before spitting, and use three to four times a day for up to 10 days. The use of topical ointments, such as triamcinolone acetonide, can be applied under the ulcer area two to three times daily for up to 7 days [112–114].

3.7 Salivary gland diseases

The enlargement of the major salivary glands affects the parotid, sublingual, and submandibular glands; clinically, xerostomia, unilateral or bilateral, and asymptomatic edema, in addition to esthetic embarrassment and social stigma, are observed. Histologically, the presence of focal sialoadenitis with an infiltrate of proinflammatory cells and CD8+ T lymphocytes can be observed [112–114].

3.7.1 Treatment

A specific treatment for the enlargement of the major salivary glands does not exist; to treat symptoms such as xerostomia, the use of artificial saliva or the habit of chewing gum to increase salivary volume is recommended, and some studies have shown that radiotherapy may be a viable treatment to reduce the size of the glands [112–114].

3.8 Melanotic hyperpigmentation

Oral melanotic hyperpigmentation is another common lesion in PLWH, and once the differential diagnosis of ethnic melanic pigmentation is removed, it can be

indicated that, once present in the oral cavity, it is a possible factor of HIV infection. Clinically, there is a black, brownish, or brown spot or macula, typically asymptomatic and may occur due to increased release and dysregulation of alpha melanocytes caused by certain types of ART, such as zidovudine and antifungal drugs, especially to treat and *Mycobacterium avium* intracellulare [112–114].

3.9 Human papillomavirus

Human papillomavirus (HPV) can infect the oral mucosa, resulting in the development of oral verrucous lesions. Oral warts (OWs) usually present nodular or pedunculated lesions with a sessile base, with a firm consistency; they can be solitary or multiple lesions, white or pink in color, and can have smooth or irregular surfaces, similar to a cauliflower. The OWs caused by HPV are among the most prevalent lesions of PLWH with a reported prevalence of about 0.5–6.9%, and HPV can be classified into subtypes according to its oncogenic level, and in the oral cavity, subtypes 6 and 11 are the most prevalent; about 90%, in OWs such as condylomas and laryngeal papillomas, have lower oncogenic potential. HPV is highly sexually transmitted; being frequent in the genital and anal region, its incidence in the oral mucosa is due to acts of self-inoculation or oral sexual contact [112–114, 136–139].

3.9.1 Treatment

The basic treatment of OW is summarized in the excisional biopsy of the nodule, either by removal with a surgical laser or by electric scalpel or cryosurgery. Topically, a cream called imiquimod (50 mg/g) serves as an immunomodulatory cream that must be applied to the wart site once a day, three times a week for up to 28 days. Systemically, the use of antivirals such as cidofovir (5 mg/kg) is recommended, which should be administered once a week for up to 14 days [112–114, 136–139].

4. Conclusion

Host's immune, oral hygiene, and HIV infection course could be considered a directly key determinant for oral mucosal infection linked to HIV. Therefore, to understand the immunological key elements in the oral health of PLWH is essential to alerted healthcare workers regarding HIV infection severity, because compromised oral barrier integrity will facilitate HIV infection, oral dysbiosis, microbial translocation along different types of mucosal tissue, and the spread of microorganism products into the oral epithelial tissue, which may predispose to opportunistic infections and systemic inflammation, such as various oral lesions and neoplasms. This chapter presented various studies and discussed the newly knowledge about HIV infection and its importance to oral mucosa infections, so this review might be helpful to the diagnosis and treatment of various oral lesions in PLWH.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

Human Immunodeficiency Virus (HIV);
HIV-type 1 (HIV-1);
HIV-type 2 (HIV-2);
People Living with HIV (PLWH);
Acquired Immunodeficiency Syndrome (AIDS);
Reverse Transcription Polymerase Chain Reaction (RT-PCR);
Oral lesions (OL);
Antiretroviral therapy (ART);
Joint United Nations Programme on HIV/AIDS (UNAIDS);
Oral candidiasis (OC);
Periodontal disease (PD);
Linear gingival erythema (LEG);
Necrotizing gingivitis (NG);
Necrotizing periodontitis (NP);
Oral hairy leukoplakia (OHL);
Human Herpes Virus-8 (HHV-8);
Non-Hodgkin's lymphoma (NHL);
Human papillomavirus (HPV);
Oral warts (OW).

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