

The influence of antiretroviral therapy on HIV-related oral manifestations

Zaid H. Khoury, Valli Meeks

Abstract: Purpose: This review aims to provide primary medical and dental healthcare professionals with the current state of information on the oral manifestations of HIV infection in the era of antiretroviral therapy (ART) advancements.

Results: Infection with human immunodeficiency virus (HIV) is associated with an increased risk of infectious, neoplastic, and immune-mediated oral complications that are regarded as a major constituent of this global epidemic. HIV-related oral manifestations have been subject to changes in their prevalence with the employment of ART, particularly in this period of enhanced patient accessibility to ART. Available antiretroviral medications (ARVs), the clinical presentation of common HIV-related oral manifestations, and patients and healthcare providers' perceptions are also discussed.

Conclusions: Screening, diagnosing, and treating patients with HIV/Acquired immunodeficiency syndrome (AIDS) has improved drastically since the isolation and characterization of HIV. Oral manifestations have been acknowledged to correlate with treatment responses and disease progression. Healthcare providers should be familiar with HIV-related oral manifestations and comfortable in managing and referring patients with HIV/AIDS, they are also key stakeholders in facilitating the elimination of the stigma associated with the infection.

Keywords: Antiretroviral therapy ■ Human immunodeficiency virus ■ Oral cavity ■ Oral manifestations

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INTRODUCTION

The human immunodeficiency virus (HIV) was first isolated in 1983 and was retrospectively identified as the cause of acquired immunodeficiency syndrome (AIDS).¹ HIV disease is classified into two main subtypes, HIV-1 and HIV-2, based on viral genetic and antigenic differences,² with HIV-1 being more common particularly in sub-Saharan Africa, while HIV-2 is more prevalent in West Africa and associated with slower disease course.³ By the end of 2019, approximately 38 million people were estimated to be living with HIV.⁴ Fortunately, recent years have witnessed enormous progression towards achieving equality in HIV surveillance

and healthcare accessibility for HIV-infected individuals, resulting in a global decrease in the number of AIDS-related deaths, and an increase in the number of people living with HIV who are receiving highly active antiretroviral therapy.^{5,6} Additionally, an overall decline in the number of new HIV cases in adults has also been observed, with the greatest decline seen in Eastern and Southern Africa, likely due to the enhanced patient coverage with antiretroviral therapy (ART) in these regions,⁵ although accessibility to ART remains significantly less than that in developed countries (38% vs 87%, respectively).⁷ Along with accessibility-related barriers, disparities in patients' levels of education and awareness, particularly in low- and middle-income countries, hindered screening individuals potentially infected with HIV and effective therapy for those patients.⁸ Even in high-income countries, such as the United States, 15% of individuals who have acquired HIV are unaware of their status, contributing to as high as 40% of continuous HIV spread.⁹

Since the late 1980s to date, oral manifestations have been acknowledged to represent a major element of HIV infection that can correlate with treatment responses and disease progression.⁶ Furthermore, oral lesions can present as an early clinical sign of HIV disease soon after seroconversion, alerting clinicians for further investigation in the appropriate clinical scenario.¹⁰ Moreover, the incorporation of ART has an impact on the prevalence and clinical presentation of HIV-related oral manifestations most notably through restoring CD4⁺ T-cell count and reducing the viral load.^{10,11}

This concise review aims to provide healthcare providers with the current state of information on the oral manifestations of HIV infection in the era of ART advancements, which is significant for appropriate recognition, management, and referral of patients with HIV/AIDS.

ANTIRETROVIRAL THERAPEUTICS

Highly active antiretroviral therapy, now known as combined antiretroviral therapy (cART) or ART, refers to

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Table 1. (A) Summary of ARVs for HIV/AIDS and Their Therapeutic Targets.^{13,14}

Category	Example(s) of medicine(s) and their brand name(s)	Mechanism of Action
CCR5 antagonists	Maraviroc (<i>Selzentry</i>)	CCR5 is a chemokine coreceptor on CD4 ⁺ cells' surface that binds to gp120 on HIV surface. CCR5 antagonists block this interaction, targeting HIV attachment.
Post-attachment inhibitors	Ibalizumab (<i>Trogarzo</i>)	Ibalizumab is a monoclonal antibody that binds to a domain of the CD4 glycoprotein, targeting HIV binding with the host cells.
Fusion inhibitors	Enfuvirtide (<i>Fuzeon</i>)	Targets gp41 subunit of the viral envelope protein and therefore inhibits cell membranes fusion of HIV-1 with CD4 ⁺ cells.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (<i>Sustiva</i>) Rilpivirine (<i>Edurant</i>) Doravirine (<i>Pifeltro</i>)	Changes the conformation of HIV-1 reverse transcriptase preventing reverse transcription of HIV RNA to DNA, blocking the virus from replicating.
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	Abacavir (<i>Ziagen</i>) Tenofovir Disoproxil (<i>Viread</i>) Tenofovir Alafenamide (<i>Vemlidy</i>) Emtricitabine (<i>Emtriva</i>) Lamivudine (<i>Epivir</i>) Zidovudine (<i>Retrovir</i>)	Once intracellular, these medications undergo activation through phosphorylation, proceeding to be incorporated into the viral DNA, causing chain termination, and blocking the virus from replicating.
Integrase strand transfer inhibitors (INSTIs)	Raltegravir (<i>Isentress</i>) Elvitegravir (<i>Vitekta</i>) Dolutegravir (<i>Tivicay</i>) Bictegravir (an ingredient of <i>Biktarvy</i>)	Prevents the insertion of HIV-1 DNA into the host DNA by binding to a magnesium element of the integrase enzyme.
Protease inhibitors	Atazanavir (<i>Reyataz</i>) Darunavir (<i>Prezista</i>)	Inhibit protease by blocking the cleavage of Gag-Pol polyproteins in virus-infected cells, hence preventing the maturation of the viral particles.
Pharmacokinetic enhancers	Cobicistat (<i>Tybost</i>)	Interfere with the breakdown of other ART medicine(s) in combination, enhancing the bioavailability of HIV regimens.

B) Examples of FDA-approved HIV Regimens¹⁴

Lamivudine & tenofovir disoproxil fumarate (*Cimduo*)
 Emtricitabine & tenofovir alafenamide (*Descovy*)
 Emtricitabine & tenofovir disoproxil fumarate (*Truvada*)
 Bictegravir, emtricitabine, & tenofovir alafenamide (*Biktarvy*)
 Emtricitabine, rilpivirine, & tenofovir disoproxil fumarate (*Complera*)
 Emtricitabine, rilpivirine, & tenofovir alafenamide (*Odefsey*)
 Elvitegravir, cobicistat, emtricitabine, & tenofovir alafenamide (*Genvoya*)
 Elvitegravir, cobicistat, emtricitabine, & tenofovir disoproxil fumarate (*Stribild*)

the antiretroviral medications (ARVs) prescribed as an HIV drug regimen for the prevention and treatment of HIV/AIDS. Guidelines developed for effective drug therapy to treat HIV/AIDS in most patients living with HIV/AIDS incorporate a three-drug regimen as a standard for long-term therapeutic effectiveness against the virus.¹² Table 1A. summarizes the classes of ARVs available for patients with HIV.^{13,14} ARVs selected as a part of an HIV regimen are tailored to fit the patient's specific

needs by taking into consideration the patient's comorbidities or previous ART for example. Table 1B. lists some examples of the Food and Drug Administration (FDA)-approved HIV regimens.¹⁴

To date, clinical studies continue to evaluate new therapeutic advancements that target HIV. The small molecule GS-6207 is a novel long-acting HIV-1 capsid inhibitor with promising antiretroviral potential that is expected to improve adherence to ART for patients on more than the

currently prescribed ARVs through its projected high potency and minimal toxicity.¹⁵

ORAL MANIFESTATIONS OF HIV INFECTION AND THE INFLUENCE OF ART

Oral manifestation of HIV infection is a significant component of its clinical presentation and can be an early sign of disease progression, therefore, the role of healthcare professionals in recognizing early HIV infection and how ART influences the presentation of its oral complications is of paramount importance. In 1993, the EC-Clearinghouse on Problems Related to HIV Infection and the WHO Collaborating centre on Oral Manifestations of the Immunodeficiency Virus (EC-Clearinghouse-WHO) classified oral lesions based on their association with HIV infection into strongly associated with, less commonly associated with, and seen in HIV infection.^{3,6,16} Although the previous classification remains widely accepted today, recent results from the 8th World Workshop for Oral Health and Disease (WWOHD) in HIV/AIDS have demonstrated that the majority of oral complications manifested in this population are candidiasis, oral hairy leukoplakia, herpes simplex virus (HSV) infections, Kaposi sarcoma, HIV-related oral ulcerations, periodontal disease, HIV-related salivary gland disease, mucosal hyperpigmentation, and human papillomavirus (HPV) infections⁷ (Figure 1). Table 2. summarizes the current reported prevalence of the most common HIV-related oral manifestations according to the 8th WWOHD. Although it is unlikely to encounter many of the oral lesions noted in Table 3^{3,6,7,10} in routine primary care and general dental practice, awareness of these oral lesions is important so that if suspicions on the presence of any arise, healthcare providers should refer the patient to infectious diseases or an oral medicine and pathology specialist for definitive diagnosis and treatment.

Consistent with the EC-Clearinghouse-WHO classification, candidiasis, oral hairy leukoplakia, periodontal disease, and Kaposi sarcoma continues to be frequently reported in patients with HIV/AIDS, however, other entities such as oral mucosal hyperpigmentation, HIV-related salivary gland disease, and possibly HIV-related oral ulcerations appear to be also strongly associated with the disease, suggesting a role of the enhanced patient accessibility to treatment with ARVs in recent years in modulating these observations. Indeed, geographical differences in the frequency of HIV-related oral manifestation between developed and developing countries have been noted and are

Table 2. Prevalence of the Most Commonly Encountered HIV-related Oral Manifestations According to the 8th World Workshop for Oral Health and Disease.

Oral Manifestation	Prevalence [†]
Candidiasis	35%
Oral hairy leukoplakia	15%
Mucosal hyperpigmentation	9%
Periodontal & gingival disease	8.2%
HIV-related salivary gland disease	8%
Recurrent aphthous stomatitis	7%
HIV-related non-specific oral ulcerations [‡]	5%
Kaposi sarcoma	5%
Herpes simplex virus (HSV) infections	4.5%
Human papillomavirus (HPV) infections	3.5%

[†] Overall prevalence acquired from the 8th WWOHD by averaging the prevalence reported from developing and developed countries (7).

[‡] The term HIV-related (non-specific) oral ulcerations is a distinct entity that should be applied to ulcers not corresponding to any pattern (minor, major, or herpetiform) of recurrent aphthous stomatitis (RAS) nor caused by fungal, bacterial, or viral organisms (16).

probably attributed to social, cultural, and healthcare availability/accessibility variables.⁶⁻⁸

Candida albicans (*C. albicans*) is a dimorphic fungus that causes oral candidiasis in immunocompromised individuals and remains to be the most common opportunistic infection among HIV-positive patients.⁷ The incorporation of ART has reduced the overall prevalence of oral candidiasis in HIV/AIDS patients by restoring underlying CD4⁺ T-helper 17 and CD4⁺ T-helper 1 cell-mediated host immune defenses against oral candidiasis.^{17,18} The clinical presentation of oral candidiasis has also been associated with the degree of immunodeficiency and ART efficacy. The prevalence of pseudomembranous candidiasis, the most common form of candidiasis in HIV-infected patients, is associated with <200/mm³ circulating CD4⁺ T-cells, while erythematous candidiasis and angular cheilitis are less commonly encountered and are associated with less severe HIV disease.¹⁹

Along with oral candidiasis, the prevalence of oral hairy leukoplakia, salivary gland disease, and non-Hodgkin lymphoma has also decreased since the introduction of ART, while HIV-related ulceration, tuberculosis, HSV infections, HPV infections, Kaposi sarcoma, and in some in-

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Figure 1. Common HIV-related oral manifestations. (A) Pseudomembranous candidiasis predominantly affecting the maxillary and mandibular gingivae. (B) Oral hairy leukoplakia on the lateral border of the tongue. (C) Mucosal hyperpigmentation. (D) Linear gingivitis. (E) Necrotizing ulcerative gingivitis demonstrating pseudomembranes and necrosis of the interdental papillae. (F) HIV-related oral ulceration of the upper labial mucosa. (G) Kaposi sarcoma of the upper lip. (H) Unilateral swelling of the parotid gland.



stances herpes zoster infection have been more frequently reported.^{3,7,10,20} The increased prevalence of tuberculosis, HSV infections, HPV infections, Kaposi sarcoma, and herpes zoster following the initiation of ART is most likely

the result of immune reconstitution syndrome (IRS).^{20,21} IRS is an exaggerated immune response towards infectious agents and pathological conditions that results from ART-mediated restored immunity. A recent study has identified

Table 3. Summary of the Main Oral and Maxillofacial Manifestations of HIV Infection in Adults.^{3,6,7,10}

Infections	
Fungal	Candidiasis (<i>Candida albicans</i>) Aspergillosis (<i>Aspergillus species</i>) Mucormycosis (<i>Mucoraceae</i>) Histoplasmosis (<i>Histoplasma capsulatum</i>) Cryptococcosis (<i>Cryptococcus neoformans</i>) Penicillinosis (<i>Penicillium marneffeii</i>)
Viral	HSV lesions Varicella-zoster virus lesions (Chickenpox and Shingles) Oral hairy leukoplakia (Epstein-Barr virus) Cytomegalovirus lesions Molluscum contagiosum (Molluscum contagiosum virus)
Bacterial	Tuberculosis (<i>Mycobacterium avium-intracellulare</i> , <i>M. tuberculosis</i>) <i>Actinomyces israelii</i> , <i>Escherichia coli</i> , and <i>Klebsiella pneumoniae</i> infections Cat-scratch disease and bacillary angiomatosis (<i>Bartonella henselae</i>) Periodontal diseases: Linear gingivitis, necrotizing ulcerative gingivitis, and necrotizing periodontitis Necrotizing ulcerative stomatitis
Salivary gland disease	Dry mouth Swelling of major salivary glands (Unilateral or bilateral)
Immune-mediated/idiopathic	Persistent generalized lymphadenopathy HIV-related ulceration Thrombocytopenic purpura Melanotic hyperpigmentation
Neoplastic	Kaposi sarcoma Non-Hodgkin lymphomas (e.g. Burkitt lymphoma, diffuse large B-cell lymphoma, primary effusion lymphoma, plasmablastic lymphoma) Squamous Cell Carcinoma
Neurologic	Facial palsy Trigeminal neuralgia
Drug-related eruptions	Erythema multiforme Lichenoid Toxic epidermolysis Drug-induced mucosal hyperpigmentation

HIV: Human immunodeficiency virus; HPV: Human papillomavirus; HSV: Herpes simplex virus.

specific types of bacteria enriching the microbiome of HIV individuals with oral Kaposi sarcoma, suggesting a relation between the oral microbiome and IRS in patients on ARVs.²² Salivary gland lesions often present as swelling which can be either unilateral or bilateral (Figure 1h).

The EC-Clearinghouse-WHO cohorts defined oral ulceration in the context of HIV as those not corresponding to any pattern (minor, major, or herpetiform) of recurrent aphthous stomatitis (RAS) nor caused by fungal, bacterial, or viral organisms.¹⁶ Figure 1g. is an example of HIV-related oral ulceration fitting the previous definition. If such ulcers are not relieved by topical or systemic drug therapy or have an atypical clinical presentation, a

biopsy may be indicated to rule out invasive fungal organisms, infection with HSV with or without cytomegalovirus co-infection, or neoplastic growth.³

Initial studies indicated that the incidence of RAS remains the same despite the progression of HIV disease, however, HIV patients presenting with RAS often suffer from the major and herpetiform variants.¹⁶ Today, RAS has been reported more frequently in patients on ART as opposed to patients not receiving therapy,⁷ hence immune reconstitution following ART initiation or changes in ARVs may also explain their increased prevalence. Erythema-multiforme-like ulcerations induced by antiretroviral therapy has also been reported.²³

Periodontitis and gingivitis are reported more frequently in HIV-positive individuals residing in developing countries as compared with developed countries, with periodontal disease being reported more frequently following ART, although some authors consider this observation to be an age-related phenomenon irrelevant to HIV or ART status.⁷

Mucosal and cutaneous hyperpigmentation may be induced by a variety of drugs taken by HIV/AIDS patients such as zidovudine and emtricitabine-based HIV regimens, or by drugs used to control microbial infections in these patients such as ketoconazole, clofazimine, and pyrimethamine.³ Destruction of the adrenal cortex by disseminated infections (e.g. deep fungal infections) in this immunocompromised population is another possible cause of the observed hyperpigmentation.³

New potential HIV-related oral manifestations continue to be reported. Six HIV-infected pediatric patients have been reported to develop deep neck space infections caused by diverse antibiotic-resistant bacteria, suggesting the possibility of HIV having a role in such clinical presentation.²⁴ Additionally, sialolithiasis (salivary gland stones) has recently been suggested to be associated with HIV infection, suggesting ART as the possible culprit.²⁵ Importantly, aggressive dental caries have been reported more frequently in HIV⁺ children, adolescents, and adults, as compared to individuals without signs of immunodeficiency. Interestingly, the reason behind this observation may be partially explained by the high level of *C. albicans* recovered from HIV⁺ individuals (due to immunosuppression) which in turn augment the carious biofilm through *C. albicans*-mediated enhanced *Streptococcus mutans* colonization.^{26–29}

PATIENTS AND HEALTHCARE PROVIDERS' PERCEPTIONS

The use of ARVs has altered the perceptions and attitudes of many stakeholders in viewing HIV/AIDS as a manageable chronic condition, as opposed to an end-stage disease.³⁰ Approximately two-thirds of HIV/AIDS-related mortality cases were reported in those HIV-infected patients not on ART,³¹ justifying the increased number of people aging with HIV and the projected 80–90% reduction in the number of newly diagnosed HIV cases by 2030.^{4–6,31} However, despite the overall benefits of ART in governing prolonged patient survival and reduced mortality, some global public health researchers hold the opinion that ARVs are responsible for the increased morbidity experienced during the ART-mediated extended course of HIV/AIDS.³⁰ Because of this, healthcare providers need to consider HIV/AIDS as a continuously evolving condi-

tion due to treatment-related repercussions in the context of persistent inequities in economic and healthcare accessibility, contributing to the uncertainty of the future of this infection.³⁰

National surveys conducted on American general dentists predicted their willingness in implementing oral HIV rapid testing during dental visits.³² Indeed, although opposed by challenges of cost, licensing, and patient acceptance, potential models for integrating HIV screening into routine dental practice have been proposed representing a step forward towards early detection of the disease and facilitating linkage to care and appropriate treatment and management of newly diagnosed cases of HIV infection.³³ Importantly, HIV stigma and discrimination posed by healthcare providers impedes accessibility of HIV/AIDS patients to health and dental care. For example, patients may fear disclosing social behaviors associated with an increased risk of HIV infection/transmission or may avoid sharing their HIV status.³⁴ In such cases, enforcing non-discrimination policies in the dental office and training healthcare professionals on how to approach patients with HIV/AIDS in a sensitive, respectful, and inclusive manner is mandated.³⁴

CONCLUSIONS

Screening, diagnosing, and treating patients with HIV/AIDS has improved drastically since the isolation and characterization of HIV. While HIV-related oral manifestations have long been acknowledged and described, they have been subject to changes in their prevalence with the employment of ART, particularly in this era of enhanced patient accessibility to antiretroviral therapy. Healthcare providers should be familiar and comfortable in managing and referring patients with HIV/AIDS and are key stakeholders in facilitating the elimination of the stigma associated with the infection.

DECLARATION OF COMPETING INTEREST

None.

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INFORMED CONSENT

The clinical images included in the manuscript were obtained as part of the standard of care for the patient and retrospectively collected for the review. No identifier information is included in the review. For this type of study formal consent is not required.

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