



# **Oral Candidiasis in Human Immunodeficiency Virus Infection: A Brief Review**

**Antoine Berberi<sup>a</sup> and Hassan Dib<sup>a\*</sup>**

<sup>a</sup> *Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Lebanese University, Hadath, Beirut, Lebanon.*

## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/JAMMR/2023/v35i74983

## **Open Peer Review History:**

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/96782>

**Review Article**

**Received: 30/12/2022**

**Accepted: 01/03/2023**

**Published: 04/03/2023**

## **ABSTRACT**

Oral cavity is one of the manifestations that results from Human Immunodeficiency Virus (HIV) infection. Some of these lesions are suggestive whilst others are specific. However, the oral candidiasis that was observed during HIV infection is specific in terms of its severity and resistance to the usual treatment. Therefore, it is important for all practitioners to know it well in order to be able to make the diagnosis and propose an adequate treatment. During HIV infection, 95% of HIV-positive people have one or more lesions in the oral cavity during their illness. Moreover, oral candidiasis is classified among these lesions. We will describe the different types of candidiasis and their treatment.

*Keywords: Candidiasis; HIV; AIDS; infection.*

*\*Corresponding author: E-mail: hassan.dib@ul.edu.lb, dibhassan@gmail.com;*

## 1. INTRODUCTION

AIDS or Acquired Immune Deficiency Syndrome is the most progressive form of Human Immunodeficiency Virus (HIV) infection. It is a disease that was first discovered in the United States in 1981 [1], and whose epidemic has since taken on global proportions. Most manifestations of HIV infection result in lesions in the oral cavity. Patients infected with HIV, present one or more clinical manifestations in the oral cavity. Some of these lesions are suggestive of this infection, whilst others are pathognomonic [2-4].

Oral candidiasis is the lesion that is most frequently encountered in HIV-infected individuals [5-7]. Schiødt and Pindborg (1987) observed that 35% of HIV-positive patients and 75% of those with proven AIDS have signs of oral candidiasis [8]. Those different clinical aspects and treatment protocols are further presented in this review.

## 2. CLASSIFICATION OF ORAL CANDIDIASIS

The lesions caused by HIV infection may be diffuse, nearly reaching the entire oral mucosa, or limited to circumscribed foci. All eventualities are possible between these two extremes. Oral candidiasis is one of the most common manifestations of HIV infection. Its clinical forms, which could be acute or chronic, are classified into [6- 9]:

- Erythematous or atrophic candidiasis
- Pseudomembranous candidiasis

- Hyperplastic candidiasis
- The black hairy tongue
- Perleche
- Cheilitis

## 3. CLINICAL SIGNS OF DIFFERENT FORMS OF ORAL CANDIDIASIS

Despite the overall deficit of cell-mediated immunity, which is one of the major consequences of HIV infection, only a small number of fungi frequently encounter it in HIV patients. Some fungal infections are superficial, cutaneous and/or mucous membranes, and generally benign. Fungal secondary infections can reveal the HIV infection by their unexpected occurrence, their resistance to treatment, or recurrence [6].

*Candida albicans* is responsible for almost all cases of oral candidiasis [8]. The diagnosis of candidiasis of the oral mucosa should be made after a clinical stage, and an equally essential mycological stage [6].

Erythematous or atrophic Candidiasis (Fig. 1): This form is observed in 30% of seropositive patients [8], most often in the form of an erythema located at the level of the palate or the dorsal surface of the tongue, without a whitish film. The tongue appears smooth, glazed, and sometimes dry. The affected areas of the tongue are usually depapillated. This is the most frequent aspect corresponding to the classic "tongue of antibiotics". Some patients complain of pain on ingesting acidic dishes. In the case of HIV infection, erythematous candidiasis is often chronic.



Fig. 1. Acute erythematous candidiasis of the palate in an HIV-positive homosexual

-Pseudomembranous candidiasis or thrush (Fig. 2): Clinically, this candidiasis is characterized by the presence of whitish or yellowish plaques on an erythematous mucosa. The whitish plaque can be removed by scraping to make way for a bloody surface. This type of candidiasis is most often observed in the palate, the labial and cheek mucous membranes, and the dorsal surface of the tongue.

-Hyperplastic candidiasis (Fig. 3): It is observed as a white, raised, and adherent keratotic lesion. The whitish plaques are very difficult to be removed by scraping. Its clinical appearance varies from a vaguely reticulated white network, having the appearance of lichen planus, to that of a homogeneous white plaque.

-The black hairy tongue (Fig. 4): In some situations, the tongue turns brown and then black. The associated papillary hypertrophy can

reach several millimeters and give the appearance of a hairy or villous tongue. The black color is attributed to the oxidation of keratin.

Angular cheilitis (Fig. 5): It is observed in children, diabetics, cirrhotic alcoholics, Asians, immuno-depressed, and in poorly fitted toothless jaws. Moreover, it is mainly due to *Candida albicans* and super-infection with frequent streptococcus. Perleche is an intertrigo of the commissure of the lips; it is also called angular cheilitis. The lesion is uni- or bilateral, erosive, bright red, and sometimes crusty, sitting at the commissures in the form of a fan-shaped epidermal erosion. The folds of the commissure are marked, pinker, with a little damp [9]. Internal oral candidiasis makes the etiological diagnosis easy. Sometimes there is an extension of the lesion on the retro-commissural mucous surface of the cheek.



**Fig. 2. Diffuse pseudomembranous candidiasis of the palate and tongue**



**Fig. 3. Hyperplastic candidiasis of the tongue in an HIV-positive drug addict**



**Fig. 4. A black hairy tongue**



**Fig. 5. A unilateral Perleche**



**Fig. 6. Angular Cheilitis in an HIV-positive homosexual**

- Cheilitis (Fig. 6): *Candida albicans* lip infection is rare, and it includes a pattern of erosive lesions on an inflamed and enlarged lip. In any

case, these candidiasis in HIV-positive subjects are often a sign of the development of AIDS.

#### 4. ORAL CANDIDIASIS CAUSING PATHOGEN



**Fig. 7. *Candida albicans* in the form of filaments and bacterial flora**

*Candida albicans* (formerly called *Monilia albicans*, *Oidium albicans*) is usually the pathogen causing oral candidiasis [10]. In the saprophytic state, it is a yeast reproducing by budding (blastospores), whilst in the parasitic state, it forms filaments (pseudo and mycelium) (Fig. 7). Among the 34 other species of *Candida*, only few are occasionally pathogenic including *C. tropicalis*, *C. pseudotropicalis*, *C. guilliermondii*, *C. krusei*, *C. brumptii*... [4,6,10,11].

#### 5. MYCOLOGICAL EXAMINATION OF ORAL CANDIDIASIS

Oral diagnosis is based on clinical examination complemented by mycological examination. Each kind of oral candidiasis may be diagnosed primarily clinically based on the detection of the lesions, which can be further supported by additional diagnostic techniques such isolation in culture and microscopic detection of *Candida* in oral samples. Moreover, it is based on the identification of fungal elements based on direct examination and cultivation in different places. The samples guided by the clinical lesions will be either swab smears or scrapings at the level of the observed lesions. However, it is necessary to know the elective points, including the corner of the lips, cheek wall, behind the commissure, posterior median part of the back of the tongue, and the palate, where there is the greatest chance of finding yeasts. Each of these points should be sampled separately.

The presence of candida on the smears revealed, by direct examination, its appearance in the form of oval or rounded elements, budding or not, and more or less regular mycelial filaments [12]. It is important to note the abundance of fungal elements on direct examination. Nevertheless, cultivation in specific environments (Sabouraud, Microstix) allows a more precise diagnosis. *Candida albicans* in the form of spore, or more rarely in the form of filaments, is a part of the normal oral flora; hence it should be emphasized that the presence of candida in the mouth does not have any pathological value. In addition, to make the diagnosis of candidiasis, there must be a large number of colonies (in cultivation) or filaments (on smears) [6,12,13]. Therefore, one of the primary techniques for identifying a fungal infection is culture. The insensitivity of culture, however, frequently causes a delay in the final therapy of invasive candidiasis (IC), which may increase death rates [14]. Blood cultures (BC) have a limit of detection of one colony forming unit (CFU)/mL and are sensitive for identifying live *Candida* cells, but they are only 50% sensitive for detecting IC overall and can take up to 5 days to identify a sample [15]. Nevertheless, BC is currently considered the "gold standard" in the event of any suspected case of invasive fungal infection, but the combination of culture with other methods can facilitate a timelier diagnosis. Although BC is still the "gold standard" in the event of any suspected instance of an invasive fungal infection, using culture in conjunction with other techniques can help make

a diagnosis more quickly. These tests are tempting for the earlier detection of IC, notably for instances of IC that are missed by culture. This is because molecular amplification techniques facilitate rapid and sensitive detection as well as recognition by immediately detecting and analyzing minute quantities of fungal DNA present in a clinical sample without the requirement for previous cultivation. For the detection of a wide variety of fungi in different specimens like blood, serum, plasma, sterile fluids,, bronchoalveolar lavage (BAL), and tissues, numerous PCR assays targeting various genetic sequences including 18S rDNA, 5.8S rDNA, 28S rDNA, internal transcribed spacer regions, and mitochondrial DNA have been developed. Fungal diseases can be identified in a panfungal or a more specialized way, depending on the primers that are used. The various methodologies' sensitivity and specificity vary, but generally speaking, an enhanced sensitivity is shown when compared to traditional, culturally-based approaches [16].

## 6. TREATMENT

Candida infection is often slow to disappear; so, treatment should be of long-term duration. The treatment must be preceded by a mycological sample, and should be associated with the search for predisposing and suppressing/eliminating factors [17]. In immune-compromised people, the combination of antifungal treatment with other drugs should be monitored. Treatment can be local or systemic. However, it is often effective but recurrence is common due to immunosuppression.

### 6.1 Local Treatment

Local treatment can be based on an oral suspension, ointment, or gel in the case of angular cheilitis and cheilitis. The most common used treatment includes mouthwashes with sodium bicarbonate combined with NYSTATIN, AMPHOTERICIN B, MICONAZOLE, or KETOCONAZOLE. [6,13-18].

### 6.2 General Treatment

General treatment includes the following:

- AMPHOTERICIN B in tablets 10 to 100 mg/6 hours.
- MICONAZOLE in tablets 250mg/6 hours.

- KETOCONAZOLE in tablets 200 to 400 mg/day.
- FLUCONAZOLE in tablets 50 to 100 mg/day.

Failures have been observed during treatment with KETOCONAZOLE. Its side effects are not negligible and liver damage is frequent [18,19]. Moreover, it seems that FLUCONAZOLE is the best tolerated in HIV-positive patients. Its effectiveness is superior to other antifungals because it is better absorbed at the intestinal level. Moreover, it was found that the lifespan is longer with minimal side effects and that a single dose of 150 mg per week is sufficient for prophylactic treatments. In addition, it was found that it does not alter taste and above all its salivary level is identical to the serum level, hence its effectiveness against oral candidiasis [19-21,22].

## 7. CONCLUSION

Odontologist plays a significant role in the epidemiology of this disease. In most cases, the first signs of HIV infection can appear in the mouth, highlighting the need of identifying the oral mucosa and carrying out an in-depth clinical examination.

The finding of oral candidiasis in young adults, its resistance to antifungal treatments, and its persistence beyond six weeks, is doubtful when the other responsible causes have been eliminated, such as antibiotic treatment, corticosteroid therapy, antidepressants, radiotherapy, and poor oral hygiene in dentures wearers... [13].

Today, our profession is facing a new pathological entity; about 95% of patients infected with HIV have one or more lesions in the oral cavity. Practitioners should know the oral manifestations associated with HIV infection.

Odontologist will have to treat the oral lesions observed during this disease. This requires a deep knowledge of the medical problem of the patients. The purpose of this treatment will be not only to relieve the pain of those HIV patients, but also to provide them with a certain physical and psychological comfort and to improve the quality of their way of life.

## CONSENT AND ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. *Curr Opin HIV AIDS*. 2017; 12(1):6-11. DOI: 10.1097/COH.0000000000000327. PMID: 27749369; PMCID: PMC5240042.
2. Brady LJ, Walker C, Oxford GE, Stewart C, Magnusson I, McArthur W. Oral diseases, mycology and periodontal microbiology of HIV-1-infected women. *Oral Microbiol Immunol*. 1996;11(6):371-80. DOI: 10.1111/j.1399-302x.1996.tb00198.x. PMID: 9467369
3. Peacock ME, Arce RM, Cutler CW. Periodontal and other oral manifestations of immunodeficiency diseases. *Oral Dis*. 2017;23(7):866-888. DOI: 10.1111/odi.12584. Epub 2016 Oct 10. PMID: 27630012; PMCID: PMC5352551
4. Khademi F, Yousefi-Avarvand A, Sahebkar A, Ghanbari F, Vaez H. Bacterial Co-infections in HIV/AIDS-positive Subjects: A Systematic Review and Meta-analysis. *Folia Med (Plovdiv)*. 2018;60(3):339-350. DOI: 10.2478/folmed-2018-0007. PMID: 30355845
5. Moosazadeh M, Shafaroudi AM, Gorji NE, Barzegari S, Nasiri P. Prevalence of oral lesions in patients with AIDS: a systematic review and meta-analysis. *Evid Based Dent*; 2021. doi: 10.1038/s41432-021-0209-8. Epub ahead of print. Erratum in: *Evid Based Dent*. 2022 Mar; 23(1):5. PMID: 34795396.
6. Erfaninejad M, Zarei Mahmoudabadi A, Maraghi E, Hashemzadeh M, Fatahinia M. Epidemiology, prevalence, and associated factors of oral candidiasis in HIV patients from southwest Iran in post-highly active antiretroviral therapy era. *Front Microbiol*. 2022;13:983348. DOI: 10.3389/fmicb.2022.983348. PMID: 36118210; PMCID: PMC9478364.
7. Berberi A, Aoun G. Oral lesions associated with human immunodeficiency virus in 75 adult patients: a clinical study. *J Korean Assoc Oral Maxillofac Surg*. 2017; 43(6):388-394. DOI: 10.5125/jkaoms.2017.43.6.388. Epub 2017 Dec 26. PMID: 29333368; PMCID: PMC5756795.
8. Aškinytė D, Matulionytė R, Rimkevičius A. Oral manifestations of HIV disease: A review. *Stomatologija*. 2015;17(1):21-8. PMID: 26183854.
9. Lomelí-Martínez SM, González-Hernández LA, Ruiz-Anaya AJ, Lomelí-Martínez MA, Martínez-Salazar SY, Mercado González AE et al. J. Oral Manifestations Associated with HIV/AIDS Patients. *Medicina (Kaunas)*. 2022;58(9):1214. DOI: 10.3390/medicina58091214. PMID: 36143891; PMCID: PMC9504409.
10. De Almeida VL, Lima IFP, Ziegelmann PK, Paranhos LR, and de Matos FR. Impact of highly active antiretroviral therapy on the prevalence of oral lesions in HIV-positive patients: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2017;46(11):1497-1504. DOI: 10.1016/j.ijom.2017.06.008. Epub 2017 Jul 3. PMID: 28684301
11. Ottria L, Lauritano D, Oberti L, Candotto V, Cura F, Tagliabue A, Tettamanti L. Prevalence of HIV-related oral manifestations and their association with HAART and CD4+ T cell count: a review. *J Biol Regul Homeost Agents*. 2018;32(2 Suppl. 1):51-59. PMID: 29460518.
12. Mohamed AA, Lu XL, Mounmin FA. Diagnosis and Treatment of Esophageal Candidiasis: Current Updates. *Can J Gastroenterol Hepatol*. 2019;3585136. DOI: 10.1155/2019/3585136. PMID: 31772927; PMCID: PMC6854261.
13. Kumar S, Mishra P, Warhekar S, Airen B, Jain D, Godha S. Oral Health Status and Oromucosal Lesions in Patients Living with HIV/AIDS in India: A Comparative Study. *AIDS Res Treat*. 2014;480247. DOI: 10.1155/2014/480247. Epub 2014 Aug 20. PMID: 25215229; PMCID: PMC4158162.
14. Fortún J, Martín-Dávila P, Gómez-García de la Pedrosa E, Pintado V, Cobo J, Fresco G, Meije Y, Ros L, Alvarez ME, Luengo J, Agundez M, Belso A, Sánchez-Sousa A, Loza E, Moreno S. Emerging trends in candidemia: a higher incidence but a similar outcome. *J Infect*. 2012;65(1):64-70. DOI: 10.1016/j.jinf.2012.02.011. Epub 2012 Feb 24. PMID: 22369861.

15. Pfeiffer CD, Samsa GP, Schell WA, Reller LB, Perfect JR, Alexander BD. Quantitation of Candida CFU in initial positive blood cultures. *J Clin Microbiol.* 2011;49(8):2879-83. DOI: 10.1128/JCM.00609-11. Epub 2011 Jun 15. PMID: 21677065; PMCID: PMC3147732
16. Willinger B, Kienzl D, Kurzai O. 13 Diagnostics of Fungal Infections. *Human Fungal Pathogens.* 2013 229–259. DOI:10.1007/978-3-642-39432-4\_13
17. Prabhu A, Rao AP, Reddy V, Krishnakumar R, Thayumanavan S, Swathi SS. HIV/AIDS knowledge and its implications on dentists. *J Nat Sci Biol Med.* 2014;5(2):303-7. DOI: 10.4103/0976-9668.136171. PMID: 25097403; PMCID: PMC4121903
18. Lam-Ubol A, Rungsiyanont S, Vacharotayangul P, Sappayatosok K, Chankanka O. Oral manifestations, salivary flow rates and Candida species in Thai HIV-infected patients. *J Clin Exp Dent.* 2019;11(2):e138-e145. DOI: 10.4317/jced.55384. PMID: 30805118; PMCID: PMC6383906
19. Rafat Z, Sasani E, Salimi Y, Hajimohammadi S, Shenagari M, Roostaei D. The Prevalence, Etiological Agents, Clinical Features, Treatment, and Diagnosis of HIV-Associated Oral Candidiasis in Pediatrics across the World: A Systematic Review and Meta-Analysis. *Front Pediatr.* 2021;9:805527. DOI: 10.3389/fped.2021.805527. PMID: 35004551; PMCID: PMC8740125
20. Lyu X, Zhao C, Yan ZM, Hua H. Efficacy of nystatin for the treatment of oral candidiasis: a systematic review and meta-analysis. *Drug Des Devel Ther.* 2016;10:1161-71. DOI: 10.2147/DDDT.S100795. PMID: 27042008; PMCID: PMC4801147
21. Osaigbovo II, Lofor PV, Oladele RO. Fluconazole Resistance among Oral Candida Isolates from People Living with HIV/AIDS in a Nigerian Tertiary Hospital. *J Fungi (Basel).* 2017;3(4):69. DOI: 10.3390/jof3040069. PMID: 29371583; PMCID: PMC5753171.
22. Goldman M, Cloud GA, Wade KD, Reboli AC, Fichtenbaum CJ, Hafner R, et al. AIDS Clinical Trials Group Study Team 323; Mycoses Study Group Study Team 40. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS Clinical Trials Group Study 323/Mycooses Study Group Study 40. *Clin Infect Dis.* 2005;41(10): 1473-80. DOI: 10.1086/497373. Epub 2005 Oct 12. PMID: 16231260

© 2023 Berberi and Dib; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

The peer review history for this paper can be accessed here:  
<https://www.sdiarticle5.com/review-history/96782>