

Orofacial Pathologies in Newly Diagnosed Adults with HIV: A Clinically Diagnostic Disease Severity Indicator in Resource-Limited Settings

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How to cite this paper: Abe, E.O., Adisa, A.O., Adeyemi, B.F. and Hawkins, C. (2025) Orofacial Pathologies in Newly Diagnosed Adults with HIV: A Clinically Diagnostic Disease Severity Indicator in Resource-Limited Settings. *International Journal of Clinical Medicine*, 16, 293-306.

<https://doi.org/10.4236/ijcm.2025.166020>

Received: March 28, 2025

Accepted: June 22, 2025

Published: June 25, 2025

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Abstract

Background: Orofacial pathologies such as oral candidiasis and melanotic hyperpigmentation are associated with HIV and are often more prevalent among those with advanced disease. This study aimed to assess the patterns of HIV-related orofacial pathologies and their associations with immune suppression among adults newly diagnosed with HIV in Nigeria. **Methods:** This cross-sectional study included newly diagnosed adult (>16 years) persons living with HIV (PWH) attending the HIV Care and Treatment Center at two leading tertiary referral hospitals in Ibadan (Southwest Nigeria). The study period ranged from April 2022 to February 2023. Oral examination was conducted by an oral medicine specialist and data on demographics and CD4+ T-cell counts/mm³ were collected. Descriptive statistics were used to describe the spectrum of orofacial pathologies among the study participants. Demographic and laboratory characteristics were compared between participants with and without orofacial pathologies using chi-square test. Data analysis was performed using SPSS (v25). **Results:** A total of 158 participants were recruited [males (40, 25.3%), females (118, 74.7%); mean age (standard deviation, SD) 39.5 (±11.9) years]. Over two-thirds (66.5%) of the participants had orofacial pathologies including candidiasis (37.3%), oral melanotic hyperpigmentation [OMH] (14.6%), combined candidiasis and OMH (11.4%). Other pathologies (3.2%) included herpes zoster, aphthous ulcer, necrotizing stomatitis, facial pruritic papular eruptions and Kaposi sarcoma. The proportion of participants with CD4 ≤ 200 cells/mm³ was significantly higher among those with orofacial pathologies (53, 74.6%) compared with those without (18, 25.4%) (p < 0.01). Across the orofacial pathology groups, the proportion of partici-

pants with $CD4 \leq 200$ versus $CD4 \geq 200$ was significantly greater among those with OMH (72.2%, 27.8%) than among those with candidiasis and OMH (64.3%, 35.7%) ($p = 0.03$). **Conclusion:** This study revealed a significant association between severe immunosuppression and HIV-related orofacial pathologies, particularly among those with OMH. Oro-facial pathologies are important markers of HIV disease severity in this population.

Keywords

CD4+ Count, HIV, Orofacial Pathologies

1. Background

In Nigeria, an estimated two million people are living with HIV, accounting for 2.1% of the burden of HIV among adults aged 15 - 49 years [1]. A recent geospatial analysis among adults living with HIV showed antiretroviral treatment (ART) coverage as 45.3%, and viral load suppression (VLS) rate as 36.6%. Despite major improvements in providing access to HIV testing and ART, geographic variations in HIV prevalence, ART availability, and persistence of viral load suppression continue to exist at both state and sub-state levels [2]. Several distinct oral pathologies have been described in persons with HIV since the beginning of the pandemic. HIV-related orofacial pathologies reported in the literature include oral candidiasis, oral hairy leukoplakia, herpes simplex virus infection, Kaposi's sarcoma, aphthous ulcers, periodontal disease, salivary gland diseases, oral melanotic hyperpigmentation, and oral warts [3]-[5]. These oral lesions associated with HIV infection have been well-documented as clinical indicators among persons with HIV and have been shown to be associated with more severe disease, which may serve as clinical indicators of immune suppression. Therefore, these oral pathologies could serve as useful prompts for HIV screening at basic healthcare facilities located within communities, providing primary healthcare services, particularly in low and middle-income countries [6]-[9].

The National Strategic Plan has been rolled out to achieve HIV epidemic control through the 95:95:95 strategy [10]. However, HIV screening rates remain low, as only 23.7% of adolescents and young adults have ever been tested for HIV in Nigeria [11]. Its implementation can be enhanced by ensuring routine HIV screening in persons with suspicious orofacial lesions. This would help to improve the rate of diagnosis and linkage to care for early treatment. Although several published Nigerian studies describing oral lesions among adults living with HIV have been published [12]-[19], few have described oral pathologies among persons newly diagnosed with HIV which were published one to two decades ago when the epidemiology of HIV was quite different [20] [21]. In this study, we characterized HIV-associated orofacial pathologies among adults newly diagnosed with HIV (ALH) in Southwest Nigeria to provide more updated data in an era where many persons with HIV present late after HIV acquisition [22].

2. Methodology

2.1. Study Design, Population, and Setting

This was a cross-sectional study conducted among newly diagnosed adult PWH attending HIV Care and Treatment clinics at the Infectious Diseases Institute of the College of Medicine, University of Ibadan and Adeoyo State Teaching Hospital, Ibadan, Nigeria. During the study period, one of the authors provided basic oral healthcare service to the study participants, which is yet to be included into routine healthcare services to clients. The study period ranged from April 2022 to February 2023.

2.2. Selection Criteria

Participants were enrolled consecutively from both clinics who presented as newly diagnosed cases throughout the study period. Those included were: 1) newly diagnosed with HIV; 2) antiretroviral therapy (ART) naïve; and 3) adults >16 years old. Persons were excluded if they were: 1) ART experienced; 2) aged 16 years old and below; 3) WHO stage IV or other severely debilitating illnesses that might not be related to HIV.

2.3. Procedures and Data Collection

After providing consent, interviewer-administered questionnaires were used to document the participants' data on age, gender, marital status, educational level, comorbid systemic disease, medication history, and WHO stage. Oral examination was conducted by an oral medicine specialist to check for the presence of HIV-related orofacial pathologies and the site(s) involved. The clinical diagnosis of HIV-associated oral pathologies was made according to the criteria proposed by the European Community-Clearinghouse on Oral Problems related to HIV infection [19]. The anatomical sites and extent of the oral lesions were documented, and clinical pictures were taken using a digital camera. Laboratory testing for CD4+ T cell count/mm³ was then performed.

2.4. Data Analysis

This was performed using SPSS version 25. The primary outcome was HIV-associated oral pathologies documented as present/absent which were expressed as proportions and percentages. Their prevalence was also described. Continuous variable such as age was summarized using means and standard deviation. Demographic and laboratory characteristics were compared between persons with and without HIV-related oral pathologies. CD4+ T cell count/mm³ was further categorized as ≤200 (severe immune suppression) or ≥200. Comparisons between categorical variables were computed using chi-square tests. The power of the study was set at 80%, and a 5% significance level was used.

2.5. Institutional Review Board Approval

Ethical approval was obtained from the University of Ibadan/University College

Hospital (UI/UCH) ethics review committee with approval number-UI/EC/21/0506.

3. Results

One hundred and fifty-eight study participants [males (40, 25.3%), females (118, 74.7%)] were enrolled in this study. The mean (SD) age was 39.5 (\pm 11.9) years. Over half of the participants were married (55.7%), and had a secondary educational status (52.9%). Approximately two-thirds (66.5%) of the participants had one or more HIV-associated orofacial pathologies which included pseudomembranous and erythematous candidiasis (59, 37.3%), oral melanotic hyperpigmentation [OMH] (23, 14.6%), combined candidiasis and OMH (18, 11.4%). Other lesions (5, 3.2%) included maxillary herpes zoster (2nd division of Trigeminal nerve), major aphthous ulcer, necrotizing stomatitis, facial pruritic papular eruptions (PPE) and Kaposi sarcoma (**Figures A1-A5** in **Appendix**). The remaining participants (33.5%) had no oral lesions (**Figure 1**).

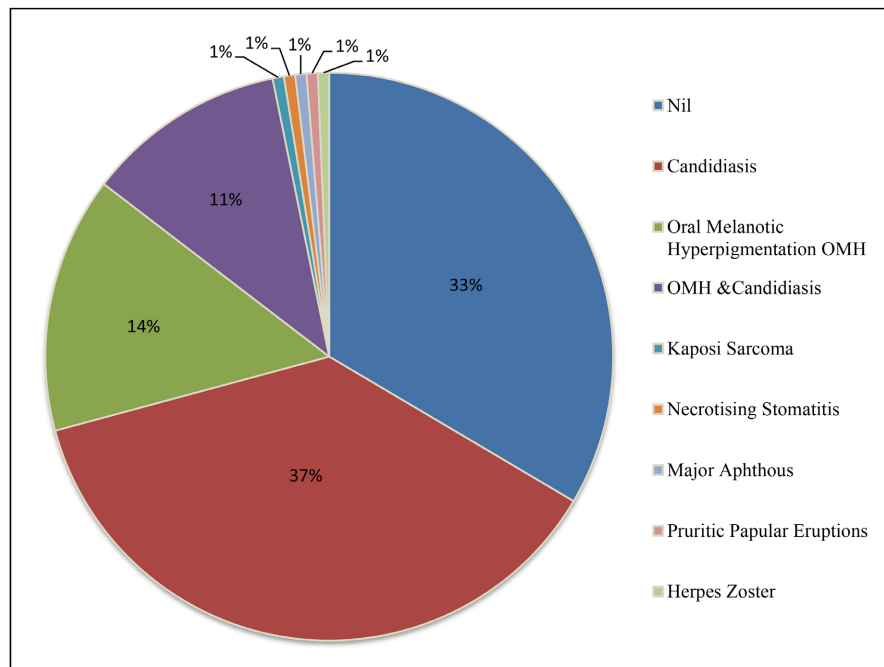


Figure 1. Distribution of orofacial pathologies among the study participants.

There was no difference in age between persons with and without HIV associated conditions. However, there was a significant association between increased aging and immune suppression; more than half of those aged >40 years had CD4 count \leq 200 ($p = 0.04$). A greater proportion of persons with oral lesions (56.4%) had CD4 \leq 200 cells/mm³ (**Table 1**).

Each orofacial lesion category was significantly associated with severe immune suppression (CD4 \leq 200) which was most pronounced in the OMH category (**Figure 2**). In addition, oral lesions were more common as single entities (54.4%) than

were combined lesions (9.5%); however, both categories were more common among those with CD4 <200 (74.7%) than among those with CD4 >200 (54.0%) ($p = 0.03$).

Table 1. Association between orofacial pathologies, demographics and CD4+ count groups.

Parameters	HIV-oral lesions		p-value (*significant)
	Present N (%)	Absent N (%)	
Gender			
Male	26 (24.8)	14 (26.4)	0.82
Female	79 (75.2)	39 (73.6)	
Age group			
≤40 years	51 (48.6)	34 (64.2)	0.06
>40 years	54 (51.4)	19 (35.8)	
Marital status			
Single	17 (17.0)	7 (14.3)	0.91
Married	55 (55.0)	28 (57.1)	
Widow/Divorced	28 (28.0)	14 (28.6)	
Educational status			
Nil/Primary	24(26.4)	13(27.6)	0.95
Secondary	49 (53.8)	24 (51.1)	
Tertiary	18(19.8)	10 (21.3)	
CD4+ T-cell count			
≤200 cells/mm ³	53(56.4)	18 (34.0)	*<0.01
≥200 cells/mm ³	41(43.6)	35 (66.0)	
Parameters	CD4+ T-cell count		p-value (*significant)
	≤200 cells/mm ³	≥200 cells/mm ³	
Gender			
Male	22 (31.0)	15 (19.7)	0.11
Female	49 (69.0)	61 (80.3)	
Age group			
≤40 years	32 (45.1)	47 (61.8)	*0.04
>40 years	39 (54.9)	29 (38.2)	

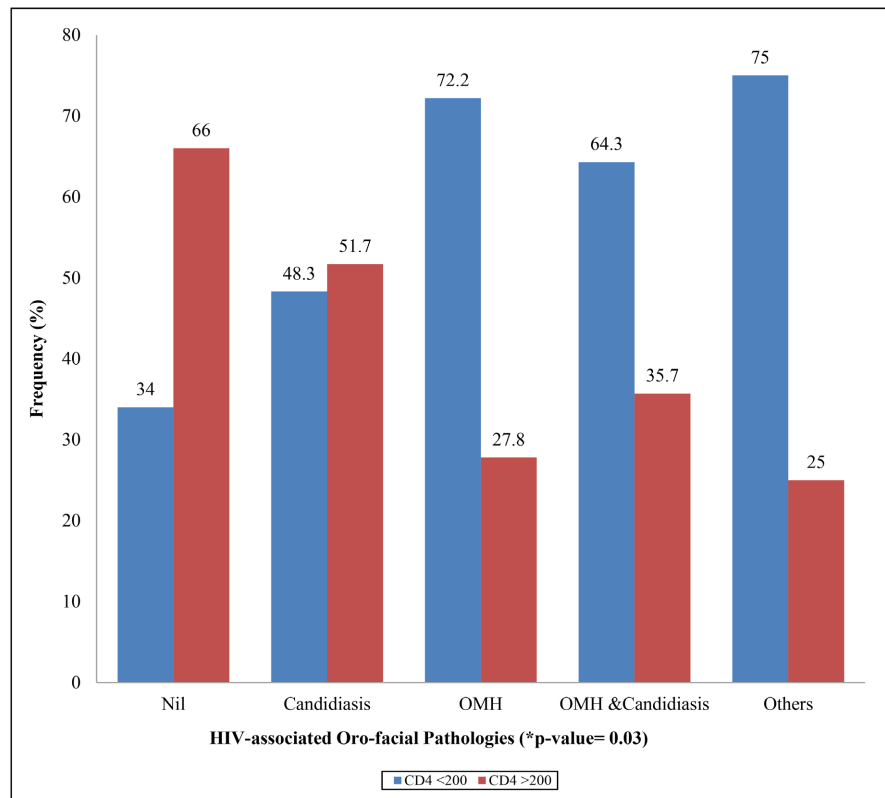


Figure 2. Distribution of orofacial pathologies according to immune status.

4. Discussion

Oral pathologies are important clinical indicators that suggest HIV infection in an undiagnosed individual and may also indicate clinical disease progression to AIDS [23]. This study aimed to assess the pattern of orofacial pathologies among newly diagnosed ALH, and how these pathologies vary with the level of immune suppression. Approximately two-thirds of our study participants had one or more orofacial lesions which is similar to the pattern described nearly two decades ago in Nigeria by Arotiba *et al.* [19] but higher than the findings of Adedigba *et al.* [18] and Frimpong *et al.* [24] in Nigeria and Ghana respectively. Despite declines in the incidence of HIV infection in Nigeria [1], the prevalence of orofacial lesions among ALH as observed in this study has not significantly decreased and this may be attributed to late presentation at diagnosis despite increased awareness of the disease entity. Some authors have reported high prevalence of late presentation for HIV care which was significantly attributed to factors including old age, unemployment, poor clinical status, poor healthcare practices, as well as fear of stigma and discrimination status [22] [25] [26].

Oral candidiasis is the most common oral lesion among PWH, ranging in prevalence from 17% to 75% [27]. Risk factors associated with oral candidiasis include CD4+ T lymphocyte count <200 cells/mm³, tobacco use, and wide spectrum antibiotic use or corticosteroids, which result in oral microbiome dysbiosis [27]. Its clinical presentations commonly described among PWH include pseudomembra-

nous (oral thrush), erythematous candidiasis, and angular cheilitis. Oral candidiasis, which was the most common orofacial pathology in this study, was in tandem with other findings among newly diagnosed PWH [20] [23]. Oral melanotic hyperpigmentation in PWH has been attributed to the use of antifungal agents or ART, whereas some studies have reported that HIV-induced cytokine dysregulation causes activation of the melanogenesis pathway [28]. This study revealed a significant association between OMH and immune suppression, either as a single lesion or its combined occurrence with candidiasis. Studies [8] [20] [29] conducted among the ART naïve population have also documented a significant association between OMH and low CD4+ count, indicating that oral lesions are clinical markers of immunosuppression in HIV infection in addition to candidiasis.

Kaposi's sarcoma (KS) is an endothelial angioproliferative neoplasm caused by human herpes virus8 (HHV8); it is the most common oral HIV-associated neoplasia, but has notably decreased due to the use of ART. The lesions have mucocutaneous morphological patterns (patches, plaques, and nodules) and may progress from papules to red-purplish plaques which may ulcerate [27]. This study identified a case of Kaposi's Sarcoma (KS) characterized by severe immunosuppression. This contrasts with a two-decade study conducted in Northern Nigeria, which reported a higher number of KS cases, likely due to the previously high prevalence of HIV/AIDS in the country [19].

Bilateral parotid swelling in patients with HIV is clinically diagnosed as HIV salivary gland disease (HIV SGD) which can be any of the following: benign lymphoepithelial cyst, benign lymphoepithelial lesion, Sjogren-like syndrome, or diffuse infiltrative lymphocytosis syndrome. These pathologies develop from lymphoproliferation of the intraparotid lymph nodes, or prolonged inflammatory processes which might induce the proliferation of glandular epithelial cells within the lymph nodes. They represent local manifestations of persistent generalized lymphadenopathy associated with HIV infection [30] [31]. HIV SGDs are mostly asymptomatic, presenting as unilateral or bilateral diffuse soft tissue swelling of one or more major salivary glands, especially the parotid, thereby causing facial disfigurement [22] [31]. A case of bilateral parotid swelling was found in this study as well as that of Moodley *et al.* [32] but slightly higher compared to the findings by Al-Attas [6] and Owotade *et al.* [33].

Herpes zoster (shingles) usually presents as localized maculo-papular cutaneous lesions evolving from vesicles or pustules in a dermatomal distribution associated with pain. The disease results from reactivation of varicella zoster virus in the sensory nerve ganglia due to decreased cellular immunity, and virus reactivation may occur in one or more ganglia with zoster eruptions appearing in non-contiguous dermatomes. The incidence of HIV-associated HZ has been reportedly associated with male gender, men who have sex with men, CD4 count <200 cells/mm³, as well as ART naïve population [34]-[36]. However, this study found a single case of HZ affecting the right maxillary region of the trigeminal nerve in an elderly woman with severe immune suppression (CD4 ≤200).

Immune aging is a risk factor for and amplifies age-related pathologies, whereas inflammatory responses mediated by the innate immune system increase in intensity and duration, rendering older individuals susceptible to tissue-damaging immunity and inflammatory disease [37]. Similarly, concomitant immune dysfunction and increased risk of age-related comorbidity have prompted the hypothesis that HIV infection accelerates the aging process including immunological aging, also known as immunosenescence [38]. This may elucidate the basis for our findings of increased age, low CD4 T-cell count and the presence of HIV-oral lesions, as increased age (>40 years) was significantly associated with severe immune suppression ($CD4 \leq 200$) and a greater proportion of PWH above 40 years of age had oral pathologies than those younger than 40 years of age. This finding agrees with another study conducted among PWH which revealed that increasing age was associated with lower proportions of CD4+ activated T-cells; this may therefore predispose them to increased risk of age-related comorbidities [38]. Furthermore, this study revealed a significant relationship between the number of oral lesions and CD4 count; oral lesions were more common as single entities compared to combined lesions, however, both categories were more common among those with $CD4 \leq 200$ than among those with $CD4 \geq 200$. In contrast, Adedigba *et al.* [18] reported higher rates of combined oral lesions compared to single pathologies. This finding further highlights the fact that low CD4 levels are associated with a greater prevalence of oral pathologies, serving as clinical indicators of lower CD4 counts and HIV progression [23].

5. Limitations of the Study

The number of study participants was restricted to the newly diagnosed patients seen during the study period. Future studies may consider enrolling a larger number of newly diagnosed patients to capture more HIV-orofacial pathologies and better represent them in their categories. Larger sample size would further allow robust statistical analysis for improved research output.

6. Conclusion

This study described the pattern of HIV-related orofacial pathologies among newly diagnosed adult PWH in Southwest Nigeria. There was a significant association between severe immunosuppression and HIV-related orofacial pathologies, particularly among those with OMH. Additionally, there was an association between increased age, low CD4 count, and the presence of oral lesions. Therefore, orofacial pathologies should be considered as diagnostic indicators for HIV screening and important tools for the assessment of disease severity among PWH, particularly in resource-limited settings.

Acknowledgements

EO is supported by Consortium for Advanced Research Training in Africa (CARTA).

Ethics Approval and Consent to Participate

This research was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the University of Ibadan/University College Hospital, Ibadan (UI/UCH) Ethics committee. The ethical approval number assigned to the study is UI/EC/21/0506. Informed consent was obtained from the study participants, and only consenting participants were enrolled in the study.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due to the potential risk of stigmatization, but are available from the corresponding author on reasonable request.

Funding

Research reported in this publication was supported by Northwestern University's Global Health Catalyzer Fund and Northwestern's Global Health Initiative, which is generously supported by Northwestern Medicine Primary and Specialty Care.

Authors' Contributions

EO, AO and BF conceptualized the study; EO collected and analysed the data; EO and CH were major contributors in writing the manuscript while all the authors read and approved the final manuscript.

Authors' Information

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Clinical photographs of HIV-related Orofacial pathologies

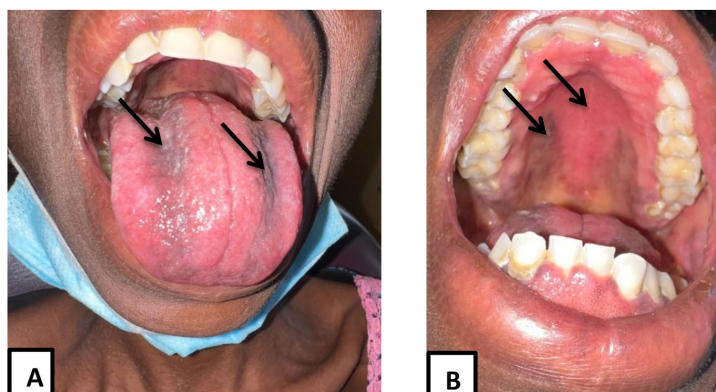


Figure A1. Coexistence of HIV-oral lesions including pseudomembranous candidiasis (dorsum of tongue) in (A); Erythematous candidiasis (palate) and oral melanotic hyperpigmentation (dorsum of tongue, buccal mucosa and palate) in (B).

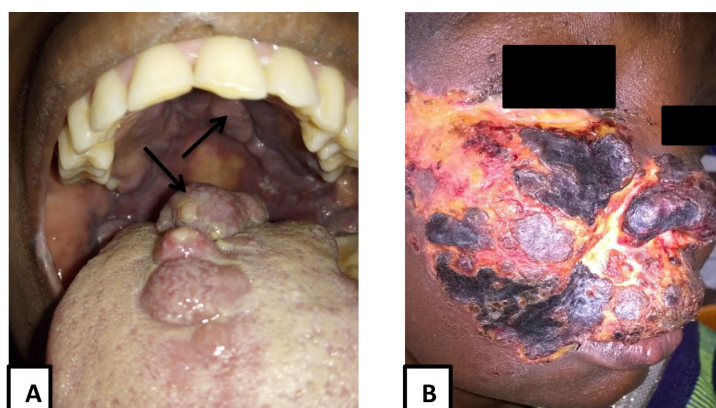


Figure A2. (A) Multiple nodular swellings on the dorsum of the tongue and palate with oropharyngeal extension—Kaposi Sarcoma; (B) Right-sided dermatomal presentation (Maxillary division of the Trigeminal nerve) of coalesced ulcerative lesions—Herpes zoster.



Figure A3. Necrotizing ulcerative stomatitis.



Figure A4. Left parotid gland enlargement.



Figure A5. Pseudomembranous Candidiasis (Oropharyngeal).