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Literature Review

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Clinical Characteristics and Microbiological Profile of Oral Candidiasis among HIV-Positive Patients in Indonesia: A Literature Review

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ABSTRACT

Background: As the country with the highest identified active cases of HIV/AIDS across Southeast Asia, Indonesia faces a massive challenge in providing adequate antiretroviral therapy (ART) coverage to prevent disease progression and mortality. Oral candidiasis (OC) is the most frequently identified oral manifestation of HIV infection and represents the degree of immunosuppression, treatment failure, and prognosis among people living with HIV/AIDS. Demographic characteristics, clinical types, and causative pathogens of OC vary between different geographical and socioeconomic settings. Hence, the role of oral candidiasis is crucial in developing effective strategies to address the HIV-related burden in Indonesia. **Review:** This literature review evaluated 11 descriptive studies conducted across eight major cities in Indonesia, comprising 764 HIV-positive patients diagnosed with OC. Most affected individuals were male and exhibited advanced immunosuppression, with the majority presenting CD4+ counts below 200 cells/mm³. Six clinical variants of OC were identified, with pseudomembranous candidiasis being the predominant form, followed by angular cheilitis, erythematous candidiasis, hyperplastic candidiasis, and sporadic cases of atrophic candidiasis and denture stomatitis. Microbiological findings showed Candida albicans as the leading etiologic species; however, non-albicans Candida (NAC)—particularly C. krusei, C. glabrata, and C. tropicalis—demonstrated notable prevalence, including mixed colonization with C. albicans. The rise of NAC species highlights concerns regarding antifungal resistance in the ART era. **Conclusion:** Oral candidiasis serves as an important clinical finding among patients living with HIV/AIDS, and its appropriate management is necessary not only to prevent further complications but also to mitigate the recent development of antifungal resistance.

Keywords: Oral candidiasis, Candida, HIV, AIDS, Indonesia.

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BACKGROUND

Oral candidiasis (OC) is an opportunistic infection that occurs in the oral cavity due to excessive colonization of Candida species, primarily *Candida albicans*.[1,2] The global incidence of oral candidiasis is being reported at an approximate rate of 2 million cases per year.[3] *Candida*, though a commensal organism that colonizes the oral mucosa, can transition to a pathogenic state when accompanied by various predisposing factors such as age, sex, smoking habits, use of dentures, oral hygiene, drug use, or immune status.[4]

Immunosuppression induced by human immunodeficiency virus (HIV) infection is frequently linked with increased incidence of *Candida* colonization and oral candidiasis.[5–7] HIV infection causes dysregulation of host-immune functions as well as an upregulation of virulence factors from *Candida*

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fungi, particularly the secreted-aspartyl proteinase (SAP), which can degrade host defense proteins, including complement, histatin-5, and E-cadherin. This phenomenon is supported by the ability of the virus to bind to fungi and/or induce the envelope protein GP160 or other viral proteins such as Tat.[8] These mechanisms contribute to the pathogenesis of oral candidiasis in HIV-infected individuals. A systematic review across studies conducted in Asia showed that oral candidiasis is the most common oral manifestation following HIV infection, with a prevalence of 37.7%.[9] Evidence from Surabaya, Indonesia, found a prevalence of 49.06% of oral candidiasis among HIV-infected transgender patients.[10]

The diagnosis of any form of OC is primarily based on clinical recognition of the presence of lesions. Based on the clinicopathological characteristics and the location of the lesions, the clinical types of OC can be classified as per Table 1. Microscopic confirmation from an oral specimen and/or isolation in culture is the gold standard for diagnosis, although the presence of *Candida* in the oral cavity does not always indicate infection since it is part of the normal flora in that region of the body. Tissue invasion by *Candida* is necessary to confirm a definitive diagnosis of candidiasis. Microbiological culture is otherwise required following diagnostic uncertainty, resistance to antifungal drugs, or a need for adjustment in the dose of antifungal drugs.[2]

Oral candidiasis in HIV-infected patients is primarily caused by *Candida albicans*, with a report showing the isolation of *C. albicans* in 95% of such patients.[1] However, recent observations have indicated an increase in the incidence of non-albicans Candida (NAC) species causing OC. Although found in low proportions, these NAC species exhibit a higher degree of resistance to commonly used antifungal drugs, posing a significant public health concern. The rise in the use of antifungal drugs for prophylactic and therapeutic purposes is associated with a corresponding increase in the prevalence of the NAC group. Notable NAC species identified in OC cases include *C. tropicalis*, *C. glabrata*, and *C. krusei*. Currently, over 20 Candida species have been implicated as the cause of oral candidiasis.[12,13]

Table 1. Clinicopathological classification of oral candidiasis[11]

Acute/Chronic Candidiasis	Suppurative Oral Candidiasis
Pseudomembranous Erythematous	Focal necrotizing ulcerative mucositis or osteomyelitis
Candida-associated Infection	Hyperplastic Candidiasis
Denture stomatitis • Localized simple inflammation • Diffuse erythematous type • Granular type Median rhomboid glossitis Angular cheilitis Cheilocandidiasis Juxtavermillion candidiasis	Plaque-like Nodular-like Granular/papillary-like
	Keratinized primary lesion with *Candida* Superinfection
	Leukoplakia Oral lichen planus Lupus erythematosus
Oropharyngeal Candidiasis	Chronic Mucocutaneous Candidiasis CMC
Warning signs Immunosuppression	Congenital CMC Acquired CMC

The distribution and prevalence of *Candida albicans* and non-albicans species can vary across different geographical and socioeconomic backgrounds. Studies conducted in various regions have shown major variation in the prevalence of different *Candida* species. For instance, in India, *C. albicans* was found in 64 of 128 isolates from HIV seropositive patients, followed by *C. glabrata* in 17.1% of isolates as the main non-albicans species.[14] Other studies have identified other predominant NACs, such as *C. tropicalis* in Brazil[15] and *C. dubliniensis* in Iran[16]. Therefore, this literature review aims to assess the currently available evidence on the clinical characteristics and prevalence of *Candida* species causing oral candidiasis in HIV-infected patients among the Indonesian population.

Table 2. Clinical Types of Oral Candidiasis

Author	Year	Signs and Symptoms	Clinical Types							Reference
			Pseudomembranous	Angular Cheilitis	Erythematous	Hyperplastic	Atrophic	Denture Stomatitis	Mixed type	
Jamil	2009	Dysphagia (4); Asymptomatic (2)	4 (66.66%)	0	2 (33.33 %)	0	0	0	0	
Sumintarti	2014	N/A	17 (56.7%)	0	2 (6.7%)	4 (13.3%)	0	0	7 (23.3 %)	
Walangare	2014	White patches (19); Red patches (5); Sores on the corners of the mouth (3)	19 (70.4%)	2 (7.4%)	5 (18.5%)	0	0	0	1 (3.7%)	
Nugraha	2018	N/A	50 (73.53%)	0	9 (13.24 %)	8 (11.76%)	0	1 (1.47%)	0	
Mensana	2018	N/A	6 (21.43%)	13 (46.43%)	4 (14.29 %)	0	0	0	0	
Murtiastutik	2022	White patches (100); Red patches and sores on the corners of the mouth (7); White and red patches (4); White patches and sores on the corners of the mouth (3)	103 (90.3%)	10 (8.8%)	0	0	1 (0.9 %)	0	0	

N/A: Not available

REVIEW

A total of 186 records were initially retrieved from the predetermined databases, comprising 13 from PubMed, 22 from Scopus, 27 from Web of Science, and 124 from Google Scholar. After the removal of 97 duplicate entries, a further 66 records were excluded during the initial screening process based on their titles and abstracts, leaving 23 records for full-text assessment. Among these, 12 studies were excluded due to incompatibility with the desired study type, resulting in the inclusion of 11 studies for subsequent analysis (Figure 1). The study and sample characteristics of oral candidiasis among HIV-positive patients in Indonesia are evaluated in 11 studies, which were published from 2009 to 2022 (Table 3). General Hospital, Malang[21]; Dr Moewardi General Hospital, Surakarta[22];

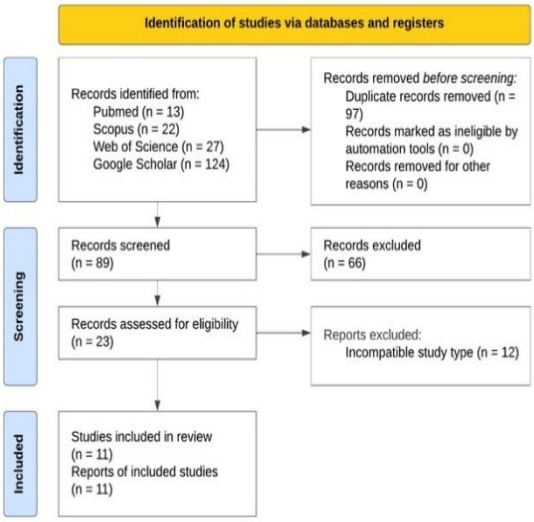

Figure 1. Flowchart Diagram for Study Inclusion

The studies were originated from several healthcare centers, including Dr Zainoel Abidin General Hospital, Aceh[17]; Dr Kariadi Central General Hospital, Semarang[18]; Dr Wahidin Sudirohusodo, Makassar[20]; Dr Saiful Anwar

Dr Soetomo General Hospital, Surabaya[23,24,27]; Universitas Airlangga General Hospital, Surabaya[25]; Dr Hasan Sadikin Central General Hospital, Bandung[26]; and Wangaya General Hospital, Denpasar[19]. A total of 764 patients were admitted during the study period. The review revealed a prevalence of 58.6% of male patients, with several studies showing a significantly higher proportion of male patients (79.4%; 72.9%; 72.8%).[19,25,27] Out of 11 studies, we identified four studies that revealed the clinical staging of HIV-positive patients.[19–21,25] Lower CD4+ cell counts (<200 cells/mm^3) are reported in 412 patients. A study by Suryana *et al.* (2020) used a different threshold, in which 133 patients showing CD4+ cell count lower than 108 cells/mm^3.[19] According to studies by Mensana *et al.* (2018) and Murtiastutik *et al.* (2022), it is reported that there are 142 HIV-positive patients with oral candidiasis, of whom 73.9% are identified as ART receivers.[24,27]

Table 3. Key Words and Search Strategy

Key words	Description	Search Terms	Search Strategies
Oral candidiasis	A fungal infection of the oral cavity	oral candidiasis oral thrush candidiasis candidosis	oral candidiasis OR oral candidiases OR candidiases, oral OR oral thrush OR candidiasis OR candidosis
Candida	A genus of yeast-like mitosporic *Saccharomycetales* fungi characterized by producing yeast cells, mycelia, pseudomycelia, and blastophores	candida thrush albicans non-albicans	candida OR thrush OR albicans OR non-albicans OR monilia OR monilias OR cyberlindnera jadinii OR candida utilis OR torulopsis utilis OR lindnera jadinii OR hansenula jadinii OR pichia jadinii OR saccharomyces jadinii OR torula utilis
HIV	An infection occurs by contact with or transfer of blood, pre-ejaculate, semen, and vaginal fluids	HIV	human immunodeficiency virus OR HIV OR virus, human immunodeficiency OR viruses, human immunodeficiency OR lymphadenopathy-associated virus OR lymphadenopathy-associated viruses OR human T-cell lymphotropic virus type III OR human T-cell leukemia virus type III
AIDS	An acquired defect of cellular immunity associated with infection by the human immunodeficiency virus	AIDS acquired immunodeficiency syndrome	acquired immunodeficiency syndrome OR AIDS OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR syndrome, acquired immuno-deficiency OR immunologic deficiency syndrome, acquired
Indonesia	A country in Southeast Asia and Oceania between the Indian and Pacific oceans	Indonesia	Indonesia

Table 4. Characteristics of the Included Studies and Samples

Author	Year	Location	Sample Size	Sex	Most Common Age Range	CD4+ Cell Count	Clinical Stage	ART Usage	Reference
Jamil	2009	Dr Zainoel Abidin General Hospital, Banda Aceh	6	5 males; 1 female	N/A	N/A	N/A	N/A	[17]
Sofro	2013	Dr Kariadi Central General Hospital, Semarang	42	29 males; 13 females	30-39 years (40.48%)	<50 cells/mm^3 = 33 50-200 cells/mm^2 = 5 >200 cells/mm^3 = 3 Unknown = 1	N/A	N/A	[18]
Suryana	2020	Wangaya General Hospital, Denpasar	207	151 males; 56 females	≥ 34 years (27.0%)	< 108 cells/mm^3 = 133 ≥ 108 cells/mm^3 = 74	I = 51 II-IV = 156	N/A	[19]
Sumintarti	2014	Dr Wahidin Sudirohusodo General Hospital, Makassar	30	19 males; 11 females	30-39 years (36.7%)	<200 cells/mm^3 = 19 >200 cells/mm^3 = 1 Unknown = 10	IV = 30	N/A	[20]
Walangare	2014	Dr Saiful Anwar General Hospital, Malang	27	18 males; 9 females	35-44 years (42.5%)	<200 cells/mm^3 = 23 >200 cells/mm^3 = 4	I = 0 II = 0 III = 18 IV = 9	No	[21]
Kusuma	2014	Dr Moewardi General Hospital, Surakarta	124	56 males; 68 females	31-40 years (39.5%)	<200 cells/mm^3 = 84 >200 cells/mm^3 = 40	N/A	N/A	[22]
Nugraha	2018	Dr Soetomo General Hospital, Surabaya	68	46 males; 22 females	26-35 years (38.24%)	<200 cells/mm^3 = 61 >200 cells/mm^3 = 7	N/A	N/A	[23]
Mensana	2018	Dr Soetomo General Hospital, Surabaya	28	14 males; 14 females	N/A	N/A	N/A	23 Yes; 5 No	[24]
Putranti	2018	Universitas Airlangga General Hospital, Surabaya	34	27 males; 7 females	40-75 years (55.8%)	N/A	I = 0 II = 2 III = 11 IV = 21	N/A	[25]
Mardhatillah	2020	Dr Hasan Sadikin Central General Hospital, Bandung	84	0 male; 84 females	20-30 years (44%)	<200 cells/mm^3 = 111 200-499 cells/mm^3 = 54 >500 cells/mm^3 = 3	N/A	Yes	[26]
Murtiastutik	2022	Dr Soetomo General Hospital, Surabaya	114	83 males; 31 females	N/A	<200 cells/mm^3 = 76 >200 cells/mm^3 = 38	N/A	82 Yes; 32 No	[27]

Table 5. Microbiological Profile of Oral Candidiasis

Author	Year	C. albicans	Non-albicans Candida	Description of Non-albicans Candida							Mixed of C. albicans and Non-albicans Candida
				C. tropicalis	C. krusei	C. glabrata	C. parapsilosis	C. stellatoidea	C. pseudotropicalis	Others	
Jamil	2009	3 (75%)	1 (25%)	1 (16.66%)	0	0	0	0	0	0	0
Sofro	2013	18 (45%)	24 (55%)	6 (15%)	3 (7.5%)	6 (15%)	5 (12.5%)	6 (15%)	6 (15%)	1 (2.5%)	0
Sumintarti	2014	15 (50%)	15 (50%)	0	9 (30%)	0	0	0	6 (20%)	0	0
Walangare	2014	24 (88.4%)	3 (11.6%)	1 (3.8%)	0	2 (7.4%)	0	0	0	0	0
Nugraha	2018	34 (50%)	34 (50%)	5 (7.34%)	7 (10.3%)	13 (19.12%)	0	0	0	9 (13.24%)	0
Murtiastutik	2022	69 (60.5%)	45 (39.5%)	1 (0.8%)	9 (7.8%)	0	0	0	0	0	35 (30.7%)

DISCUSSION

The currently available literature regarding manifestations of oral candidiasis among HIV/AIDS patients in Indonesia is relatively limited compared to other countries. A higher rate of studies were originally conducted in Surabaya, East Java, compared to other major cities in Indonesia, which indicates a higher probability of case identification and research regarding oral candidiasis among HIV/AIDS patients in that region.[23–25,27] In Asia, the prevalence of oral candidiasis is 37.7%, which is lower than in Africa (52%), and comparable to the rates in Europe (29%) and America (30%).[9,28] Among the pediatric population residing in India, Brazil, and several African countries, the prevalence of oral candidiasis continues to be the most common oral manifestation of HIV infection, with reported prevalence varying from 4% to 80%.[29] Evidence has consistently demonstrated a marked decrease in the prevalence of oral manifestations of HIV infection in response to increased use of antiretroviral therapy.[30] Hence, oral manifestations of HIV could potentially create a significant public health burden in regions where access to antiretroviral therapy for individuals with HIV/AIDS is limited.[31–34]

The included studies in our review reported a predominance of oral candidiasis among HIV-infected male patients, except in a study conducted by Kusuma *et al.* (2014), Mensana *et al.* (2018), which include the same amount in both sexes, and Mardhathillah *et al.* (2020), which only included female patients.[22,24,26] Evidence from Wangaya General Hospital, Denpasar, demonstrated that HIV-infected male patients had an 88% higher risk of developing oral candidiasis in comparison to their female counterparts (OR 1.88; 95% CI [1.26-2.80]; p=0.002).[19] A higher rate of risky sexual conduct, illegal drug injections, and migrations among the male population was among the many predisposing factors for increased transmission of HIV from sexual partners. However, evidence from Iran and Nigeria demonstrated significantly higher rates of oropharyngeal *Candida* infection in females compared to men with HIV/AIDS.[35,36] One plausible explanation for these findings is that male patients may exhibit lower willingness and compliance when undergoing routine medical checkups, which in turn could lead to a relatively lower identification rate of oral candidiasis.[37,38] Regardless, the prevailing consensus suggests that there is a lack of notable association between sex and oral manifestations in patients diagnosed with HIV/AIDS.[39]

In general, oral manifestations represent the earliest and one of the most commonly identified signs of HIV infection, which occur for up to 50% and 80% of HIV-infected patients and AIDS patients, respectively.[40] Additionally, the presence of oral manifestations in HIV-infected patients is highly predictive of compromised immune status.[41–43] Eight studies that were included in our review identified substantial immunosuppression among HIV-positive patients with oral candidiasis in Indonesia, as indicated by the low CD4+ count.[18–23,26,27] A study conducted in Uganda identified that across all oral manifestations of HIV infection, oral candidiasis was the only one that was significantly predictive of immunosuppression (CD4 <350 cells/mm^3; OR 2.56; 95% CI [1.52-4.30]; $p < 0.001$).[44] Evidence from China also demonstrated that oral candidiasis and oral *Candida* load were associated with a low CD4+ count and CD4/CD8 ratio, in which CD4+ <200 cells/mm^3 were also independently associated with oral candidiasis at baseline and 3, 6, and 12 months following HAART initiation in a multivariable logistic regression.[45] Therefore, oral candidiasis may serve as a crucial clinical indicator to aid healthcare providers to determining the progression of HIV infection in a resource-constrained setting where CD4+ count tests may not be readily available for patients.

The most common clinical types of oral candidiasis among HIV-positive patients in Indonesia are pseudomembranous candidiasis, angular cheilitis, erythematous candidiasis, hyperplastic candidiasis, atrophic candidiasis, and denture stomatitis, respectively. Comparably, a systematic review by Sharma *et al.* (2015) showed that pseudomembranous and erythematous candidiasis are the most commonly observed clinical types of oral candidiasis among HIV-positive patients in Asia (20.4% and 20.9%, respectively), followed by angular cheilitis (8.1%) and hyperplastic candidiasis (1%).[9]

In line with the general evidence across the globe, *Candida albicans* is the most common species causing HIV-associated oral candidiasis in Indonesia. However, evidence from Semarang suggests that *C. albicans* accounts for only 45% of the species diversity of oral candidiasis in HIV-positive patients.[18] These findings are consistent with recent studies conducted in India[46] and Cameroon[47], which reported a higher prevalence of NAC species compared to *C. albicans* among HIV-positive patients. Interestingly, one study by Murtiastutik *et al.* (2022) showed a high occurrence and diversity of NAC isolation within cultures that also grew *C. albicans*.[27] The presence of *C. glabrata* presumably aided the colonization and infection of *C. albicans*, while the presence of *C. krusei* inhibited that process.[27,48] The recent increase in prevalence of NAC in the HAART era provides an additional challenge for disease management due to antifungal resistance.[49]

From 2009–2020, 11 studies have highlighted the occurrence of oral candidiasis among HIV-positive patients in Indonesia, noting the predominance of oral candidiasis in HIV-infected male patients and identifying *Candida albicans* as the most common species found. The most typical clinical signs and symptoms found may range from asymptomatic, dysphagia, white patches, and red patches to sores on the corner of the lips.

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