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LITERATURE REVIEW

Management of Oral Candidiasis in People Living with HIV

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ABSTRACT

Background: *The incidence of HIV/AIDS has increased significantly over the last decade, both globally and in Indonesia. In this situation, the patient has severe impairment in their cellular immunity, making them susceptible to various kinds of opportunistic infections. Oral candidiasis is the most common oral lesion related to HIV/AIDS. Oral candidiasis in people living with HIV (PLHIV) needs to be treated because it can evolve into a systemic infection through the lymphatic system that attacks vital organs.* ***Objective:*** *To know the management of oral candidiasis in PLHIV.* ***Methods:*** *A web-based search was conducted using the PubMed, ScienceDirect, and Google Scholar database. Original research and case reports (2018–2023) published in English and Indonesian were included to evaluate various topics. The number of articles included in the review amounted to 9 articles.* ***Literature Study:*** *Management of patients with oral candidiasis in PLHIV by eliminating predisposing factors, improving oral hygiene, and administering antifungal drugs such as topical agents and/or systemic triazoles.* ***Discussion:*** *In cases of oral candidiasis associated with immunodeficient individuals, topical agents may not be effective in such cases, hence triazole systemic administration is necessary. Oral candidiasis in PLHIV is less responsive to polyene antifungal drugs (nystatin and amphotericin B).* ***Conclusions:*** *Management of oral candidiasis in PLHIV sufferers are eliminating predisposing factors, Improving oral hygiene and stopping habits that can worsen the patient's oral hygiene, administration fluconazole antifungal drugs, giving chlorhexidine gluconate mouthwash, and antiretroviral (ARV) treatment.*

Keywords: *Antifungal Drugs, Azole Systemic, Oral Candidiasis, HIV*

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INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that attacks CD4 cells and decreases human immunity. Acquired Immune Deficiency Syndrome (AIDS) is a condition induced by HIV infection that results in decreased immunity.[1] HIV/AIDS is a serious global epidemic problem and needs to be addressed because HIV/AIDS is a case of secondary immune deficiency disease that often occurs and is the most common in the world.[2]

The incidence of HIV/AIDS has increased significantly over the last decade, both globally and in Indonesia. In this situation, the patient has severe impairment in their cellular immunity, making them susceptible to various kinds of opportunistic infections.[3] The most common oral lesion associated with HIV/AIDS is oral candidiasis.[4] Opportunistic infections caused by fungi are either the cause of high morbidity and mortality rates, also decreased quality of life of HIV/AIDS patients.[3]

Around 20–25% of the population in Indonesia has candidiasis. Based on data from the Mycology Division of the Outpatient Skin and Sexual Health Unit, Dr. Soetomo Surabaya In 2013–2016, there were 16 patients suffering from oral candidiasis with a percentage of 5.3% of the total candidiasis cases[5]. According to research from an oral observational clinical examination of patients at RSUD Dr. Soetomo Surabaya in 2011–2012, there were 41 cases of oral pseudomembranous candidiasis (47.13%), 10 cases of angular cheilitis (11.49%), and 4 cases of Chronic hyperplastic candidiasis (4.59%).[6]

Fungal opportunistic infections in people living with HIV/AIDS (PLHIV) are a major cause of morbidity, mortality, and reduce individuals quality of life.[7] Oral candidiasis in PLHIV needs to be treated not only because of the discomfort of PLHIV, but also because the foci can act as reservoirs for spread. In patients with severe immunodeficiency it is necessary to prevent colonization and infection, because the oropharyngeal area can be a major source of initial colonization and allows the spread of infection later.[8]

Early detection and treatment of oral lesions have a major impact on the patient's overall health and may decrease disease mortality. It is therefore important for dentists to have the appropriate knowledge and experience to manage the oral manifestations of HIV infection.[9]

METHODS

A web-based search was conducted using the PubMed, ScienceDirect, and Google Scholar database with the keywords (((Management) OR (treatment)) AND ((Oral Candidiasis) OR (candidosis))) AND (((HIV) OR (PLHIV)) OR (People Living with HIV)). Original research and case reports (2017–2023) published in English and Indonesian were included to evaluate various topics. The following subsections provide a summary of the findings.

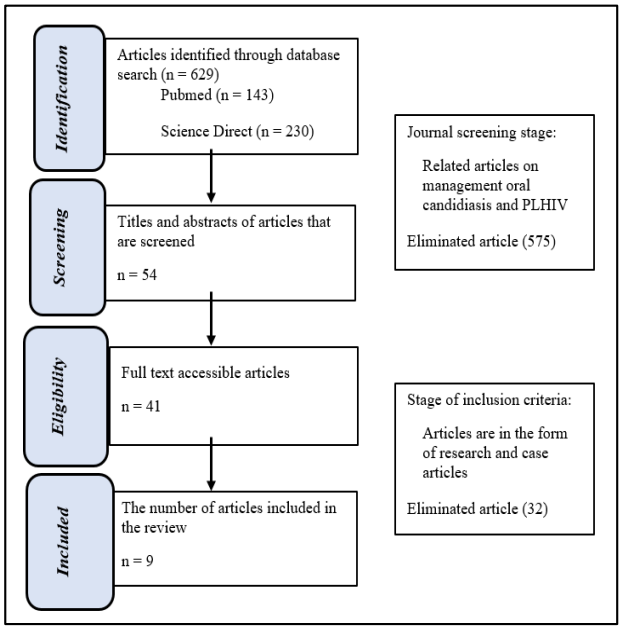

Figure 1. Flowchart for article selection

Figure 1. shows the selection of articles on searches through a database with predefined keywords. The results of the articles obtained

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reached 453 articles. However, there were 399 articles that did not discuss the topic of management oral candidiasis and PLHIV, so they were not included in the search, which were then excluded. The number of articles included in the review amounted to 9 articles.

REVIEWS

HIV and AIDS

HIV affects the immune system and reduces an individual's capacity to fight against many illnesses and some cancers, which healthy immune systems are able to resist. Infected people become immunodeficient as the virus destroys and inhibits the function of immune cells. The CD4 cell count is commonly used to assess immune function.[10] HIV is a cytopathic virus classified in the Retrovirus family, subfamily Lentivirinae, and genus Lentivirus. Two types of HIV can cause AIDS, namely HIV-1 and HIV-2[11]. Clinical and laboratory studies are more often carried out on HIV-1 because HIV-1 is more often found than HIV-2.[12]

AIDS is the most severe stage of HIV, which can take many years to occur if HIV is not managed. AIDS is defined by the emergence of specific malignancies, infections, or additional severe long-term clinical manifestations.[10]

Oral Manifestations of HIV/AIDS

PLHIV will experience immunodeficiency along with the stages of HIV. After the initial infection, a PLHIV may not feel any symptoms. however, symptoms commonly arise after the second stage. Opportunistic infections will start to manifest once individuals have reached the AIDS stage since the failure of the body's defenses.[13] Oral HIV/AIDS manifestations have a detrimental influence on the quality of life of infected people and make treating many systemic diseases difficult.[14]

Oral manifestations such as oral candidiasis (OC), oral Hairy leukoplakia (OHL), linear gingival erythema, non Hodgkin's lymphoma, necrotizing ulcerative periodontitis Kaposi's sarcoma, and necrotizing ulcerative gingivitis, are seriously associated with HIV and have been recognized globally, as well as the earliest and most critical indications of HIV infection.[4]

Oral Candidiasis

Oral candidiasis is an opportunistic infection of the oral cavity caused by Candida overgrowth. Candida yeast is part of the normal flora found in the body, which generally does not cause symptoms.[15] The pathogenesis is not fully understood, but several predisposing factors have been shown to change *Candida albicans* from normal commensal flora (saprophytic stage) to pathogenic organisms (parasitic stage) in oral candidiasis.[16] Oral candidiasis levels may be elevated in PLHIV. Oral candidiasis is the most common opportunistic infection in PLHIV and is often associated with an early manifestation of HIV infection symptoms.[17]

Candida albicans often cause oral candidiasis, but oral candidiasis can also be caused by *Candida glabrata, Candida krusei,* and *Candida tropicalis*[15]. Candida species are normal flora found in the human body, But they can potentially induce a various infections in susceptible patients (elderly patients, patients who require hospitalization, or patients with immunodeficiency).[18] In the situation where candida can cause various infections due to the balance of a person's normal flora being disturbed, then the commensal nature of Candida can turn into a pathogen.[3]

Oral candidiasis can be diagnosed based on the clinical condition of the lesion and the detection of the lesion by a professional who can be confirmed by microscopic identification of candida. Available techniques for the isolation of oral Candida include Direct examination or cytologic smear, microorganism culture, biopsy, histology stained with periodic acid–Schiff (PAS), and PCR studies.[19] The timing of the sampling and the handling of the specimen can affect the diagnosis of candidiasis. Immune

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function testing is recommended, especially for PLHIV or chronic mucocutaneous candidiasis.[19]

Oral candidiasis appears in one of two forms: white or erythematous. White oral candidiasis is characterized by white lesions, such as hyperplastic candidiasis and pseudomembranous candidiasis. Erythematous oral candidiasis is characterized by red lesions, such as linear gingival erythema, angular cheilitis median rhomboid glossitis, and acute/chronic atrophic candidiasis.[20]

Oral candidiasis in PLHIV needs to be treated not only because of the discomfort of the patient, but also because the foci can act as a reservoir for spread to other organs, especially the esophagus. In patients with severe immunodeficiency, it is necessary to prevent colonization and infection, because the oropharynx can be a major source of initial colonization and allow further spread of infection.[17] candidiasis can develop into a fatal systemic infection through the lymph flow that targets the kidneys, lungs, brain, and blood vessel walls, among other essential organs.[21]

Antifungal Drugs: Azole Systemic

Fluconazole

Fluconazole is the most commonly used antifungal agent in the treatment of oral candidiasis in PLHIV.[7,16] Kidneys are the main site for fluconazole to be metabolized and excreted. Fluconazole can be taken on day 1 as an initial dose of 200 mg, and for later doses daily for 7 to 14 days in 50 mg, 100 mg, 150 mg, 200 mg, or 3 mg /day.[20] Recently, a single-dose fluconazole regimen of 750 mg and fluconazole gel in situ are as effective as the standard 14 days regimen in achieving clinical and mycological cures in the treatment of oral candidiasis in PLHIV[16]. Mild side effects of fluconazole drugs such as headaches and gastrointestinal disturbances.[20]

Itraconazole

Useful for targeting fluconazole-resistant candida strains, including *Candida krusei* and *Candida glabrata.* The liver is the site for itraconazole to be metabolized. Patients are instructed to take the drug with acidic foods and drinks to enhance absorption since itraconazole capsules require an acidic pH for absorption. Itraconazole capsules should be taken at a dose of 100 / 200 mg daily for 14 days. Itraconazole at a dose of 200 mg is given three times daily for 3 days if the patient has severe disease. Side effects of itraconazole such as headache, dizziness, liver dysfunction, hypokalemia, and gastrointestinal disturbances.[20]

Posaconazole

The latest triazole that has been approved for the treatment of cases of acute oral and/or esophageal candidiasis and azole refractory in PLHIV is posaconazole. The liver is the site for posaconazole to be metabolized. Relapse was less common in the Posaconazole group.[16] Posaconazole is used for fluconazole-resistant strains of candida. Posaconazole suspension is prescribed on day 1 as an initial dose of 100 mg twice daily, and then for 13 days at a dose of 100 mg daily. For refractory cases, posaconazole may be given as an initial dose of 400 mg twice daily for 3 days, then 400 mg once or twice daily for 25 to 28 days. Side effects of posaconazole such as neutropenia and gastrointestinal disturbances.[20]

Ketoconazole

Ketoconazole is an antifungal agent and is part of the azole imidazole category of drugs. This drug is fungistatic and can inhibit the cytochrome P450 pathway, this drug can also inhibit the 14-demethylation of lanosterol thus preventing the formation of ergosterol in fungal cell membranes.[16] Ketoconazole 200 mg can be used once or twice daily for 2 weeks for oral candidiasis. The most common side effects of oral ketoconazole are gastrointestinal, such as vomiting and nausea. Avoid giving to pregnant women or women planning to become pregnant, the possible effect on male fertility by decreasing nephrotoxicity, hair loss, hepatotoxicity, and

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testosterone production. Combination therapy with proton pump inhibitors, antihistamine agents, or antacids may decrease ketoconazole absorption.[2]

RESULT

Table 1. The results of the search case report and original research. [7,15,22–28]

No	Author	Type of Article	Type of Oral Candidiasis	Management	Antifungal Drug	Treatment Result
1	Riyanto et al., 2020[7]	Case Report	pseudomembranous candidiasis	First visit 1. oral health care 2. mouthwash 0,2% chlorhexidin gluconate 3. CIE Second visit 4. fluconazole 100mg/day intravenously Third visit 5. taken two kinds of ARV 6. fluconazole tablet	fluconazole	Patient stated that there were no more white plaques in his mouth and did not breathless. The pseudomembranous candidiasis had healed and treatment was complete.
2	Hapid et al., 2023[22]	Case Report	pseudomembranous oral candidiasis	First visit 1. education and oral hygiene instruction 2. nystatin oral suspension 4 times 2 mL per day by swishing for a minute before spit Second visit 3. discontinue nystatin → replaced with fluconazole 4. chlorhexidine gluconate mouthwash 0.2% of 10 mL swish and spit three times a day Third visit 5. apply a thin layer of Vaseline album on the upper and lower lips	fluconazole	The white plaque that covered the patient's tongue was totally removed and without any shortness of breath
3	Usman et al., 2017[15]	Case Report	pseudomembranous oral candidiasis	First visit 1. fluconazole 150 mg tablet once a day for 7 days 2. mouthwash 0,1% chlorhexidin gluconate with a dose of 3x a day each time as much as 10 ml 3. CIE Second and Third visit	fluconazole	The patient is feeling better and there are no complaints on the tongue. On the dorsum of the tongue, a white pseudomembrane is visible, it can be scraped off without pain, diffuse borders, irregular edges. For the oral cavity,

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				4. Continuing the previous drug prescription Fouth visit 5. The patient has been taking ARVs (nevirapine, lamivudine, and tenofovir at a dose of 1x1)		the patient is instructed to maintain oral hygiene, namely cleaning the tongue
4	Murtiastutik et al., 2020[23]	Case Report	Acute pseudomembranous candidiasis	First visit 1. fluconazole of 150 mg/ day 2. duviral of 1 tablet/day (300 mg zidovudine and 150 mg lamivudine) 3. multivitamin B complex and iron 1 tablet/day 4. educated to oral hygiene Second visit 5. resistance test: fluconazole, ketoconazole, and nystatin Third visit 6. suspension of nystatin, three times a day as much as 5 ml (500,000) for fourteen days 7. multivitamin B complex and iron 1 tablet/ day	nystatin	The pseudomembrane began to thin considerably on the sixth day of treatment (with nystatin). The pseudomembrane vanished on the tenth day of treatment (with nystatin). There was no sign of problems or recurrence on the fourteenth day.
5	Ding et al., 2022[24]	Case Report	oral candidiasis	First visit 1. ART was continued with lamivudine and dolutegravir Second visit 2. fluconazole injection 3. sodium bicarbonate gargle	fluconazole	Three immediate days of testing showed negative outcomes. The patient was allowed to depart.
6	Ramadurai et al., 2019[25]	Case Report	chronic hyperplastic candidiasis, atrophic candidiasis, and pseudomembranous candidiasis	First visit 1. Topical clotrimazole 1% thrice daily over the affected tissues Second, Third, and Fourth follow up 2. Topical clotrimazole 1% thrice daily over the affected tissues. 3. HAART	clotrimazole	Three months follow up: Relapse of all the lesions
7	Rosa and Sufiawati, 2023[26]	Case Report	angular cheilitis and chronic atrophic candidiasis	First visit 1. Patient was referred to Internal Medicine	-	All lesions were totally healed three weeks later, on the second visit.

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8	Mushi et al., 2021[27]	Original Research	oral candidiasis	Compare Agents 1. Fluconazole 2. Voriconazole 3. Posaconazole 4. Caspofungin 5. Micafungin 6. 5-Fluorocytosine	fluconazole	The majority of the isolates were extremely sensitive to commonly used antifungal agents such as fluconazole.
9	Kirti,2019[28]	Original Article	Oral candidiasis (Acute pseudomembranous candidiasis, Acute atrophic candidiasis, Chronic hyperplastic candidiasis)	Treatment procedures 1. patients already receiving HAART 2. chlorhexidine mouthwash & clotrimazole mouth paint 3. oral fluconazole tablet was added for 14 days in severe or persistent cases	Clotrimazole & fluconazole	There is a definite correlation between falling CD4 count and the prevalence of oral candidiasis. Eminent fall in CD4+ cell count can be anticipated in view of the clinical presentation, and timely HAART can be started, before further worsening takes place.

DISCUSSION

Treatment options for oral candidiasis include topical and systemic methods. The treatment should be continued for seven days. Response to treatment is frequently positive, oral lesions and symptoms may disappear quickly (between 2 and 5 days), but relapse is usual due to the patient's immunodeficiency.[19] Before undergoing treatment, patients who have just found out that they are infected with HIV/AIDS need to go through many laboratory tests, including normal blood tests, to establish their hematologic state, because many studies report that PLHIV patients frequently have hematological disorders.[13]

Management of patients with oral candidiasis is by eliminating predisposing factors, improving oral hygiene, and administering antifungal drugs such as topical agents (nystatin, amphotericin B, and Gentian violet) and/or systemic triazoles (Fluconazole, Itraconazole, Posaconazole, and Ketoconazole).[17]

Management of oral candidiasis in PLHIV are eliminating predisposing factors, such as hyposalivation and smoking should be addressed first. Improving oral hygiene and stopping habits that can worsen the patient's oral hygiene are also needed.[17] The daily maintenance of oral hygiene includes brushing and flossing the teeth, tongue, and, if necessary, dentures.[29]

Administration of antifungal drugs for oral candidiasis. In cases of oral candidiasis associated with immunodeficient individuals, topical agents may not be effective in such cases, hence systemic triazole administration is necessary.[30] Oral candidiasis in HIV patients is less responsive to polyene antifungal drugs (nystatin and amphotericin B), so the most common indication for the administration of antifungal drugs is azole systemic drugs.[17] Fluconazole is a azole systemic antifungal drug that is widely used for the treatment of Candida spp. Infection.[7,15,16] Azole antifungal drugs are fungistatic and work by inhibiting fungal

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ergosterol synthesis resulting in defects in the fungal membrane.[15]

The oral application of 0.2% chlorhexidine gluconate mouthwash to PLHIV is also beneficial as an antiseptic with broad-spectrum antibacterial characteristics and an antifungal effect to suppress Candida colonies, besides that the alcohol content in this mouthwash also functions as an astringent.[15,22] These topical bactericidal characteristics also help to prevent subsequent infection, which is important when healing an oral lesion.[22]

The management of oral candidiasis as well as all secondary/opportunistic infections in patients with HIV/AIDS must involve other fields in the management of HIV-AIDS and antiretroviral therapy (ARV).[15] ARV is part of HIV/AIDS treatment to reduce the risk of transmission, inhibit worsening conditions due to opportunistic infections, reduction of oral lesions, and improvement of PLHIV quality of life.[7,14] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) seem to be the most efficient in reducing candidiasis by consistently following current therapy guidelines that NNRTI-based therapy is recommended as the first-line treatment for ARVs.[17] If HIV can be suppressed properly, opportunistic infections can also be treated adequately.[15]

CONCLUSION

Management of oral candidiasis in PLHIV sufferers are eliminating predisposing factors, improving oral hygiene and stopping habits that can worsen the patient's oral hygiene, administration fluconazole antifungal drugs, giving chlorhexidine gluconate mouthwash, and antiretroviral (ARV) treatment.

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