The antifungal susceptibility of Candida albicans isolated from HIV/AIDS patients

by Basri A. Gani

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The antifungal susceptibility of *Candida albicans* isolated from HIV/AIDS patients

Sri Rezeki[1], Siti Aliyah Pradono[2], Gus Permana Subita[2], Yeva Rosana[3], Sunnati[4] and Basri A. Gani[5]
[1] Department of Oral Medicine, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia
[2] Department of Oral Medicine, Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia
[3] Department of Microbiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[4] Department of Periodontics, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia
[5] Department of Oral Biology, Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia

ABSTRACT

Background: *Candida albicans was found to be dominant in patients with human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS). The antifungals fluconazole, ketoconazole, and nystatin were used as oral candidiasis therapy for HIV/AIDS, each of which has differing susceptibility in oral candidiasis therapy.* **Purpose:** *The present study aimed to evaluate the susceptibility and antifungal resistance to oral C. albicans in HIV/AIDS patients.* **Methods:** *The subjects followed the universal precaution principles. Oral Candida species were isolated from the saliva of 98 HIV/AIDS subjects. Identification of Candida species was carried out by the mycobiotic agar of API 20 C Aux system. Susceptibility and resistance antifungal tests on the Candida species were performed using a Fungus ATB Kit.* **Results:** *Candida albicans was the most dominant species found from 98 subjects (95%). The rest were other Candida species. There are 41 subjects (42%) with a history of oral candidiasis, and 57 subjects (58%) without. The history of those who used antifungals were: nystatin = 60 subjects (61%), fluconazole = 39 subjects (40%), and ketoconazole = two subjects (2%). These antifungals have a susceptibility above 80% against C. albicans, except the nystatin group (79%) (p>0.05; 0.628), but fluconazole has a strong correlation (r=0.820) to susceptibility, susceptibility-dependent dose, and resistance.* **Conclusion:** *Candida albicans was dominant in the saliva of HIV/AIDS patients. This fungus was effectively treated by fluconazole, ketoconazole and nystatin. These antifungals had a high susceptibility at ≤ 8 µg/mL to C. albicans.*

Keywords: *antifungal; Candida albicans; HIV/AIDS; susceptibility and resistance*

Correspondence: Sri Rezeki, Department of Oral Medicine, Faculty of Dentistry, Universitas Syiah Kuala. Jl. Teuku Nyak Arief Darussalam, Banda Aceh, 23111 Indonesia Email: iy_99fkg@unsyiah.ac.id

INTRODUCTION

In Indonesia (data 2005–2019), the number of people living with human immunodeficiency virus (HIV) was 338,363. Meanwhile, an acquired immunodeficiency syndrome (AIDS) was reported in 115,601 cases.[1] One of the conditions experienced by people with HIV/AIDS is mucosal candidiasis in the oral, esophageal, or vaginal regions. The circumstances of oral candidiasis in HIV infections vary from 7% to 93%, depending on the patient mix, diagnostic criteria, and research methods.[2] It is considered an important marker of immune decline as an early manifestation of HIV infection. In addition, there is a decrease in CD4 lymphocyte cells <200.[3]

Oropharyngeal and esophageal candidiasis are common manifestation in HIV patients. The disease is caused by *C. albicans* and other oral *Candida* species. Antiretroviral therapy (ART) can reduce the prevalence of oropharyngeal and esophageal candidiasis in refractory disease.[4] The resistance of fluconazole or azole is influenced by repeated long-term exposure. In this permutation, the majority of cases relate to the acquisition of resistance to *C. albicans*.[5] Both local and systemic predisposing factors lead to *Candida's* commensal changes, developing into oral candidiasis. These infections of esophageal candidiasis, as well as morbidity, and even mortality, were reported as secondary complications.[6]

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The antifungal drugs fluconazole, ketoconazole, and nystatin effectively treat HIV oropharyngeal and esophageal candidiasis. Therefore, their widespread use has the potential to increase *C. albicans* resistance. These antifungals, when observed in different groups of HIV patients, were resistant to *C. albicans*. One-third of *C. albicans* HIV isolates were resistant to several antifungals.[7] Mohamadi et al.[8] revealed that *C. albicans* remains the most common species that rapidly developed into fluconazole, ketoconazole, and nystatin resistant. The resistance of these antifungals has an impact on dehydration, malnutrition, and increased HIV infection. It is often reported in cases of esophageal and oropharyngeal candidiasis. Monroy-Pérez et al.[9] reported that fluconazole, ketoconazole, and nystatin have varying susceptibility to *C. albicans*. However, these three antifungals have the same principle action for inhibiting the development of *C. albicans* by damaging the cell walls and inhibiting synthesis protein.[10]

Susceptibility of fluconazole, ketoconazole, and nystatin to *C. albicans* in HIV/AIDS patients can be used as a reference for determining relevant and appropriate doses for HIV/AIDS oral candidiasis, which can reduce the prevalence of resistance. This study evaluated the susceptibility of antifungals to oral *C. albicans* isolates from HIV/AIDS patients.

MATERIALS AND METHODS

The research was approved ethical clearance by the Faculty of Dentistry, Universitas Syiah Kuala, Banda Aceh, Indonesia, No.187/KE/FKG/2020. Saliva was collected from 98 people with HIV/AIDS at the AIDS center of Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia. The isolation and characterization of *Candida* species from the samples were carried out at the Microbiology Laboratory, Faculty of Medicine, University of Indonesia. Criteria for inclusion were patients with HIV/AIDS who had not used antifungal drugs for the previous week, were communicative and were cooperative. The patients included male and female patients. Meanwhile, the exclusion criteria included people living with HIV/AIDS who have refused to be research subjects, who have used antifungal drugs for the past week, were non-communicative and were non-cooperative.

The subjects were asked to sign an informed consent, and questionnaire sheets were filled in with the subjects' demographic data obtained from interviews. Interviews were conducted before sampling, and the medical records of subjects were obtained from the RSCM's AIDS clinic, Jakarta, Indonesia. The researcher applied the sampling procedure to people with HIV/AIDS using personal protective equipment and precautions, such as gloves and masks, hand hygiene and sterility, disposing of medical waste contaminated with the saliva of research subjects, and applying laboratory work safety procedures.

The following oral rinse technique was used to collect the saliva: the subjects were instructed to rinse their mouths in 10 mL of phosphate buffer saline (PBS) (Sigma-Aldrich, Darmstadt, Germany) for 15 sec. The saliva was then expectorated into sterile containers and stored at -25°C.[11] Next, the oral saliva specimen was cultured on Mycobiotic® agar at 35°C for 48 h for identified a *Candida* species.[12] The suspensions of *C. albicans* cultured on the Mycobiotic® agar medium using 0.85% NaCl and adjusted to McFarland 2 (6×10^8 CFU/mL).[13] Then, 100 μL of *Candida* suspension in 0.85% NaCl was mixed to API 20 liquid medium. Then homogenization was carried out. Subsequently, 200 μl was taken and placed into a test vial. A fermentation assay was conducted on several carbohydrates in parallel. After 48 h of incubating at 30°C, a well-observed growth was taken randomly. A positive reaction was characterised by turbidity in each well observed after incubation at 30°C for 48 h.[9]

The Fungus ATB® commercial kit was used to evaluate the susceptibility test, with the maximal assay in 128 μg/mL. A 20 μL suspension of *C. albicans* in 0.85% NaCl was added to the Fungus ATB® media. After homogenisation, each well was inoculated with 135 μl of homogeneous inoculums and incubated at 37°C for 24 h. The growth of *C. albicans* on the strip was read visually, according to the instructions kit, with baseline turbidity as the indicator of the growth of *C. albicans* in fluconazole, ketoconazole and nystatin in concentrations of <1, 2, 4, 64, and >128 μg/mL, which was an indicator of susceptibility (≤8 μg/ml), susceptibility-dose dependent (S-DD) (16–64 μg/mL) and resistance (>128 μg/mL). The growth of *C. albicans* characterised by turbidity relates to the ATB® kit: 0 (no growth), 1 (weak growth), 2 (reduction in growth), 3 (growth reduced slightly), and 4 (no reduction in growth).[14]

The Kruskal–Wallis test analysed the data of susceptibility, S-DD, and fluconazole-resistant against *C. albicans*. The significance limit of $p < 0.05$ and the correlation coefficient (r = 1) was strongly correlated.

RESULTS

Data from study subjects included in this study are shown in Table 1, representing age group, sex, history of HIV/AIDS transmission, history of antifungal agents and oral candidiasis. These indicators could be the reference for this study, which also correlated with *Candida* species susceptibility.

C. albicans were found predominantly in HIV/AIDS subjects without a history of candidiasis (Table 2). Its antifungals were reported susceptible to *C. albicans* and other *Candida* species. The data from Table 2 refer to an in vitro assay related to antifungal susceptibility to *C. albicans*, which were selected to represent the dominant population of *Candida* species from HIV/AIDS subjects.

Table 3 shows that the three antifungal drugs have a high susceptibility above 80%, but not significantly

(*p*> 0.05; 0.628), which means that all drugs have a potential antifungal effect on *C. albicans*. Three antifungal drug concentrations showed significant differences in fluconazole's susceptibility against *C. albicans* (*p*<0.05; 0.024). It means that the concentration of the three drugs has a strong influence on fungicidal or fungistatic properties. The subject status was related to susceptibility, S-DD, and resistance of the three antifungal drugs against *C. albicans* (*p*> 0.05; 0.175). Based on Spearman's rho correlation, drug status (susceptibility, S-DD, and resistance) has a strong relationship with the concentration of the three groups of antifungal drugs (r = 0.820). The standard susceptibility ≤ 8 µg/mL, S-DD 16-64 µg/mL, and resistant ≥ 128 µg/mL is based on the ATB® Fungus kit.

Table 1. Distribution and frequency characteristics of HIV/AIDS subjects

Characteristics	N	%
Gender		
Female	10	10
Male	88	90
Age (Year)		
20–29	47	48
30–39	40	41
40–49	10	10
50–59	1	1
Risk factors for HIV transmission		
Intravenous drug users (IVDU)	61	69
Homosexual intercourse	1	1
Heterosexual intercourse	22	22
IVDU and homosexual intercourse	1	1
IVDU and heterosexual intercourse	5	5
IVDU and tattoo/piercing	2	2
History of antifungal agents		
Fluconazole		
No	59	60
Yes	39	40
Nystatin		
No	38	39
Yes	60	61
Ketoconazole		
No	96	98
Yes	2	2
Oral candidiasis		
No	57	58
Yes	41	42

Table 2. Susceptibility and resistance antifungal on the *Candida* species and oral candidiasis history in HIV/AIDS patients

Candida species	N	%	Fluconazole		Ketoconazole		Nystatin		Oral candidiasis history	
			Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant	Yes	No
C. albicans	93	95	80	13	81	12	80	13	39	50
C. dubliniensis	2	2	2	0	1	1	2	0	1	2
C. guillermondii	1	1	1	0	1	0	1	0	1	2
C. famata	1	1	1	0	1	0	1	0	0	2
C. tropicalis	1	1	1	0	1	0	1	0	0	1

Table 3. Antifungal Susceptibility on *C. albicans* in HIV/AIDS patients

Antifungals (µg/mL)	Fluconazole				Ketoconazole				Nystatin				p-value
	N	%	Status	Turbidity	N	%	Status	Turbidity	N	%	Status	Turbidity	
1	74	80	Susceptible	0	75	81	Susceptible	0	73	79	Susceptible	0	
2	3	3	Susceptible	1	1	1	Susceptible	1	1	1	Susceptible	1	
4	3	3	Susceptible	1	1	1	Susceptible	1	1	1	Susceptible	1	*p>0.05 (0.628)
64	1	1	S-DD	2	1	1	S-DD	2	1	1	S-DD	2	
128	12	13	Resistant	3	15	16	Resistant	3	17	18	Resistant	3	

* Kruskal–Wallis test and Spearman's rho correlation; S-DD (Susceptibility-Dose Dependent); Susceptible ≤ 8 µg/mL, S-DD 16-64 µg/mL, Resistant ≥ 128 µg/mL, and 250 µg/mL not recommended: Turbidity indicator, 0 (no growth), 1 (weak growth), 2 (reduction in growth), 3 (growth reduced slightly), 4 (No reduction in growth).

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DISCUSSION

This research reported that subjects without candidiasis are more dominant than with oral candidiasis. These subjects have susceptibility and resistance to fluconazole, ketoconazole, and nystatin in low. Generally, these antifungals have a vulnerability to the oral *Candida* species, mainly *C. albicans*. The presence of *C. albicans* in the oral candidiasis of HIV patients is confirmed by Patil et al.[15] who found 95.2% of *C. albicans* cases leading to oropharyngeal candidiasis in HIV/AIDS.

This study indicates that the male population is higher than the female population with an average age of 20–29 years and ages 30–39 (Table 1). The most dominant transmission is through intravenous and heterosexual injections. Glick et al.[16] reports that men who have sex with men (MSM) have higher rates of HIV and sexually transmitted infections (STIs) than women and other heterosexual men. This increased risk persists across all age groups and reflects various biological and behavioural factors, but there are some direct comparisons of sexual behaviour patterns between populations.[16] In this research, we found the different effects of three antifungal types to treat oral candidiasis on HIV/AIDS subjects (Table 3). They have a susceptibility to preventing the oral candidiasis treatment of subjects with HIV/AIDS. The oral candidiasis prophylaxis used fluconazole (200 mg/day) with a CD4 count <100 cells/µL also in patients with CD4 100–200 cells/µL. Additionally, long-term oral candidiasis prophylaxis with fluconazole is likely to lead to resistance.[17]

Based on the characteristics analyses of HIV/AIDS, 42% of the subjects had a history of candidiasis, 58% had no history of candidiasis. The *Candida* species cultures from the 98 subjects showed 95% *C. albicans,* while the rest were other *Candida* species. It is, therefore, explained that in HIV, oral candidiasis is related to the history of antifungal use (Table 1). The subjects had a history of antifungal use with different percentages of antifungals. Garcia-Cuesta et al.[18] explain that the oral antifungal of candidiasis of a patient with HIV status is often given several antifungal types to prevent oral *Candida* species symptoms and infection. The use of an antifungal mixture to maintain the fungal population's balance in the oral cavity can also help increase the mucosal oral defence system to prevent *Candida* species' adhesion.[19]

The development of oral candidiasis in HIV/AIDS patients is highly dependent on the history of antifungal treatment. It is reasonable to suspect that some subjects in this study have had proper oral candidiasis treatment. Nevertheless, the prevalence of *C. albicans* in HIV is always associated with resistance to fluconazole.[20] In general, the injection of narcotic drugs and heterosexual relationships tend to be experienced by other people living with HIV. These trends indicate that the susceptibility population is strongly related to the level of resistance to fluconazole or other antifungal drugs such as nystatin and ketoconazole. Maheshwari et al.[21] reported that in general HIV-positive patients with CD4+ cell counts between 200 and 400/µL had more colonisation of *C. albicans* and *C. dubliniensis.*

Table 3 shows that the lowest concentration of fluconazole has susceptibility to oral *C. albicans*. In contrast, the highest concentration of fluconazole is resistant to the antifungal of *C. albicans* essence of HIV/AIDS. Thus, fluconazole toxicity to *Candida* species at the lowest concentration is becoming higher. This antifungal has the ability to prevent *Candida* infections by inhibiting DNA synthesis and ergosterol biosynthesis in fungal cell membranes, changing cell surface hydrophobicity, and influencing the synthesis of triglycerides and phospholipids.[22]

Based on this study, resistance occurs due to intense administration with varying doses. This finding concurs with previous research showing that resistance occurred, on average, in minimal inhibition concentration (MIC) of fluconazole concentrations of up to three times due to long-term treatment.[23] Patil et al.[24] reported that the subject's decreased resistance could support oral candidiasis development. As many as 95% of *C. albicans* cases were reported as a trigger factor for oral candidiasis. The oral *Candida* species' resistance was reported to be less than sensitive, but it can threaten oral candidiasis if HIV/AIDS infection persists.[24] This study found that susceptibility frequency is higher than that of resistance, so these antifungals are recommended to prevent oral candidiasis in HIV/AIDS.

The antifungal drugs used in this research have different susceptibility and resistance properties. However, they have the same tendency to suppress the growth of *C. albicans*, as shown in Tables 2 and 3. It is indicated that fluconazole, ketoconazole, and nystatin have a high susceptibility, with an average above 80%. These antifungals have a substantial effect on *C. albicans*, both fungicidal and fungistatic. Other findings from this study are that the three drugs' susceptibility and resistance. Whaley et al.[25] reported that in the treatment of HIV, the administration of azole groups could cause *C. albicans* resistance or trigger the development of non-*C. albicans* species, such as *C. glabrata* and *C. krusei,* which intrinsically cause resistance. The opposition to one of the azole antifungal drugs is often associated with other azole resistance.[25] Period exposure is a risk factor in fluconazole resistance. Refractory oropharyngeal candidiasis of treatment by fluconazole is most frequently used in HIV.[8]

The tracing of the possible history of antifungal drug administration was obtained through periods of HIV infection and diagnosed HIV patients. The higher possibility of opportunistic infections impacts oral candidiasis with treatment by antifungals, which then affects susceptibility. However, these allegations still need further analysis regarding the relationship between the length of HIV infection with a history of antifungal use and susceptibility based on more accurate data. In this study,

the susceptibility test was not carried out on other *Candida* species because the population was too small. There was also no antifungal combination to test the susceptibility to *C. albicans*. It can be concluded that *Candida albicans* was dominant in the saliva of HIV/AIDS patients. This fungus was effectively treated by fluconazole, ketoconazole, and nystatin. These antifungals had high susceptibility at ≤ 8 μg/mL to *C. albicans*.

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