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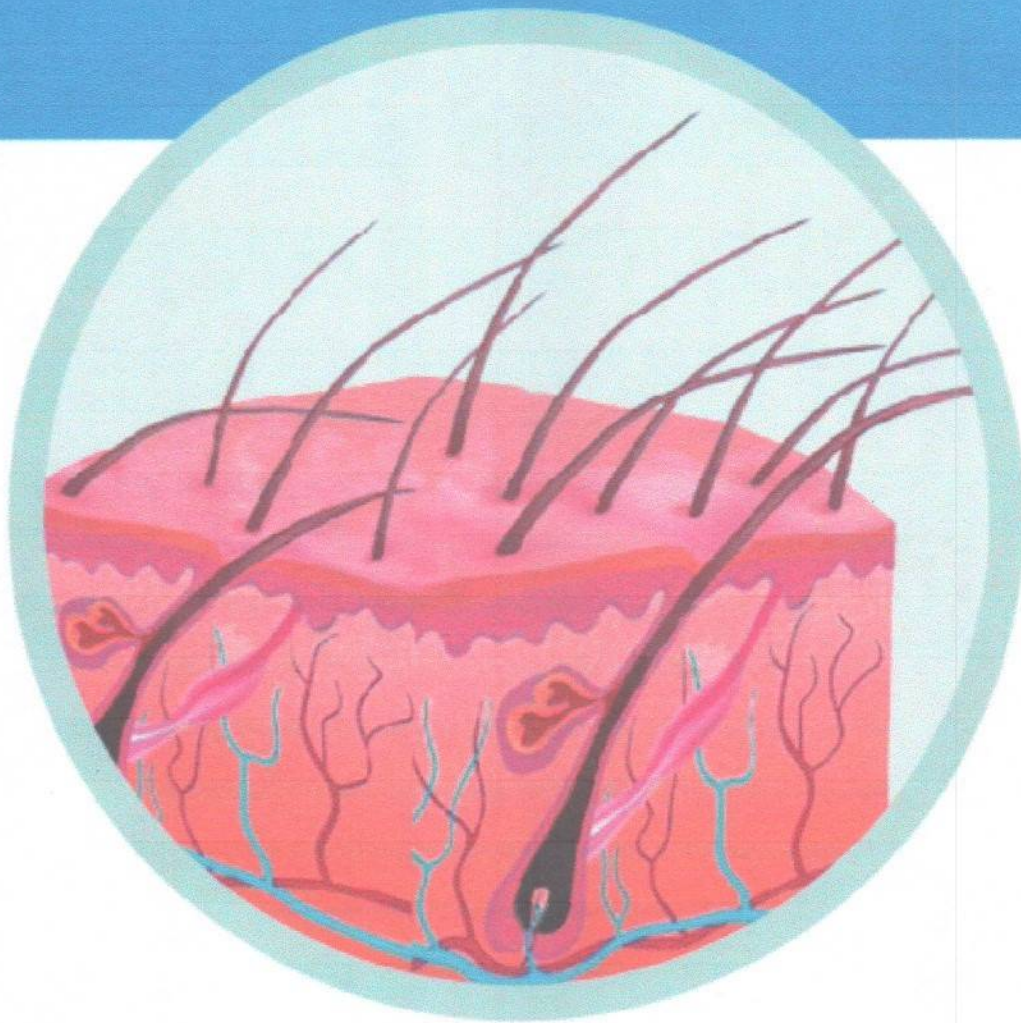
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Berkala Ilmu Kesehatan Kulit dan Kelamin



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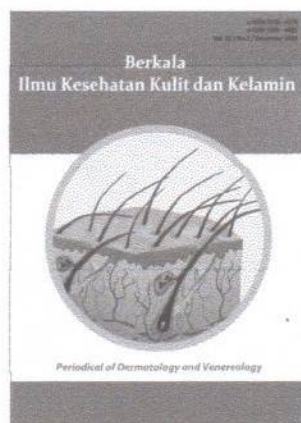
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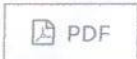
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Sensibility Test of *Candida species* against Nystatin, Ketoconazole, and Fluconazole on Oral Candidiasis with HIV/AIDS using Disc Diffusion Method

Cut Shelma Maharani, Rahmadewi, Afif Nurul Hidayati, Dwi Murtiastutik

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ABSTRACT

Background: Oral candidiasis is one of the most common infections in Human Immunodeficiency Virus/Acquired Immuno Deficiency Syndrome (HIV/AIDS) patients. Some studies have reported an increased number of resistances of *Candida sp.* against several antifungal therapies. **Purpose:** To evaluate the pattern of *Candida sp.* causing oral candidiasis and the pattern of resistance among the *Candida sp.* against nystatin, ketoconazole, and fluconazole in oral candidiasis patients with HIV/AIDS infection. **Methods:** This was a descriptive observational study conducted at the Infectious Disease Intermediate Care Unit (UPIPI) Dr. Soetomo General Academic Teaching Hospital. *Candida sp.* was identified using conventional methods, while the sensibility test was done by using disc diffusion methods. **Result:** There were 26 subjects with 50 isolates of *Candida sp.* that had been cultured successfully. Non-*albicans Candida sp.* was the most common species, which was observed in 28 subjects (56%). The results of the sensibility test on *Candida sp.* against nystatin, ketoconazole, and fluconazole were 0 (0%), 3(6%), dan 23(46%) respectively. **Conclusion:** The increased resistance among *Candida sp.* against antifungal drugs, especially fluconazole, could raise awareness in drug prescription, especially for HIV/AIDS patients.

Keywords: sensibility test, *Candida sp.*, antifungals, oral candidiasis.

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BACKGROUND

It has been four decades since Acquired Immune Deficiency Syndrome (AIDS) was first discovered, and Human Immunodeficiency Virus (HIV) transmission still has a major impact on developing countries and become a global crisis.¹ Directorate General of Disease Prevention and Control of the Indonesian Ministry of Health (Ditjen PP & PL Kementerian Kesehatan) in 2016 reported 7,491 new cases of HIV/AIDS and a total of 86,780 cases from 1987 to 2016.²

People infected with HIV have a weakened immune system; therefore, they become vulnerable to opportunistic infections. Fungal opportunistic infections in HIV patients are one of the causes of morbidity and decreased quality of life. Oral Candidiasis (OC) has been reported as the most common opportunistic fungal infection in HIV patients.³ Genus *Candida* are the most commonly found fungi in the oral cavity. The most commonly reported etiology of OC is *Candida albicans*. There has been an etiological change of non-*albicans Candida*.^{3,4} It has been reported that almost all people infected with HIV have *Candida* colonization up to 90 – 95% and the fungi developed into clinical lesions, especially in the oral cavity.⁴ A retrospective study in 2013 at Dr. Soetomo General Academic Teaching Hospital

Surabaya showed that of 301 HIV/AIDS patients at Infectious Disease Intermediate Care Unit (UPIPI) with manifestations on the skin, there were 244 (81.1%) patients diagnosed with OC.⁵

OC patients with HIV often have an extended duration of illness, recurring illness, and more severe clinical symptoms.⁶ Further examination to establish OC diagnosis is a direct mycological examination with potassium hydroxide (KOH) followed by planting specimens in CHROMagar™ media to grow the *Candida* colonies.⁷ Identification of *Candida* species now can be made through several methods, namely conventional, automatic, and molecular. Conventional *Candida sp.* identification includes CHROMagar™ *Candida*, cornmeal agar-Tween 80, and carbohydrate tests. Accurate results can be achieved by combining the three conventional methods to complement the results of each method.⁸ Research on comparison of the three *Candida* identification methods by Kaur in 2016 in India showed that a combination of the three conventional methods had higher results (99.4%) compared to Vitek 2 (90.1%).⁹

The management of OC shall consider many factors. However, in some cases, OC is treated empirically with antifungal.⁶ Referring to the clinical practice guidelines of the Dermatology and

Venereology Department Dr. Soetomo General Academic Teaching Hospital Surabaya in 2014, the drugs that are often prescribed for OC therapy are nystatin, ketoconazole, and fluconazole.¹⁰

Since its discovery in 1990, the incidence of resistance to antifungal agents in patients with HIV/AIDS has been reported to increase, especially in azole antifungal agents. Studies from various places show the resistance of *Candida sp.* to fluconazole ranges between 6% – 36%, while the azole group is increasingly being used due to numerous medical indications. Increased use of antifungal agents to treat fungal infections in immunocompromised patients is said to be one of the factors causing the emergence of drug resistance to *Candida* isolates.⁴ Another factor is the improper doses in terms of duration, which will trigger secondary resistance. The etiology of OC that was caused by non-albicans *Candida* group is also shown to correlate with azole antifungal resistance and recurrent and refractory candidiasis infections.¹¹ Some strains of non-albicans *Candida* are intrinsically resistant to azole and polyene groups without prior drug exposure, which is the cause of primary resistance.⁴

Research on antifungal agent resistance rates in OC patients with HIV/AIDS in Indonesia conducted in Malang by Reza in 2014, using Vitek 2 as a resistance test method, found that 8% of *Candida* isolates were resistant to fluconazole and caused by *Candida krusei*.¹² A 2015 Jakarta study, comparing the Vitek 2 method of resistance testing with the diffusion disc method, showed that 9 of 137 *Candida* isolates were caused by *Candida krusei*, and this species was 100% resistant to fluconazole.¹³ A study by Moges on the resistance rates of several antifungals with diffusion disc testing in HIV/AIDS patients with OC in Ethiopia 2013 – 2014 showed that of all *Candida* isolates found 12.3% resistant to fluconazole, 8.4% to ketoconazole, and 1.3% to nystatin.⁴

The examination of *Candida sp.* resistance to antifungal drugs can be done with several methods. The conventional method consisted of a dilution method and an agar diffusion disc method. Both examinations are more affordable compared to methods with commercial tools such as Vitek 2, Etest, and SensitreYeastOne.¹⁴

In vitro examinations of species identification culture and resistance patterns in *Candida sp.* are not routinely done in Indonesia, so there are only a few recent data on this, especially in Surabaya.¹⁵ This study aimed to evaluate the patterns of *Candida sp.* that cause OC in HIV/AIDS patients and *Candida sp.* resistance patterns against antifungal drugs commonly used in the treatment of OC.

METHODS

This was a descriptive observational study to evaluate the patterns of *Candida sp.* that cause OC and *Candida sp.* resistance patterns against antifungal nystatin, ketoconazole, and fluconazole at the Infectious Disease Intermediate Care Unit (UPIPI) Dr. Soetomo General Academic Teaching Hospital Surabaya. The study was conducted from May 2018 to September 2018. The sample size, which was calculated based on a categorical descriptive formula, was 26 patients. The samples of this study were patients with a confirmed clinical diagnosis of OC from history taking, clinical manifestations, and direct microscopic examination with KOH. The inclusion criteria was that the patient was willing to participate in the study, while the exclusion criteria was that the patient was taking antifungal drugs in the last 2 weeks. Subjects who had fulfilled those criteria would have their lesions in the oral cavity scraped, and then the specimen would be implanted in CHROMagar™ media until the colonies grew. Subsequent tests were Cornmeal agar-Tween 80 and carbohydrate tests for species identification. The identified *Candida sp.* were then tested for resistance by the disc diffusion method on Mueller Hinton agar with 2% glucose and methylene blue. *Candida sp.* isolates were implanted in the agar, then paper disc containing the potential of nystatin, ketoconazole, and fluconazole was placed on it. Observation in 24 – 48 hours was carried out until a barrier zone appears around the paper disc. The interpretation of inhibition zone diameter readings was according to Rosco Diagnostica Company.⁴

RESULT

As many as 26 patients in Infectious Disease Intermediate Care Unit (UPIPI) Dr. Soetomo General Academic Teaching Hospital that fulfill inclusion criteria were involved in this study. Sampling was done by consecutive sampling method.

Demographic distribution in this study revealed that 20 subjects (76.9%) were males, and 6 (23.1%) were females. The age group varied between 17 – 25 years old to 56 – 65 years old. The age classification based on the World Health Organization (WHO) criteria. The largest age group was 36 – 45 years old with 7 subjects (26.9%), and the smallest age group was 18 – 25 years old with 3 subjects (11.5%). None of the subjects was categorized as an elderly (> 66 years). The most common formal education level was the high school with 11 subjects (42.3%), and the highest (34.6%) occupation group of the research subjects was unemployed (Table 1). The twenty-six patients showed various chief complaints of OC clinical features, and one patient might have more than one

chief complaint. The most common complaint was white patches in the oral cavity, as observed in 25 (96.2%) subjects. Furthermore, 5 (19.2%) patients also complained of odynophagia or a burning sensation in the throat. All OC patients in this study, 100% had lesion that located on the tongue, and all subjects also

had mixed lesion sites (mucosa/palate/corners of the lips). There were 11 (42.3%) patients who had a history of OC before, while 15 (57.7%) patients had OC for the first time. There were 5 patients (19.2%) prescribed with systemic drugs, and 10 patients (38.5%) prescribed with topical antifungal drugs (Table 2).

Table 1. Demographic data of research subjects

No	Basic Data		N	%
	Categories	Groups		
1	Sex	Male	20	76.9%
		Female	6	23.1%
2	Age	Late Teen (18 – 25 years old)	3	11.5%
		Early Adulthood (26 – 35 years old)	6	23.1%
		Late Adulthood (36 – 45 years old)	7	26.9%
		Early Middle Age (46 – 55 years old)	6	23.1%
		Late Middle Age (56 – 65 years old)	4	15.4%
		Elderly (> 66 years old)	0	0
3	Formal Education Level	No History of Formal Education	4	15.4%
		Primary/Middle School Graduate	8	30.8%
		High School Graduate	11	42.3%
		Bachelor Degree	3	11.5%
4	Occupation	Unemployed	9	34.6%
		Housewife	5	19.2%
		Civil Worker	2	11.5%
		Private Employee	5	19.2%
		Driver	2	7.7%
		Student	1	3.8%
		Sex Worker: - Direct (Transwoman) - Indirect (Hairdresser)	1 1	3.8% 3.8%

Table 2. Distribution of research subjects based on clinical features of oral candidiasis

No	Clinical Features		N	%
	Categories	Groups		
1	Chief complaints*	White patches on the oral cavity	25	96.2
		Red patches on the oral cavity	1	3.8
		Spots and sores on the corners of the lips	1	3.8
		Spotting or sores accompanied by odynophagia or a burning sensation in the throat	5	19.2
2	Locations*	Mucosa	1	3.8
		Tounge	26	100
		Corners of the Lips	1	3.8
3	Frequency	Recurring	10	38.5
		Once	16	61.5
4	History of treatment*	Systemic Antifungal Yes	5	19.2
		No	21	80.8
		Topical Antifungal Yes	10	38.5
		No	16	61.5

* Patients may have >1 chief complaints, locations, and history of treatments

Sixteen people (61.5%) with HIV/AIDS were infected from heterosexual intercourse and six people (26.9%) from homosexual intercourse. Subject might get infected from more than one HIV transmissions. Most of the subjects were in clinical stage III and IV HIV, which were 14 people (53.8%) and 11 people (42.3%), respectively. There were 21 study subjects (80.8%) with a history of having antiretroviral (ARV) therapy (Table 3).

The most common diagnosis of OC was pseudomembrane candidiasis found in 21 patients (80.8%), followed by plaque hyperplastic type, atrophic type, and cheilitis types in 7 (26.9%), 1 (3.8%), and 1 (3.8%) patient respectively. The systemic treatment plan of OC cases using fluconazole was found in 7 cases (26.9%), while topical oral nystatin was found in 19 cases (73.1%) (Table 4).

The identification of *Candida sp.* revealed that 28 isolates (56%) were non-albicans *Candida sp.*, which was more significant than the 22 *Candida albicans* isolates (44%). The number of non-albicans *Candida sp.* were *Candida tropicalis*, *Candida glabrata*, and *Candida krusei*, as many as 9 (18%), 8 (16%), and 7 (14%) isolates respectively. This study also found rare

isolates of *Candida*, namely *Candida parapsilosis*, *Candida dubliniensis*, and *Candida guilhermondii* (Table 5).

Fifty species of isolates that were tested for resistance, reveal most *Candida sp.* species were still sensitive to ketoconazole and nystatin, respectively 42 (84%) isolates and 49 (98%) isolates. On the other hand, only 27 isolates (54%) were sensitive to fluconazole. *Candida albicans* species were still sensitive to the three antifungal drugs ketoconazole, nystatin, and fluconazole, respectively 22 (100%), 21 (95.5%), and 16 (72.7%). Another case with non-albicans *Candida sp.*, although most were sensitive to the ketoconazole and nystatin, which were 20 (71.4%) and 28 (100%) isolates, only 11 isolates (39.3%) were sensitive to fluconazole. The overall pattern of antifungal resistance in *Candida sp.* isolates was varying. The number of isolates resistant to ketoconazole, nystatin, and fluconazole were 3 (10.7%), 0 (0%), and 23 (46%). The number of *Candida* isolates resistant to fluconazole was mostly caused by non-albicans *Candida* species was 17 (60.7%) (Table 6).

Table 3. Characteristics of research subjects based on HIV status

No	Categories	HIV Status	
		Groups	N %
1	HIV possibility mode of transmission*	Homosexual	7 26.9
		Heterosexual	16 61.5
		Bisexual	1 3.8
		Injected Narcotics/Tatto	5 19.2
		Transfusion	1 3.8
2	Duration of HIV	< 1 year	12 46.2
		1 – 3 years	9 34.6
		> 3 years	5 19.2
3	HIV clinical stages	Stage I	0 0
		Stage II	1 3.8
		Stage III	14 53.8
		Stage IV	11 42.3
4	Absolute CD4 count	> 500 cells/ μ L	0 0
		200 – 500 cells/ μ L	10 38.5
		< 200 cells/ μ L	16 61.5
5	History of antiretroviral therapy	Yes	21 80.8
		No	5 19.2

* Patient can be infected by >1 HIV mode of transmission
HIV = human immunodeficiency virus

Table 4. Distribution of subjects based on diagnosis and therapy

No	Diagnosis and Therapy		N	%
	Categories	Groups		
1	Diagnosis*	Pseudomembrane candidiasis	21	80.8
		Plaque hyperplastic candidiasis	7	26.9
		Atrophic candidiasis	1	3.8
		Cheilitis candidiasis	1	3.8
2	Treatment Planning	Systemic:		
		Fluconazole	7	26.9
		Ketoconazole	0	0
		Topical:		
		Nystatin	19	73.1

*Patient may have >1 diagnosis

Table 5. Distribution based on the identification of *Candida species* isolates that cause Oral Candidiasis with HIV/AIDS

No	Colony Colors of CHROMagar™	Urea hydrolysis	Fermentation				Temperature 42-45°C	Microscopic Features	Identification Results	N	%		
			Glucose	Lactose	Sucrose	Maltose						Galactose	Trehalose
1	Green	(-)	(+)	(-)	(-)	(+)	(-)	(-)	Grow	Terminal chlamydo-spores, blastoconidia forming pseudohyphae	<i>Candida albicans</i>	2	44
2	Turquoise Blue	(-)	(+)	(-)	(-)	(+)	(-)	(-)	Not Growing	Abundant chlamydo-spores appear singular, in pairs, or groups. Pseudohyphae and hyphae in the blastoconidia cluster	<i>Candida dubliniensis</i>	1	2

3	White	(-)	(+)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	-	<i>Candida parapsilosis</i>	2	4
<p>Blastoconidia forms a small unit along the relatively short and curved pseudohyphae. There is a "Giant Cell"</p>														
4	Prussian Blue	(-)	(+)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	<i>Candida tropicalis</i>	9	18
<p>Small and single blastoconidia with pseudohyphae and true hyphae</p>														
5	Baby Purple	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	<i>Candida glabrata</i>	8	16
<p>Yeast cells are present, without pseudohyphae</p>														
6	Pink	Variable	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	<i>Candida krusei</i>	7	14
<p>Pseudohifa with oval-shaped blastoconidia that form cross-match-sticks or tree-like</p>														
7	White-Pink	(-)	(+)	(-)	(+)	(-)	(-)	(+)	(+)	(+)	(+)	<i>Candida guilliermondii</i>	1	2
<p>Blastoconidia in small groups with short pseudohyphae and relatively few yeast cells</p>														
Total Species*													5	100
Total Species*													0	

* One research subject can have several *Candida* species isolates
 HIV = Human Immunodeficiency Virus
 AIDS = Acquired Immune Deficiency Syndrome

Table 6. Distribution of *Candida* species isolates resistance to antifungal ketoconazole, nystatin, and fluconazole

No	Species	Sum (n=50)	%	Ketoconazole			Nystatin			Fluconazole										
				S	%	I	R	%	S	%	I	R	%							
1	<i>Candida albicans</i>	22	44%	22	100	0	0	0	21	95.5	1	4.55	0	0	16	72.7	0	0	6	27.27
2	<i>Non-albicans Candida:</i>	28	56%	20	71.4	5	17.9	3	10.7	28	100	0	0	0	11	39.3	0	0	17	60.7
	- <i>Candida dubliniensis</i>	1	2%	1	100	0	0	0	1	100	0	0	0	0	1	100	0	0	0	0
	- <i>Candida glabrata</i>	8	16%	7	87.5	1	12.5	0	0	8	100	0	0	0	5	62.5	0	0	3	37.5
	- <i>Candida guilliermondii</i>	1	2%	1	100	0	0	0	1	100	0	0	0	0	1	100	0	0	0	0
	- <i>Candida krusei</i>	7	14%	4	57.14	3	42.86	0	0	7	100	0	0	0	0	0	0	0	7	100
	- <i>Candida parapsilosis</i>	2	4%	1	50	1	50	0	0,	2	100	0	0	0	1	50	0	0	1	50
	- <i>Candida tropicalis</i>	9	18%	6	66.66	0	0	3	33.3	9	100	0	0	0	3	33.33	0	0	6	66.67
	TOTAL	50	100%	42	84	5	10	3	6	49	98	1	2	0	27	54	0	0	23	46

* A research subjects may have multiple isolates of *Candida* species

DISCUSSION

The distribution of research subjects were 20 males (76.9%) and 6 (23.1%) females. OC is not similar to vulvovaginal candidiasis, which is influenced by hormonal factors. Thus, in general, no difference in terms of sex was observed.¹² The largest age group in the study was 36 – 45 old years with 7 (26.9%) patients, followed by 26 – 35 and 46 – 55 years old, with each 6 (23.1%) patients. These findings suggested that adults who are in the productive age and sexually active are more likely to engage in unprotected sexual behavior at risk for HIV transmission.¹² The distribution of the highest formal education levels was 4 people (15.4%) who never attended school, and 8 people (30.8%) were primary/middle school graduates. HIV/AIDS patients with low educational background have low oral health knowledge and prone to oral diseases.¹² An educated person has a better understanding of information, especially health information, about the prevention of opportunistic diseases such as OC in HIV/AIDS.¹⁶ The distribution of occupational backgrounds showed that 9 (34.6%) patients were unemployed. Patients with HIV/AIDS in the course of their illness will experience opportunistic infections affecting the quality of life, one of which is their jobs.¹²

OC patients with HIV/AIDS, in this study, had more than one chief complaint. The most common complaint is white patches in the oral cavity 25 (96.2). White patches in the oral cavity are found in the pseudomembranous type of OC and plaque hyperplastic type, which is the most common type of OC.¹⁵ Recurrence in OC can occur in those who have low immune status and/or do not receive appropriate and adequate antifungal therapy. This study showed that 10 subjects (38.5%) had recurring OC, while 16 (61.5%) subjects only had it once. This finding is supported by a study conducted by Reza in Malang in 2014, which showed that 79% of the subjects had OC for the first time.¹²

Candida species resistance in OC can occur secondarily from the inappropriate use of antifungals, and this is most commonly found in systemic antifungals.¹¹ 5 patients (19.2%) were known to have systemic antifungal treatment; 10 patients (38.5%) received topical antifungals and no history of systemic antifungal treatment found in the rest patients. Several patients also have difficulty recalling their previous treatments. This was influenced by various factors, especially their level of education.¹⁶

The most common mode of HIV transmission was heterosexual intercourse as many as 16 subjects (61.5%), possibility by homosexual transmission with 7 subjects (26.9%). This study also found 2 people with

two HIV transmission modes, which were heterosexual intercourse and Injection Drug Users (IDUs). 9 HIV/AIDS patients have been suffering from the disease for more than one year, as found in 12 (46.2%) people, while 9 people (34.6%) have suffered from HIV infection for one to 3 years. The survival rate of HIV patients depends on the patient's immunity status and viral load. HIV-infected persons may find themselves asymptomatic until the occurrence of opportunistic infections, one of which is OC, due to weaker immune.⁶

WHO classifies HIV clinical stage into four stages based on several clinical symptoms related to HIV infection. OC can be found in patients in clinical stage II to clinical stage IV with at various severity. In clinical stage IV, severe OC affecting the esophagus, larynx, and trachea can be found.⁶ Most of the research subjects in this study were classified into clinical-stage group III as many as 14 (53.8%) people. The absolute CD4 cell count of HIV/AIDS patients is an important parameter for the course of HIV/AIDS. OC can be found in an HIV-infected patient with an absolute CD4 cell count of 200 – 500 cells/uL. Furthermore, a severe and recurrent OC can be found in patients with an absolute CD4 cell count <200 cells/uL.⁶ This study revealed that sixteen patients (61.5%) had CD4 counts of <200 cells/ μ L. This data is supported by a 2015 study by Kumar in India that showed 71.4% of patients with a CD4 cell count <200 cells/ μ L had fungal growth of *Candida sp.* from oral candidiasis lesions.¹⁷

As many as 21 (80.8%) HIV/AIDS patients in this study had treated therapy, while 5 (19.2%) patients had not yet received but were planned to receive antiretroviral therapy (ARV). ARV has been reported to decrease the incidence of opportunistic infections successfully. OC is a disease associated with HIV. Although patients are on ARV therapy, another factor such as the changes of virulence spectrum makes *Candida sp.* no longer the main cause of recurring case and complexity the treatment of OC. Research by Moges in Ethiopia in 2013 showed that OC was mostly found in patients who were not on ARV therapy (58.7%). However, it was found in 41.3% of OC patients under ARV therapy.⁴

The identification of *Candida sp.* using mouth scrapings of 26 OC patients with HIV/AIDS resulted in 50 isolates of *Candida sp.* variants. *Candida albicans* was found in 22 (44%) isolates, whereas non-*albicans Candida sp.* was found in 28 (56%) isolates. This proves that there has been a change in the spectrum of causative species in OC with HIV/AIDS.⁴ Research in India by Dar in 2015 comparing *Candida sp.* in HIV-seropositive patients and HIV-seronegative patients showed that colonies of *Candida albicans* species in

HIV-seropositive were lesser than the HIV-seronegative. *Candida sp.* that are rarely found in immunocompetent patients were also found in HIV-seropositive patients, namely *Candida dubliniensis*, *Candida glabrata*, and *Candida guillemontii*.¹⁸ A meta-analysis study conducted in Sub-Saharan Africa in 2005 – 2015 showed a prevalence of non-albicans *Candida* species as much as 33.5% dominated with *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*. The high prevalence of *Candida krusei* and *Candida glabrata* in HIV-infected populations in Sub-Saharan Africa has become a public health concern because this species is associated with fluconazole resistance.¹⁹

An increasing number of non-albicans *Candida* colony isolates in the oral cavity HIV/AIDS patients is a public health concern as it is often associated with azole group antifungal resistance, that difficult to treat. Previous treatment may increase non-albicans *Candida* species colonies in HIV-infected individuals, especially antibiotics and antifungal therapy because it can affect the fungal colonization in the oral cavity. The broad-spectrum antibiotics are able to change the normal bacterial flora by killing bacteria and increasing the proliferation of *Candida* species. A study conducted by Mushi in 2016 in Tanzania suggested that prior antibiotic use was a statistically significant factor in increasing the colonization of non-albicans *Candida* species.²⁰

The pattern of resistance of *Candida sp.* was 3 (6%) isolates resistant to ketoconazole, none of the isolates were resistant to nystatin, and 23 (46%) isolates were resistant to fluconazole. The higher rate of fluconazole resistance of *Candida sp.*, mainly non-albicans *Candida*, is in line with research and literature.^{4,12,13}

Nystatin has sensitivity up to 98%, and it is still the drug of choice for the treatment of mild OC. The results of this study are in line with the findings of Moges of Ethiopia in 2013 that 96.8% of *Candida* isolates were still sensitive to nystatin.⁴ Meanwhile, the study by Dar in India in 2015 showed that only 61.1% isolates were sensitive, 36.1% moderate, and 2.8% resistant to nystatin.¹⁹ In general, the nystatin intrinsic and extrinsic resistance of *Candida* species is sporadic. The polyene (nystatin) resistance caused by change of sterol composition, which then decreases the polyene affinity to the plasma membrane. However, the highly resistant strain of *Aspergillus terreus* turned out to have ergosterol as the main sterol in its plasma membrane. This suggests that resistance to polyene is not always associated with changes in sterol composition, making mechanism of resistance to nystatin is not fully known.²¹ The nature of nystatin, which is non-soluble

in water and non-absorbable through the intact skin, digestive tract, or vagina, is also one of the causative factors of such resistance.⁶

The difference between ketoconazole and fluconazole resistance in some *Candida sp.*, although both are from the same azole drug group, was also reported in a study by Khan in India in 2015. In this study, *Candida krusei* species, which are primarily resistant to fluconazole, were found to be still sensitive to ketoconazole. Meanwhile, increased primary resistance to fluconazole was found in *Candida glabrata*. However, in Khan's study, no *Candida glabrata* resistance observed. On the other hand, it was found that none of the *Candida tropicalis*, which is the second-largest type of *Candida* after *Candida albicans*, was resistant to both azole drugs.²² The Moges' study, which was conducted in Ethiopia in 2013, reported diverse resistance figures, 6.6% *Candida albicans* were resistant to fluconazole, and 5.7% resistant to ketoconazole. Different results were also reported on non-albicans *Candida* where 16.6% of *Candida glabrata* were resistant to fluconazole and 12.5% resistant to ketoconazole, 35.3% of *Candida tropicalis* were resistant to fluconazole and 17.6% resistant to ketoconazole, 50% of *Candida krusei* were resistant to fluconazole, and none was resistant to ketoconazole.⁴ This study, however, only takes one sample from each patient. Ideally, to find out and evaluate the type of pattern and resistance, sample collection should be done repeatedly.²²

Variation of the resistance rates of each *Candida* species to each antifungal drug proves that the factors that play a role include the host, drug, and pathogenic factors of the fungus itself. The different resistance mechanisms of each *Candida sp.* (fungal pathogenic factor) are the factors that mostly influence the antifungal resistance, especially the azole group, which has several mechanisms of resistance. Each species can play a role in different cellular target points. For example, *Candida krusei*, in particular, has a low affinity of the Ergosterol biosynthesis 11 (ERG11) gene naturally (intrinsically) so that the fluconazole drug cannot bind to the ERG11 protein; *Candida glabrata* can absorb exogenous sterols that changes the composition of fungal cell membrane sterols, which are not recognized by the azole antifungal; *Candida albicans* and *Candida tropicalis* can inactivate the Ergosterol biosynthesis 3 (ERG3) gene, changing the composition of the fungal membrane sterols, and both species are also able to increase the expression of the ERG11 gene, preventing the azole agent from binding. The difference between resistant azole antifungals (fluconazole and other azole groups) is the efflux pump process in fluconazole, involving different specific

protein genes compared to other azole groups. Particularly to fluconazole, multiple drug resistance (MDR) gene expression causes an efflux pump process. An excessive expression is not effective as the drug will be removed from fungal cells even before the drug works. As for other azole groups, the *Candida* drug resistance (CDR) gene plays a role in the efflux pump process. The above mentioned can cause various resistant *Candida* species to antifungal agents.^{6,22}

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