ORAL CANDIDIASIS IN HIV PATIENT SUFFERING PNEUMOCYSTIC CARINII PNEUMONIA

Dahlia Riyanto1, Rindang Tanjungsari1, Tri Pudy Asmarawati2, Desiana Radithia3
1Resident of Oral Medicine Specialistic Programme, Faculty of Dental Medicine, Universitas Airlangga
2Internal Medicine Specialist of Airlangga University Hospital
3Oral Medicine Departament, Faculty of Dental Medicine, Universitas Airlangga

ABSTRACT
Background: HIV/AIDS infection provoked opportunistic infection systemically and intraorally. Pneumocystic carinii pneumonia (PCP) and Oral candidiasis (OC) is the most prevalent opportunistic infection among HIV/AIDS patient and may serve as indicator of low CD4 count in HIV infection. Objective: This paper reports management of oral candidiasis in pneumocystic carinii pneumonia that affects a patient with HIV. Case: A 39 year-old man was hospitalized for pneumocystic carinii pneumonia with weakness of gait and emaciated posture. He was also diagnosed of HIV/AIDS infection through CD4 count and HIV rapid test. Introraol white patches was reported occurred within 2 days being hospitalized. Several tests were ordered resulting, metabolic acidosis, CD4 count were 10 cells/μL, HIV rapid test (ICT) was reactive for 3 methods, and microbiologic examination was positif to C.albicans from the smear of white plaque. The patient also diagnosed with OC pseudomembranous type. Case Management: Patient was treated using intravenous fluconazole 100 mg/day for five days and antiseptic mouthwash. Recovery was achieved within 3 weeks follow-up along with given anti retroviral (ARV) treatment by the internist. Conclusion: Management of OC in HIV/AIDS patient with PCP infection in this case were used systemic antifungal and antiseptic mouthwash. The multidiciplinary approach in managing this case obtained successful therapy.

Keywords: AIDS/HIV, oral candidiasis, Pneumocystic carinii pneumonia

Correspondence: Dahlia Riyanto, Departement of Oral Medicine Departement, Faculty of Dental Medicine, Universitas Airlangga, email: dahliarivanto7358@gmail.com

INTRODUCTION
Acquired Immune Deficiency Syndrome (AIDS) is a collection of symptoms or diseases caused by decreased immunity due to infection with Human Immunodeficiency Virus (HIV), which belongs to the family of RNA human retroviruses (Retroviridae) and the subfamily of lentiviruses. The main target cell of HIV is the CD4+ helper T lymphocyte. HIV can be transmitted through sexual contact, blood exposure, needle-stick injuries, and transmission from mother to fetus. In most viral infections, the antibody hosts protective against organisms usually formed. In people with HIV infection, antibodies are developed but not protective. Viruses may remain silent, cause cell death, or produce synchronous fusion from cell, which interferes with its normal function, decreases in the number of T-helper cells, and loss of immune function. Normal response to viruses, fungi, and encapsulated bacteria reduced. 1-4 The high severity and mortality level of AIDS sufferers caused by various factors, one of which is the improper management of patients, including the delay in diagnostic of opportunistic infections in AIDS patients. A number of protozoa, fungi, viruses, and bacteria are responsible for the infections. The World Health Organization reports that the proportion of opportunistic infections in different countries varies. Data from the Ministry of Health of the Republic of Indonesia (2007) shows the largest proportion of opportunistic infections in AIDS patients in Indonesia are Oral Candidiasis (80.8%), Tuberculosis (40.1%), Cytomegalovirus (28.8%), Toxoplasma Ensefilitis (1.2%), PCP (13.4%), Herpes Simplex (9.6%), Mycobacterium Avium Complex (4%), Cryptosporidiosis (2%) and Lung Histoplasmosis (2%). Fungal opportunistic infections in HIV infected patients are a major cause of morbidity, mortality, and reduce the quality of life of these individuals.1,5
Pneumocystis carinii pneumonia (PCP) (known as Pneumocystis jiroveci pneumonia) and candidiasis is a common opportunistic fungal infection in HIV patients, especially in patients with CD4 less than 200 cell/µl. Before PCP prophylaxis and antiretroviral (ARV) were present, PCP occurs in 70-80% patients and almost 90% in HIV. However, after PCP prophylaxis and ARV were present, the incidence of PCP in HIV patients decreases. Candidiasis is one thing that can be an indicator of HIV infection and prediction of progression to AIDS infection that are related to the level of immunosuppression.

CASE

A 39-year-old male patient was hospitalized at the Airlangga University Hospital, Surabaya with complaints of breathless, in the last one month that worsening since 2-3 days ago, rarely coughing, there was no stomatitis, and have loss weight 4-5 kg since the last 2 months. The general condition of the patient was weak, comos mentis (GCS 456). Examination of vital signs included blood pressure 99/65 mmHg, pulse 109 times per minute, and respiratory rate 24 times per minute, temperature 36°C. The patient was hospitalized with a diagnosis of pneumonia and suspected HIV infection. The diagnosis of pneumonia is based on the results of a lung x-ray examination, examination of blood gas analysis, complete blood count (CBC) test, liver function, and kidney function. Patient had been treated with 2x1gr ceftriaxone injection, nebulae with ventolin 4x daily, ambroxol orally 3x1, and infusion asserting 14 drops per minute for PCP.

The patient was refered to oral medicine clinic on the next day. Extra oral examination found white exfoliated, itchy and slightly hot in the perioral area. In addition there was desquamation on the upper lip with multiple fissures, but asymptomatic or painless. Intra oral examination found white plaques on the dorsum of the tongue, on the right and left buccal mucosa, with diffuse borders, and irregular edges. The surrounding area looks reddish, the plaque can be scraped and leave the atopic area, and also painless (Figure 1). Plannings included swab on lesions and oral health care.

On this visit the working diagnosis was suspect pseudomembranous candidiasis and cheilitis exfoliative. Treatments include oral health care, swab in lesions for KOH staining and Candida culture, administration and prescription of mouthwash containing 0.2% chlorhexidin gluconate, CIE (Communication, Information, Education) including taking medication and using mouthwash as recommended, also instruction for adequate hydration. Plannings from a Internist at this visit include CD4+, HBsAg and anti HCV laboratory examinations.

CASE MANAGEMENT

In the second visit, the patient stated using mouthwash as recommended for two days and antifungal medicine given by nurse once a day. Internist prescribed fluconazole 100mg/day intravenously. The previous complaints of the tongue had diminished, but the skin peeling around the mouth still existed. The patient felt better and did not itch. Patient complained that he was still congested and unable to walked because he was easily tired, still tight when talking, but no complaints when eating and drinking.

Extra oral examination found desquamation in the upper lip had been greatly reduced, but still there was painless multiple fissures in the upper lip. The white plaques have decreased a lot on the tongue, and dissapeared on the right and left of the buccal mucous, but left a little reddish multiple macule, with smooth surface, diffuse borders, and irregular edges (Figure 2). In this visit, the cheilitis exfoliative for extra oral examination and pseudomembranous candidiasis were in the healing process. CIE was continued, included taking medication and using mouthwash as recommended, and adequate hydration. The diagnosis of pseudomembranous candidiasis has been proven by KOH examination and fungal culture.

In the third visit, the patient stated that had taken two kinds of ARV since one day before, and the oral condition was improved. He had learned to walked without being guided.

On extra oral examination found asymptomatic desquamation around the chin, that could be exfoliated. There was no fissure and desquamation on upper and lower lips. On intra oral examination the white plaque on the dorsum of the tongue has dissapeared (Figure 3). On this visit, the working diagnosis cheilitis and pseudomembranous candidiasis were healed. The patient was still given intravenous fluconazole but would be replaced in tablet preparations because the patient has been allowed to go home. CIE was included the instruction to keep using mouthwash, take medication according to recommendations, bed rest, and routine control.
In fourteen days as an outpatient, patient sent the photo of his oral condition via whatsapp. Patients could not come to control because he had to go to work after getting sick for a long time. Patient stated that his conditions was improved, has been active again, did not breathless, and able to walk as usual. Patient routinely take tenofovir, duviral, and fluconazole during that time, but the fluconazole has run out. The patient stated that the skin on his face was clean, did not peel and he could use the usual face soap again. In addition, the patient stated that no more white plaques or stomatitis in his mouth. The upper lip slightly peels but the color looked normal and painless. At this time, the pseudomembranous candidiasis had healed and treatment was complete. Considering the patient was people living with HIV/AIDS (PLWHA), then the CIE include to continue taking ARV treatment egularly, follow the control schedule regularly, maintain body condition with light activity, remain optimistic about medication, nutritious food and adequate rest.

DISCUSSION

Acquired Immune Deficiency Syndrome (AIDS) is a collection of symptoms that appear after decreased immunity caused by the entry of the HIV virus in a person's body. In this case, an HIV diagnosis is made based on the results of anti-HIV serological examination (rapid test) which is reactive in methods 1, 2 and 3, and showed several clinical signs that determine the clinical phase. AIDS has several clinical phase that useful for assessing initial or advanced conditions, and other interventions for HIV therapy. In this case the patient has been in the clinical phase 4 because there has been a decrease in weight more than 10% without cause, oral candidiasis and PCP infection. The other criteria for phase 4 were pneumonia, new pulmonary tuberculosis, and intermittent fever> 1 month, did not exist in this patient. CD4 examination in this patient showed a value of 2.44% (normal value 31-60%), an absolute CD4 value of 10 cells/µL (normal value 410-1590 cells/µL). CD4 can be a clue as an early progression of the disease because the CD4 count decreases first compared to clinical conditions. CD4 monitoring can be used form start giving ARV or drug replacement. Initiation of ARV in HIV-infected people in clinical stages 3 and 4, or if the CD4 count is ≤ 350 cells /µL. 8,9

HIV is a RNA virus with characteristic of reverse transcription of its genomic RNA into DNA by the enzyme reverse transcriptase. The main target cell of HIV is CD4 helper T lymphocytes, although other CD4 cells (such as macrophages and dendritic cells) can also be infected. HIV cell infection begins when the envelope gp120 glycoprotein from the virus binds to two proteins in the host cell, CD4 and co-receptor which are usually chemokine receptors. The CD4 molecule is a 55-kDa protein found mainly in the T lymphocyte subset which is responsible for the helper function in the immune system. The viral RNA genome in reverse is transcribed into complementary DNA and inserted into the DNA of the host cell. After the virus completes its life cycle in infected cells, free

Figure 2. (a) White plaque on the tongue, diffuse borders, irregular edges, the area around redness, can be scraped and leave the atopic area, painless. (b)(c) Reddish macule, multiple, on the right and left bucal mucous, smooth surface, diffuse borders, irregular edges

Figure 3. White plaque on the dorsum of the tongue has dissapeared
virus particles are released from infected cells and bind to uninfected cells, thereby spreading infection. HIV infection results in impaired adaptive and innate immune systems. The most prominent defect is cell-mediated immunity, which results from the destruction of CD4 T cells. Death of CD4 T cells is associated with the production of viruses in infected cells and can contribute to a decrease in the number of these cells. CD4 is the best parameter for measuring immune deficiency.\textsuperscript{2,3,8,10}

Low CD4 causes a weakened immune system which increases the risk of various kinds opportunistic infections in infected people. PCP is an opportunistic pathogen that often occurs in people with high mortality rates and is strongly associated with HIV/AIDS. PCP lives almost exclusively in pulmonary alveoli in humans. The genome does not have virulence factors and most amino acid biosynthesis enzymes, suggesting that PCP is a obligate pathogen that specializes in colonizing the human lungs and causing disease only in immunocompromised individuals. In HIV-infected patients, the reported colonization rate is as high as 69%. Before PCP prophylaxis and antiretroviral (ARV), PCP occurs in 70-80% of HIV patients and almost 90% occur in HIV patients with CD4 counts less than 200 cells/ul. However, after the presence of PCP prophylaxis and ARV, the incidence of PCP in HIV patients has been significantly reduced. The decrease of CD4 lymphocytes are very important to eradicate PCP infection and contribute to inflammatory lung damage. CD4 cells proliferate in response to Pneumocystis antigens and produce interferon (IFN) -γ, which induces further recruitment of macrophages. Interleukin-8 (IL-8), which is released from epithelial cells and macrophages, greatly increases neutrophil recruitment which not only contributes to cleansing of the organism but also mediates lung injury through the release of proteases and oxygen radicals. Severe PCP is characterized by inflammation of the neutrophilic lungs which can cause diffuse alveolar damage, gas exchange disorders, and respiratory failure.\textsuperscript{11,12}

As does PCP, the oral manifestations of HIV infection are sometimes as the first sign of infection and often show its progression to AIDS. Oral candidiasis is found in 30-80% as the initial manifestation of HIV infection and also the most common opportunistic infection in people with HIV, about 90%. Oral candidiasis can affect men and women and all ages. Oral candidiasis in HIV patients, include: pseudomembranous candidiasis, erythematous candidiasis, angular cheilitis, chronic hyperplastic candidiasis, and mucocutaneous candidiasis. Oral candidiasis in this case is a pseudomembranous type which has a lesion appearance in the form of a creamy white lesion, can be scraped and leaves the reddish in mucous surface. Spectrum Candida infections range from asymptomatic colonization into oropharyngeal candidiasis (OPC), esophagitis, onychomycosis, vulvovaginitis, candidiasis of the skin, and includes invasive systemic candidiasis or candidiasis candidemia, and can cause morbidity and mortality.\textsuperscript{1,5}

*Candida albicans* is the most commonly isolated species as oral mucosal pathogen colonies, others Candida species, such as *C. tropicalis, C. krusei, C. glabrata, C. dubliniensis, C. guilliermondii, C. parapsilosis, C. kefyr,* and *C. pelliculosa,* has been a significant cause of fungal infection in patients with HIV infection. In this case oral candidiasis is caused by *C. Albican* which is proven by KOH examination and fungal culture. *C. albicans* is a fungus that become components of normal oral microflora but its will turn into a pathogen when the host's immune system decreases. *Candida albicans* can grow as yeast, pseudohyphae, or true hyphae depending on environmental conditions.\textsuperscript{1,5,13,14}

The pathogenicity mechanism of *C. albicans* begins with the stage of adhesion of yeast cells to the surface of the host by mediating the expression of adhesin namely agglutinin like sequence (ALS) 1-7 and ALS 9. ALS3 is of the nature increase extensive regulation during infection and ability to binds cadherin to the host cell and induces endocytosis from pathogens. Hyphal wall protein 1 (Hwp1; coded by the HWP1 gene) is another protein involved in *C. Albicans* adhesion to epithelial cells. This adhesin induces covalent bonds between hyphae and host cell as Hwp1 is the substrate for transglutaminase. This interaction has been shown to be important for colonization of *C. albicans* in the oral cavity. Fungal cell attachment is followed by cell division, proliferation, and biofilm development. Biofilms are defined as complex structured microbial communities that are attached to the extracellular matrix (ECM) for provide protection by preventing penetration of host immune factors and antifungal factors into the ECM. Candida species can grow into hyphae or pseudohyphae are considered as more virulent. Infiltration to epithelial cells is more effective by filamentous morphologies because of the pressure produced by the tip of the hyphae. The tip is also a place for secreting enzymes and other ingredients that can weaken and damaged cell walls. Several hydrolase groups are released by Candida species, including: proteases, phospholipases, and lipases. Protease produced is family secreted aspartic protease (Sap) 1-10. Aspartil secreted protease (SAP) functions to disrupt the host membrane, allowing for pathogenic invasion. Ten SAP proteins have been identified, with some having a more prominent role in pathogenicity than others. SAP8 is secreted, while SAP9-10 remains bound to the fungal membrane.
Biofilm formation also has a positive correlation with SAP expression. 15,16

There are various host defense mechanisms against C. albicans infection which mainly include phagocytosis of fungal cells by innate immune system (macrophages and neutrophils). Clearance phagocytosis of fungal pathogens can be consist of four different stages: 1) phagocyte accumulation at the site where fungal cells are located; 2) recognition of fungal pathogens by specific receptors; 3) ingesting fungal cells bound to phagocytic cell membranes, and 4) processing cells that are ingested in phagocytes through fusion with lysosomal vesicles to form phagolysosomes. The form of C. albicans cell yeast is more effective ingested by macrophages than hyphae. The cells of hyphae are ingested at a slower rate than yeast cells. Delay in ingesting can cause fungal cell release. Furthermore, the yeast form of C. albicans that are phagocytosis by macrophages switch to hyphae and escapes from the macrophages. This change is very important in escaping from the host defense mechanism. The function of the disrupted salivary gland can predispose oral candidiasis. Salivary antimicrobial proteins such as lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides and specific anti-candida antibodies, interact with the oral mucosa and prevent excessive growth of candida. Disorders of cellular immunity regulated by CD4 T cells reduce protection against mucosal infections. There is a correlation of a decrease in the number of CD4 T cells with the onset of oral candidiasis because it affects the need for CD4 T systemic thresholds to protect the oral mucosa and local immune status. The onset of oral candidiasis is influenced by the level of CD4 T cells, a 25% reduction from the normal level can cause manifestations and affect the progression of the disease. HIV positive patients have a 4.3 times greater risk of oral Candida colonization than being HIV negative and HIV patients with oral candidiasis have a 2.5 times more progressive risk of AIDS than HIV patients without oral candidiasis. 1,13,17,18

Treatment of oral candidiasis includes therapy with topical and systemic antifungal agents. In this case, fluconazole 100 mg was given intravenously. Fluconazole is a triazole antifungal agent that is widely used for the treatment of Candida spp. infection. Antifungals work by inactivating lanosterol 14α-demethylase, thereby inhibiting ergosterol biosynthesis, an important compound for cell integration and membrane function. This results in a decrease in the level of ergosterol available for membrane functions and an increase in the number of intermediate metabolites. 19,20

In this case, the patient was treated by chlorhexidine gluconate. Chlorhexidine is the ideal broad-spectrum antimicrobial. This effective against Gram-positive bacteria, Gram-negative bacteria, and fungal. In low concentrations it affects cell wall integrity. After the cell wall is damage, Chlorhexidine then crosses into the cell and attacks cytoplasmic membrane (inner membrane). Damage semipermeable cytoplasmic membrane followed by component leakage that causes cell death. High concentration, chlorhexidine causes cytoplasm freezes or hardens. Chlorhexidine is able to overcome candida adhesion on biological and inert surfaces. It acts as a fungicide and has a fungistatic function, which is directs at nucleoprotein coagulation and changes in cell walls that allow the release of cytoplasmatic components through cell membranes. Chlorhexidine has some effectiveness against microorganisms in other forms, including spores and protozoa. It also shows activity against envelope viruses in vitro, such as: the herpes simplex virus, HIV, cytomegalovirus, influenza, and Respiratory Syncytial Virus (RSV) but substantially less activity against non envelope viruses (eg, rotavirus, adenovirus, and enterovirus). 21,22

Antiretroviral treatment (ARV) is part of HIV/AIDS treatment to reduce the risk of transmission, inhibit worsening conditions due to opportunistic infections, improve the quality of life of people with HIV, and reduce the amount of virus (viral load) in the blood until undetectable. Antiretroviral is divided into 4 groups, namely nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease Inhibitors (PIs), and fusion inhibitors. Recommendations from the WHO and the Ministry of Health of the Republic of Indonesia for current ARV first-line regimens are a combination of 2 NRTIs and 1 NNRTI. In this case, the patient is treated with administration of duviral and neviral ARVs. Duviral is an antiretroviral which contains lamivudine (3TC) and zidovudin (AZT). Both types of drugs are nucleoside analogues or nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs are intracellular phosphorylated into active diphosphate or triphosphate metabolites, which then inhibit the enzymatic action of HIV transcriptase by entering into nucleotide analogues that cause the cessation of DNA chains or by competing with the natural substrate of the virus. This stops the conversion of viral RNA to double-stranded DNA. Zidovudine is a thymidine analogue that is converted into an intracellular active triphosphate form, which is then attached to the DNA polymerase from reverse transcriptase which leads to chain termination. Lamivudine is active against hepatitis B virus (HBV) and should be used as part of a regimen in hepatitis B co-infected patients. Nevirapine is the trade name for nevirapine, a non-nucleoside reverse transcriptase inhibitor. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) differ from NRTIs. NNRTIs are
powerful agents for virological suppression by non-competitive inhibitors of reverse transcriptase, which produce conformational changes that reduce the action of this enzyme. NNRTI use is limited by drug interactions, selected side effects, and overall low threshold for the emergence of resistant mutants. Nevirapine is widely metabolized by CYP3A4 and 2B6 and undergoes entero-hepatic recirculation. When patient was allow to go home, the antiretroviral drugs given are duviral and tenofovir. Tenofovir (tenofovir disoproxil fumarate) is also an NRTI. Tenofovir disoproxil fumarate is a nucleotide analog that inhibits reverse transcriptase from HIV and HBV. This is uses as part of the treatment of HIV and HBV infection. The advantage is quickly absorbs orally and remove renally by glomerular filtration and active tubular secretion.5,23,24

In this patient, the ARV has been given were duviral and neviral. The ARV treatment will reduce viral load in the blood and inhibit worsening conditions due to opportunistic infections, so that the ARV treatment can improve the body and oral condition. HIV/AIDS infection characterized by decreasing CD4 which reduce the body’s defences and trigger opportunistic infections. The management of oral candidiasis in pneumocystis carinii pneumonia that affects 39 years old men with HIV in this case, with chlorhexidine digluconate as topical antiseptic (mouthwash), Fluconazole injection and per oral as an antifungal.

REFERENCES

1. Putranti A, Asmarawati TP, Rachman BE, Hadi U, Nasronudin. Oral candidiasis as clinical manifestation of HIV / AIDS infection in Airlangga University hospital patients. IOP Conf Ser Earth Environ Sci. 2018;125(012063):1–6.
2. Kasper D, Fauci A. Infectious disease. 17th ed. USA: The McGraw-Hill Companies, Inc; 2010. 792-886 p.
3. Neville BW, Damm DD, Allen CM, Chi AC. Oral and Maxillofacial Pathology. 4th ed. St Louis: Elsevier; 2016. 140 p.
4. Hupp JR, Ferneini EM. Head, Neck, and Orofacial Infection: An Interdisciplinary Approach. St Louis: Elsevier; 2016. 42-43 p.
5. Maheshwari M, Kaur R, Chadha S. Candida Species Prevalence Profile in HIV Seropositive Patients from a Major Tertiary Care Hospital in New Delhi , India. J Pathog. 2016;2016:1–8.
6. Agustina DR, Efriyanti C, Yunihastuti E, Ujainah A, Rozaliyani A. Diagnosis and Treatment of Pneumocystis Carinii Pneumonia (PCP)/ Pneumocystis Jirovecii Pneumonia in HIV patient: A Case Report. J Penyakit Dalam Indones. 2017;4(4):209–13.
7. Caceres N de A, Vieira MMC, Viera IF, Monteleone VF, Neto LJM, Bonafe S. Opportunistic Infections in Aids Patients Abstract Pneumocystosis Introduction. iMedPub Journals. 2015;7(5):1–17.
8. Health M of. Regulation of The Minister of Health of The Republic of Indonesia Number 87 of 2014 Concerning Antiretroviral Treatment Guidelines. 2014;1–121.
9. Weinberg JL, Kovarik CL. The WHO clinical staging system for HIV/AIDS. Am Med Assoc J Ethics. 2010;12(3):202–6.
10. Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology. ninth edit. Philadelphia: Elsevier; 2018. 475-487 p.
11. Widya AM, Mertaniah NM, Kwalarang AP, Marhana IA. Low Cd4 Lymphocyte Count Related Risk to Pneumocystis Jiroveci Pneumonia in HIV / AIDS Patients From Bronchoalveolar Lavage Specimens Using Real Time PCR Detection. Indones J Trop Infect Dis. 2017;6(6):145–9.
12. Tasaka S. Pneumocystis Pneumonia in Human Immunodeficiency Virus – infected Adults and Adolescents : Current Concepts and Future Directions. Clin Med Insight Circ Respir Pulm Med. 2015;9:19–28.
13. Singh A, Verma R, Murari A, Agrawal A. Oral candidiasis : An overview. J Oral Maxillofac Pathol. 2014;18(1):81–5.
14. Mukaremera L, Lee KK, Moramontes HM, Gow NAR, Templeton S. Candida albicans Yeast , Pseudohyphal , and hyphal Morphogenesis Differentially affects immune recognition. Front Immunol. 2017;8(June):1–12.
15. Kabir MA, Hussain MA, Ahmad Z. Candida albicans : A Model Organism for Studying Fungal Pathogens . ISRN Microbiol. 2012;2012:1-15.
16. Rosa EAR. Oral candidosis epidemiology. Oral Candidosis: Physiopathology, Decision Making, and Therapeutics. Parana: Springer; 2015. 7-20 p.
17. Nadeem SG, Shafiq A, Hakim ST, Anjum Y, Kazm SU. Effect of Growth Media , pH and Temperature on Yeast to Hyphal Transition in Candida albicans. Open J Med Microbiol. 2013;3:185–92.
18. Yitayew B, Woldeamanuel Y, Asrat D, Tenna A. Oral Candida carriage among HIV infected and non infected individuals in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Glob J Med Public Heal. 2015;4(2):1–8.
19. Katragkou A, Alexander EL, Eoh H, Raheem SK, Rolides E, Walsh TJ. Effects of fluconazole on the metabolomic profile of Candida albicans. J Antimicrob Chemother. 2016;71:635–40.

20. Benedetti VP, Savi DC, Aluizio R, Adamoski D, Kava V, Terasawa LVG, et al. ERG11 gene polymorphisms and susceptibility to fluconazole in Candida isolates from diabetic and kidney transplant patients. J Brazilian Soc Trop Med. 2019;52:1–6.

21. Kumar SB. Chlorhexidine Mouthwash- A Review. J Pharm Sci Res. 2017;9(9):1450–2.

22. Shino B, Peedikayil FC, Jaiprakash SR, Bijapur GA, Kottayi S, Jose D. Comparison of Antimicrobial Activity of Chlorhexidine , Coconut Oil , Probiotics , and Ketoconazole on Candida albicans Isolated in Children with Early Childhood Caries : An In Vitro Study. Scientifica (Cairo). 2016;1–5.

23. Wardani PK, Ulfa NM, Natalia ACA. Study of Effectiveness of Fixed Dose Combination Antiretroviral Drug Regime (Tenofovir / Lamivudin / Efavirenz) Based on Increased Levels Cd4 T- Lymphocyte (Study conducted at Pharmacy Installation in Hospital X Surabaya). J Pharm Sci. 2017;2(1):22–8.

24. Pau AK, George JM. Antiretroviral Therapy : Current Drugs. Infect Dis Clin North Am. 2015;28(3):371–402.